SECTION 5

The patient with reduced renal function

CHAPTER 94

Chronic kidney disease: definition, classification, and approach to management

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Introduction

Chronic kidney disease (CKD) is an important global public health problem (Levey et al., 2007). More than 2 million people worldwide are estimated to be receiving treatment with dialysis or transplantation for chronic kidney failure, and this population has been growing at an approximate rate of 7% per year (Lysaght, 2002). However, poor outcomes from CKD are not limited to kidney failure but also include a wide array of morbidity and mortality related to complications, particularly from decreased kidney function and cardiovascular diseases (CVD).

The National Kidney Foundation (NKF) sponsored the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines in 2002, which described the conceptual model, definition, and classification of CKD (Kidney Disease Outcomes Quality Initiative (K/DOQI), 2002). These guidelines were subsequently adopted with minor modifications by the international guideline group Kidney Disease Improving Global Outcomes (KDIGO) in 2004 (Levey et al., 2005). The CKD guidelines represented a fundamental paradigm shift, from viewing kidney disease as a life-threatening condition affecting few people requiring care by nephrologists, to a common condition meriting attention by general internists, and requiring a concerted public health approach for prevention, early detection, and management (Rettig et al., 2008; Levey et al., 2009a). In less than a decade, the guidelines have had a major effect on clinical practice, research, and public health, but have also generated substantial controversy (Eckardt et al., 2009; James et al., 2010; Levey and Coresh, 2012). In 2009, KDIGO held a controversies conference to re-examine the CKD definition and classification. Participants at this conference reached a consensus to retain the 2002 KDOQI definition of CKD, but recommended including the cause of CKD and the level of albuminuria in the revised classification system (Levey et al., 2011). Based on these recommendations, KDIGO recently updated the 2002 KDOQI guidelines in 2012 (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013).

The goal of this chapter is to review the current conceptual model and definition, current and proposed classification systems, the rationale for the definition and classification, as well as approach to the care of patients with CKD.

Definition and classification of chronic kidney disease

Conceptual model of CKD

Fig. 94.1 shows the KDOQI conceptual model for the development, progression, and complications of CKD (Levey et al., 2009a; Kidney Disease Outcomes Quality Initiative (K/DOQI), 2002). This model describes the natural history of CKD. Kidney failure is identified as the end stage of CKD, which is preceded by the stages of decreased glomerular filtration rate (GFR), kidney damage, and antecedent conditions associated with higher risk for developing CKD. The model suggests that kidney disease worsens over time by transitioning through a defined sequence of stages, regardless of the cause and rate of progression through each stage. Thus, it should be possible to detect CKD prior to kidney failure by testing for markers of kidney damage and estimating the level of GFR. The horizontal arrows pointing from left to right emphasize the progressive nature of CKD. However, the rate of progression is variable and not all CKD progresses; thus, a diagnosis of CKD does not equate with eventual development of kidney failure. Interventions in earlier stages may slow or prevent the progression to later stages. Early stages of kidney disease may be reversible, and individuals with kidney failure can revert to earlier stages through kidney transplantation, shown as dashed arrowheads pointing from right to left. Recent studies suggest that CKD is a risk factor for development of acute kidney injury (AKI), and that episodes of AKI may increase the risk for progression of CKD (Ishani et al., 2009; Lo et al., 2009; Pannu et al., 2011).

The model also highlights that adverse outcomes of CKD are not limited to progressive decline in kidney function. Other complications include metabolic and endocrine complications of decreased GFR, such as anaemia, bone and mineral disorders, malnutrition and neuropathy, representing mild forms of uraemic manifestations, nephrotic syndrome in patients with marked albuminuria, and CVD, often leading to death. More recently recognized complications are threats to patient safety from systemic toxicity and nephrotoxicity due to drugs and procedures, infections, and impaired cognitive and physical function. These complications may arise at earlier stages and patients with CKD can suffer from complications of CKD without progression to kidney failure. Strategies for prevention, early detection, and treatment of CKD complications

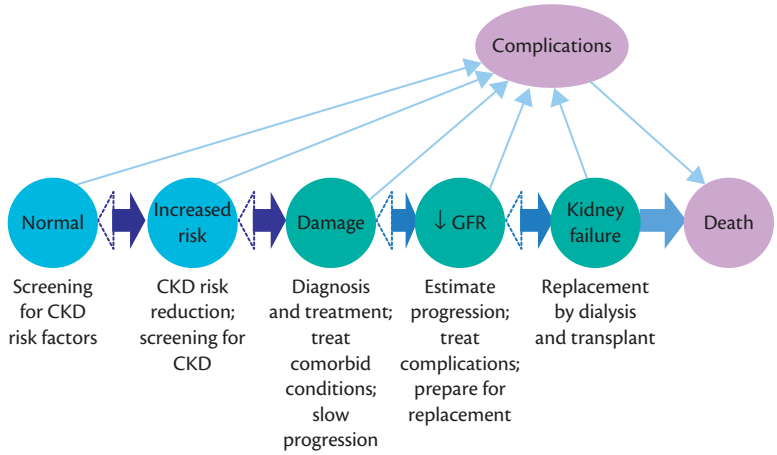

Fig. 94.1 Conceptual model for chronic kidney disease. This diagram presents the continuum of development, progression, and complications of chronic kidney disease (CKD) and strategies to improve outcomes. Green circles represent stages of CKD; aqua circles represent potential antecedents of CKD; lavender circles represent consequences of CKD; and thick arrows between circles represent the development, progression, and remission of CKD. 'Complications' refers to all complications of CKD, including complications of decreased GFR and cardiovascular disease. Complications may also arise from adverse effects of interventions to prevent or treat the disease. The horizontal arrows pointing from left to right emphasize the progressive nature of CKD. Dashed arrowheads pointing from right to left signify that remission is less frequent than progression.

Modified from *American Journal of Kidney Diseases* (Kidney Disease Outcomes Quality Initiative (K/DOQI), 2002; Levey et al., 2009a).

may prolong survival and improve quality of life even if there is no effect on kidney disease progression.

Finally, the conceptual model also identifies a population at increased risk for developing CKD. Attributes which differentiate the population at higher risk from the population at lower risk are defined as 'risk factors' for development of CKD. Increased risk can arise from exposure to factors that cause kidney damage, such as hypertension or diabetes, or increased susceptibility to kidney damage, such as older age or reduced nephron mass. Some risk factors may be modifiable and, in principle, detection and modification of these risk factors could delay or prevent the development of CKD.

Definition of chronic kidney disease: diagnostic criteria and their rationale

Definition

CKD is defined as the presence of kidney damage or GFR < 60 mL/min/1.73 m^2 (GFR in mL/min/1.73 m^2 may be converted to mL/s/1.73 m^2 by multiplying by 0.01667) for ≥ 3 months, irrespective of cause (Table 94.1) (Kidney Disease Outcomes Quality Initiative (K/DOQI), 2002; Levey et al., 2005). An important aspect of the definition is that the criteria are objective and can be ascertained by simple laboratory tests, and can be irrespective of cause. Kidney failure is defined as either (a) GFR < 15 mL/min/1.73 m^2 (which in most cases will be accompanied by signs and symptoms of uraemia) or (b) a need to start kidney replacement therapy (dialysis or transplantation). Kidney failure is not synonymous with end-stage renal disease (ESRD), the administrative term in the United States and elsewhere that indicates treatment by dialysis or transplantation. The term ESRD does not include patients with kidney failure who are not treated with dialysis and transplantation.

Rationale for kidney damage as a diagnostic criterion for the definition of CKD

Presence of kidney damage qualifies for the definition of CKD even in the absence of low GFR as kidney damage portends a poor prognosis for the major outcomes related to CKD. Ascertainment of damage is usually made without kidney biopsy. Because most kidney disease is due to diabetes or hypertension, persistent proteinuria or albuminuria is the principal marker. Epidemiologic studies in diverse populations have shown graded relations between higher albuminuria and mortality and kidney outcomes, in addition to, and independent of, low GFR and risk factors for CVD (Chronic Kidney Disease Prognosis Consortium et al., 2010; Hemmelgarn et al., 2010; Astor et al., 2011; Gansevoort et al., 2011). In addition, albuminuria has also been shown to be independently associated with other CKD complications like anaemia, acidosis, hypoalbuminaemia, hyperparathyroidism, and hypertension (Inker et al., 2011). The generally accepted threshold for albuminuria as a marker of kidney damage is 30 mg/day, roughly equivalent to a urinary albumin to creatinine ratio of > 30 mg/g or > 3 mg/mmol. Apart from albuminuria and proteinuria, abnormalities in urine sediment (e.g. presence of red blood cells, white blood cells, tubular cells, or casts), imaging studies (e.g. hydronephrosis, asymmetry in kidney size, polycystic kidney disease, small echogenic kidneys), and blood and urine chemistry measurements (those related to altered tubular function, such as renal tubular acidosis) may reflect kidney damage and can fulfil the criterion for kidney damage.

Rationale for decreased GFR as a diagnostic criterion for the definition of CKD

Reduced kidney function, specifically a GFR < 60 mL/min/1.73 m^2, is also defined as CKD. The level of GFR is usually accepted as the best overall index of kidney function in health and disease (Smith, 1937). The normal level of GFR varies according to age, sex, and body size. GFR in healthy young adults is approximately 120–130 mL/min/1.73 m^2 and declines by approximately 1 mL/min/1.73 m^2 per year after the third decade (Davies and Shock, 1950; Lindeman et al., 1985). Thus, a GFR level of < 60 mL/min/1.73 m^2 represents the loss of half or more of the adult level of normal kidney function. More than 25% of individuals aged 70 years and older have a GFR < 60 mL/min/1.73 m^2 in the United States, which may reflect intrinsic

Table 94.1 Criteria for definition of chronic kidney disease

Criteria	Comment
Duration ≥ 3 months, based on documentation or inference	Duration is necessary to distinguish chronic from acute kidney diseases: ◆ Clinical evaluation can often suggest duration ◆ Documentation of duration is usually not available in epidemiologic studies
Glomerular filtration rate (GFR) <60 mL/min/1.73 m^2	GFR is the best overall index of kidney function in health and disease: ◆ The normal GFR in young adults is ~ 125 mL/min/1.73 m^2. GFR < 15 mL/min/1.73 m^2 is defined as kidney failure ◆ Lower levels are rare in young individuals (<40 years), are associated with increasing complications of CKD, and are associated with adverse outcomes, including cardiovascular disease morbidity and mortality in individuals with or without diabetes ◆ Decreased GFR can be detected by current estimating equations for GFR based on serum creatinine (estimated GFR) but not by serum creatinine alone ◆ Decreased estimated GFR can be confirmed by measured GFR.
Kidney damage, as defined by structural abnormalities or functional abnormalities other than decreased GFR	Pathologic abnormalities (examples). Clinical diagnosis is based on pathology and cause. Markers of kidney damage may reflect pathology: ◆ Glomerular diseases (diabetes, autoimmune diseases, systemic infections, drugs, neoplasia) ◆ Vascular diseases (atherosclerosis, hypertension, ischaemia, vasculitis, thrombotic microangiopathy) ◆ Tubulointerstitial diseases (urinary tract infections, stones, obstruction, drug toxicity) ◆ Cystic disease (polycystic kidney disease)
	History of kidney transplantation. In addition to pathologic abnormalities observed in native kidneys, common pathologic abnormalities include the following: ◆ Chronic allograft nephropathy (non-specific findings of tubular atrophy, interstitial fibrosis, vascular and glomerular sclerosis) ◆ Rejection ◆ Drug toxicity (calcineurin inhibitors) ◆ BK virus nephropathy ◆ Recurrent disease (glomerular disease, oxalosis, Fabry disease)
	Albuminuria as a marker of kidney damage (increased glomerular permeability, urine albumin-to-creatinine ratio (ACR) >30 mg/g):[a] ◆ The normal urine ACR in young adults is <10 mg/g. Urine ACR categories 10–29, 30–300 and > 300 mg are termed 'high normal, high, and very high, respectively. Urine ACR > 2000 mg/g is accompanied by signs and symptoms of nephrotic syndrome (low serum albumin, oedema and high serum cholesterol) ◆ Threshold value corresponds approximately to urine dipstick values of trace or 1+, depending on urine concentration ◆ High urine ACR can be confirmed by urine albumin excretion in a timed urine collection ◆ Higher levels are associated with adverse outcomes, including progression of kidney disease and cardiovascular disease in individuals with or without diabetes mellitus ◆ Therapies that reduce albuminuria are associated with slowing the progression of diabetic and non-diabetic kidney disease
	Urinary sediment abnormalities as markers of kidney damage: ◆ Red blood cell casts in proliferative glomerulonephritis ◆ White blood cell casts in pyelonephritis or interstitial nephritis ◆ Oval fat bodies or fatty casts in diseases with proteinuria ◆ Granular casts and renal tubular epithelial cells in many parenchymal diseases (non-specific)
	Imaging abnormalities as markers of kidney damage (ultrasound, computed tomography, and magnetic resonance imaging with or without contrast, isotope scans, angiography): ◆ Polycystic kidneys ◆ Hydronephrosis due to obstruction ◆ Cortical scarring due to infarcts, pyelonephritis or vesicoureteral reflux ◆ Renal masses or enlarged kidneys due to infiltrative diseases ◆ Renal artery stenosis ◆ Small and echogenic kidneys (common in later stages of CKD due to many parenchymal diseases)

(*continued*)

Table 94.1 Continued

Criteria	Comment
	Renal tubular syndromes as markers of kidney damage: ◆ Renal tubular acidosis ◆ Nephrogenic diabetes insipidus ◆ Bartter and Gitelman syndromes ◆ Fanconi syndrome ◆ Cystinuria ◆ Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC)

[a] Albumin-to-creatinine ratio (ACR) conversion factor 1.0 mg/g = 0.113 mg/mmol. Urinary creatinine excretion reflects muscle mass; it varies with age, sex, race, diet, and nutritional status, and generally exceeds 1.0 g/day in healthy adults. Therefore urine ACR (mg/g) is usually less than urinary albumin excretion rate (mg/day). Urine albumin excretion rate of 30–300 and > 300 mg/day correspond to microalbuminuria and macroalbuminuria, respectively. Normal urine contains small amounts of albumin, low molecular weight serum proteins, and proteins derived from renal tubules and the lower urinary tract. In most kidney diseases, albumin is the predominant urine protein, comprising approximately 60% of urine total protein when total protein is very high. Values corresponding to normal, high-normal, high, very high and nephrotic range total protein are approximately < 50, 20–50, 50–500, > 500, and > 3500 mg/day. Reproduced from *The Lancet* (Levey and Coresh, 2012).

degenerative processes or the high prevalence of systemic vascular diseases that affect the kidney (Coresh et al., 2007). The definition of decreased GFR as a criterion for CKD does not vary with age. Whatever its cause, a GFR < 60 mL/min/1.73 m^2 in the elderly is an independent predictor of adverse outcomes such as death and CVD, and is associated with an increased prevalence of systemic complications (Chronic Kidney Disease Prognosis Consortium et al., 2010). Similar to younger patients, adjustment of drug doses is required in the elderly with lower GFR.

Classification of chronic kidney disease

The NKF/KDOQI classification of CKD is based solely on the severity of the disease as indicated by the level of GFR, with higher stages representing lower GFR levels: GFR > 90 mL/min/1.73 m^2 (stage 1), 60–89 mL/min/1.73 m^2 (stage 2), 30–59 mL/min/1.73 m^2 (stage 3), 15–29 mL/min/1.73 m^2 (stage 4), and < 15 mL/min/1.73 m^2 (stage 5) (Kidney Disease Outcomes Quality Initiative (K/DOQI), 2002). Patients receiving treatment with dialysis are subclassified as GFR stage 5D to highlight the specialized care required for dialysis. As growing volume of evidence suggested an important role of albuminuria in the pathogenesis of disease progression and complications, the KDIGO sponsored an international conference in 2009 to examine the relationship of GFR and albuminuria to mortality and kidney outcomes (Levey et al., 2011). On the basis of data from 45 cohorts with > 1.5 million participants, the KDIGO conference recommended to modify the KDOQI classification by adding albuminuria stages, subdivision of stage 3, and the underlying cause of CKD (Levey et al., 2011). Based on these recommendations, KDIGO recently updated the 2002 KDOQI classification system (Tables 94.2, 94.3, and 94.4,) (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013). The combination of GFR, albuminuria and cause will help to classify patients according to their risk for CKD complications (Table 94.5).

Use of GFR and albuminuria categories to assess for future complications

Both lower GFR and higher albuminuria are independently associated with a higher risk for all of the major CKD complications, including all-cause mortality, cardiovascular mortality, progressive kidney disease, kidney failure, and AKI (Figs 94.2 and 94.3) (Levey et al., 2011). The KDIGO conference put forth a 'heat map' that combines GFR and albuminuria categories into four groups based on a composite of risks for the five outcomes: low (green), moderate (yellow), high (orange), and very high (red) (Fig. 94.4) (Levey et al., 2011).

Use of GFR and albuminuria categories to assess for concurrent complications

Concurrent complications of decreased GFR include anaemia, acidosis, bone and mineral disorders, malnutrition, hypertension, neuropathy, and decreased quality of life (Kidney Disease Outcomes Quality Initiative (K/DOQI), 2002). As shown in Fig. 94.5, the burden of complications is especially high in CKD GFR stages 4–5 (GFR < 30 mL/min/1.73 m^2) (Inker et al., 2011). A recent analysis of data from the United States-based National Health and Nutrition Examination Surveys (NHANES) showed a minimal association between higher levels of albuminuria and a higher prevalence of anaemia, hypoalbuminaemia, acidosis, hypertension, and hyperparathyroidism (Inker et al., 2011). Higher albuminuria was not associated with hyperphosphataemia. Lower estimated GFR, on the other hand, was strongly associated with all six of these complications. Susceptibility to side effects of medications or diagnostic and therapeutic procedures, such as imaging studies, are increased at lower GFR, and are not known to vary by the level of albuminuria.

Approach to the care of patients with chronic kidney disease

CKD care is directed by the cause of CKD and the levels of GFR and albuminuria. Identification of the cause may allow for a 'specific' therapy directed at the underlying pathologic processes. Thereafter, staging based on GFR and albuminuria can be used to guide 'non-specific' therapies to slow progression and reduce complications (Tables 94.2 and 94.3).

Evaluation

Fig. 94.6 provides a five-step guide for the detection and evaluation of CKD (Levey and Coresh, 2012). During routine health

Table 94.2 Categories of CKD by the level of GFR

Category	GFR levels (mL/min/1.73 m$^{2)}$	Terms	Clinical action plan
G1[a]	> 90	Normal or high	Diagnose and treat the cause Treat comorbid conditions Evaluate for CKD risk factors Start measures to slow CKD progression Start measures to reduce CVD risk
G2[a]	60–89	Mildly decreased[b]	Estimate progression
G3a	45–59	Mildly to moderately decreased	Adjust medication dosages as indicated Evaluate and treat complications
G3b	30–44	Moderately to severely decreased	
G4	15–29	Severely decreased	Prepare for kidney replacement therapy (transplantation and/or dialysis)
G5	< 15	Kidney failure (add D if treated by dialysis)	Start kidney replacement therapy (if uraemia present)

[a] GFR stages G1 or G2 without markers of kidney damage do not fulfil the criteria for CKD.

[b] Relative to young adult level.

GFR in mL/min/1.73 m^2 may be converted to mL/s/1.73 m^2 by multiplying by 0.01667.

CVD = cardiovascular diseases; GFR = glomerular filtration rate.

Table 94.3 Categories of CKD by the level of albuminuria

Category	AER (mg/day)	Approximately equivalent ACR		Terms	Clinical action plan
		(mg/mmol)	(mg/g)		
A1	< 30	< 3	< 30	Normal to mildly increased	Diagnose and treat the cause Treat comorbid conditions Evaluate for CKD risk factors Start measures to slow CKD progression Start measures to reduce CVD risk
A2	30–299	3–30	30–299	Moderately increased[a]	Treatment with renin–angiotensin system blockers and lower blood pressure goal if hypertensive
A3	≥ 300	≥ 30	≥ 300	Severely increased	Treat nephritic or nephrotic syndrome (if present)

[a] Relative to young adult level.

AER = albumin excretion rate; ACR = albumin-to-creatinine ratio; CVD = cardiovascular diseases.

Table 94.4 Classification of CKD based on presence or absence of systemic disease and location of pathologic-anatomic findings

	Examples of systemic diseases affecting the kidney	Examples of primary kidney diseases (absence of systemic diseases affecting the kidney)
Glomerular diseases	Diabetes, autoimmune diseases, systemic infections, drugs, neoplasia (including amyloidosis)	Diffuse, focal or crescentic proliferative glomerulonephritis; focal and segmental glomerulosclerosis; membranous nephropathy; minimal change disease
Tubulointerstitial diseases	Systemic infections, autoimmune, sarcoidosis, drugs, urate, environmental toxins (lead, aristolochic acid), neoplasia (myeloma)	Urinary tract infections, stones, obstruction
Vascular diseases	Decreased perfusion (heart failure, liver disease, renal artery disease); atherosclerosis, hypertension, ischaemia, cholesterol emboli, vasculitis, thrombotic microangiopathy, systemic sclerosis	ANCA-associated vasculitis; fibromuscular dysplasia
Cystic and congenital and diseases	polycystic kidney disease, Alport syndrome, Fabry disease, oxalosis	Renal dysplasia, medullary cystic disease
Diseases affecting the transplanted kidney	Acute rejection; chronic rejection; calcineurin inhibitor toxicity; recurrence of native kidney disease (diabetes, oxalosis, Fabry disease)	BK virus nephropathy; recurrence of native kidney disease (glomerular disease)

ANCA = antineutrophil cytoplasmic antibody.

Note: genetic diseases are not considered separately because some diseases in each category are now recognized as having genetic determinants.

Table 94.5 Kidney measures as risk factors for CKD complications

Complications (current and future)	Kidney measures			Other risk factors for complications
	GFR	Albuminuria	Cause	
Progressive decline in GFR	+	+++	+++	High blood pressure, male sex, black race, younger age
Worsening albuminuria	+	+++	+++	High blood pressure
Acute kidney injury	+++	+	-	Age, comorbid conditions
Kidney failure	+++	+	+++	
CVD and mortality	+++	+++	++	Age, history of CVD, CVD risk factors
Drug toxicity	+++	+		Drug exposure, liver disease
Metabolic/endocrine	+++	+	+	
Others (infection, cognitive impairment, frailty, etc.)	++	++	++	Age, comorbid conditions

CVD = cardiovascular diseases; GFR = glomerular filtration rate.

check-ups, efforts should be made to identify individuals who are at high risk for CKD (Table 94.1). Those deemed at high risk should at a minimum have a measurement of serum creatinine to estimate GFR and an assessment of albuminuria. The optimal frequency of testing for high-risk individuals, however, has not been well studied. Various guideline groups recommend yearly testing for patients with diabetes, hypertension, human immunodeficiency virus infection, hepatitis C infection, and malignancies (Chobanian et al., 2003, 2011; Gupta et al., 2005; Kidney Disease: Improving Global Outcomes (KDIGO), 2008b). Until evidence is available, it is reasonable to suggest that individuals at increased risk who do not have these conditions be tested at least

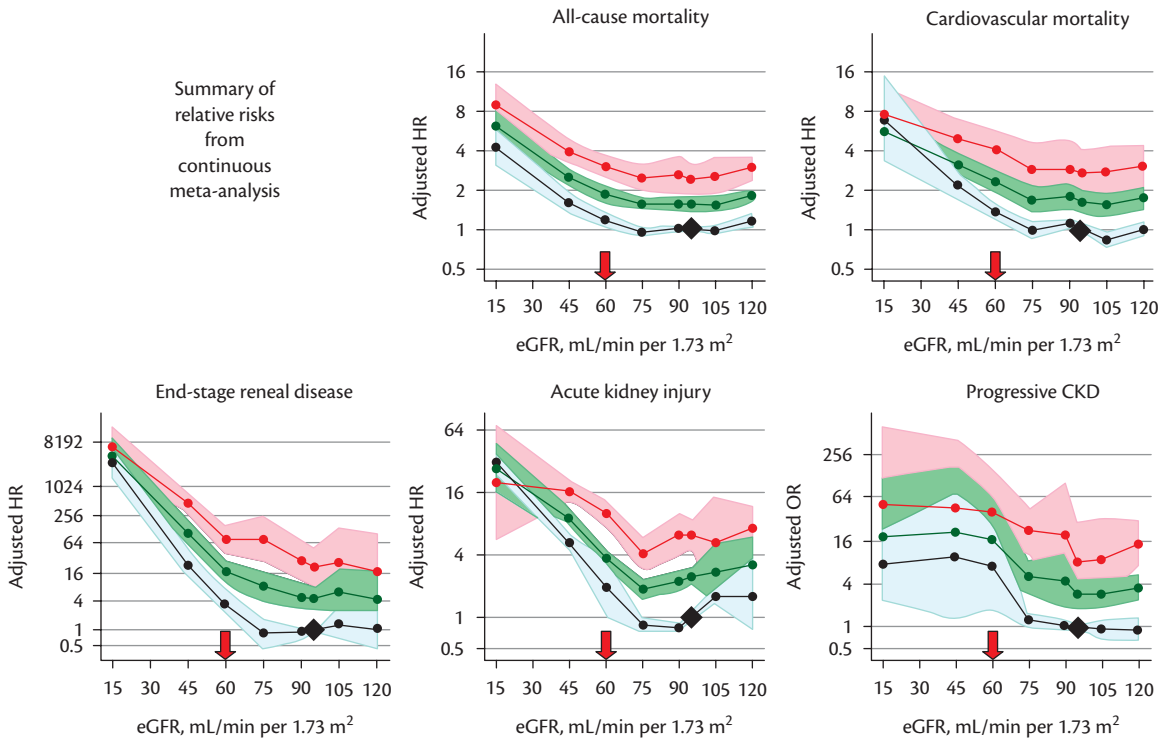

Fig. 94.2 CKD complications by estimated GFR and albuminuria. Summary of CKD complications by estimated GFR (eGFR) and albuminuria in general population cohorts. eGFR is a continuous variable. The three lines represent urine albumin-to-creatinine ratio (ACR) of < 30mg/g or dipstick negative and trace (blue), urine ACR 30–299 mg/g or dipstick 1+ positive (green), and urine ACR ≥ 300mg/g or dipstick ≥ 2+ positive (red). All results are adjusted for age, sex, race, history of clinical cardiovascular disease, and cardiovascular disease risk factors (smoking, systolic blood pressure, diabetes, and serum total cholesterol), and compared with reference point of eGFR of 95 mL/min/1.73 m^2 and ACR of < 30 mg/g or dipstick negative (diamond). Each point represents the pooled relative risk from a meta-analysis. Solid circles indicate statistical significance compared with the reference point ($P < 0.05$); triangles indicate non-significance. Red arrows indicate eGFR of 60 mL/min/1.73 m^2. HR = hazard ratio; OR = odds ratio.

Reproduced from *Kidney International* (Levey et al., 2011).

Summary of relative risks from categorical meta-analysis (dipstick included [−, ±, +, ≥++])

All-cause mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR >105	1.1	1.5	2.2	5.0
eGFR 90–105	Ref	1.4	1.5	3.1
eGFR 75–90	1.0	1.3	1.7	2.3
eGFR 60–75	1.0	1.4	1.8	2.7
eGFR 45–60	1.3	1.7	2.2	3.6
eGFR 30–45	1.9	2.3	3.3	4.9
eGFR 15–30	5.3	3.6	4.7	6.6

Cardiovascular mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR >105	0.9	1.3	2.2	2.0
eGFR 90–105	Ref	1.5	1.7	3.7
eGFR 75–90	1.0	1.3	1.6	3.7
eGFR 60–75	1.1	1.4	2.0	4.1
eGFR 45–60	1.5	2.2	2.8	4.3
eGFR 30–45	2.2	2.7	3.4	5.2
eGFR 15–30	1.4	7.9	4.8	8.1

Kidney failure (ESRD)

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR > 105	Ref	Ref	7.8	18
eGFR 90–105	Ref	Ref	11	20
eGFR 75–90	Ref	Ref	3.8	48
eGFR 60–75	Ref	Ref	7.4	67
eGFR 45–60	5.2	22	40	147
eGFR 30–45	56	74	294	763
eGFR 15–30	433	1044	1056	2286

Acute kidney injury (AKI)

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR >105	Ref	Ref	2.7	8.4
eGFR 90–105	Ref	Ref	2.4	5.8
eGFR 75–90	Ref	Ref	2.5	4.1
eGFR 60–75	Ref	Ref	3.3	6.4
eGFR 45–60	2.2	4.9	6.4	5.9
eGFR 30–45	7.3	10	12	20
eGFR 15–30	17	17	21	29

Progressive CKD

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR >105	Ref	Ref	0.4	3.0
eGFR 90–105	Ref	Ref	0.9	3.3
eGFR 75–90	Ref	Ref	1.9	5.0
eGFR 60–75	Ref	Ref	3.2	8.1
eGFR 45–60	3.1	4.0	9.4	57
eGFR 30–45	3.0	19	15	22
eGFR 15–30	4.0	12	21	7.7

Fig. 94.3 CKD complications based on estimated GFR and albuminuria. Summary of CKD complications by estimated GFR (eGFR) and albuminuria in general population cohorts. eGFR is a categorical variable. All results are adjusted for age, sex, race, history of clinical cardiovascular disease, and cardiovascular disease risk factors (smoking, systolic blood pressure, diabetes, and serum total cholesterol), and compared with the reference cell (Ref). Each cell represents a pooled relative risk from a meta-analysis; bold numbers indicate statistical significance at $P < 0.05$. Incidence rates per 1000 person-years for the reference cells are 7.0 for all-cause mortality, 4.5 for cardiovascular disease mortality, 0.04 for kidney failure, 0.98 for acute kidney injury (AKI), and 2.02 for kidney disease progression. Absolute risk can be computed by multiplying the relative risks in each cell by the incidence rate in the reference cell. Colours reflect the ranking of adjusted relative risk. The point estimates for each cell were ranked from 1 to 28 (the lowest RR having rank number 1, and the highest number 28). The categories with rank numbers 1–8 are green, rank numbers 9–14 are yellow, the rank numbers 15–21 are orange, and the rank numbers 22–28 are coloured red.
Reproduced from *Kidney International* (Levey et al., 2011).

every 3 years. If CKD is diagnosed, the cause should be sought, and staging should be done on the basis of GFR and albuminuria levels.

Determination of the cause

A presumptive cause for CKD (Table 94.4) is generally established after a complete review of medical history, clinical course, and the assessment of urine, laboratory, and imaging findings. Specialized diagnostic tests, such as kidney biopsy and invasive imaging studies, are only performed when a definitive diagnosis is expected to change treatment or provide a better understanding of prognosis. Hence, it is anticipated that the underlying cause may not be known with certainty in many patients.

It is also important to understand that there are geographic variations in the cause of CKD. Diabetes and hypertension are the most common causes in Europe and North America whereas glomerular diseases are predominant in East Asia. Glomerular and interstitial diseases related to chronic infections are more common in the developing world. Tubulointerstitial diseases are known to be endemic in certain areas like the Balkans and Scotland.

Assessment of kidney damage

Urine examination, laboratory measurements, and imaging of kidney and urinary tract are used in the assessment of kidney damage. Urinalysis entails macroscopic, dipstick, and microscopic examination of urine to assess for specific gravity, pH, blood, protein, glucose, abnormal cells, casts, and crystals that might indicate damage. Laboratory measurements are important to quantify proteinuria, or to look for urine and serum measurements related to abnormal tubular function. Imaging studies are especially important to assess damage in individuals with a history of polycystic kidney disease, kidney stones, or childhood vesicoureteral reflux.

Albuminuria is the principal marker of damage. In addition to albumin, other types of urine protein includes low-molecular-weight proteins that are filtered by the kidney and incompletely reabsorbed by the tubules, proteins derived from tubular epithelium (e.g. Tamm–Horsfall protein), and proteins derived from the lower urinary tract. Healthy persons usually excrete only 50–100 mg/day of total protein in the urine. However, because of the wide range and multiple potential causes for transient increases in proteinuria, such as fever, urinary tract infections, and exercise, the upper

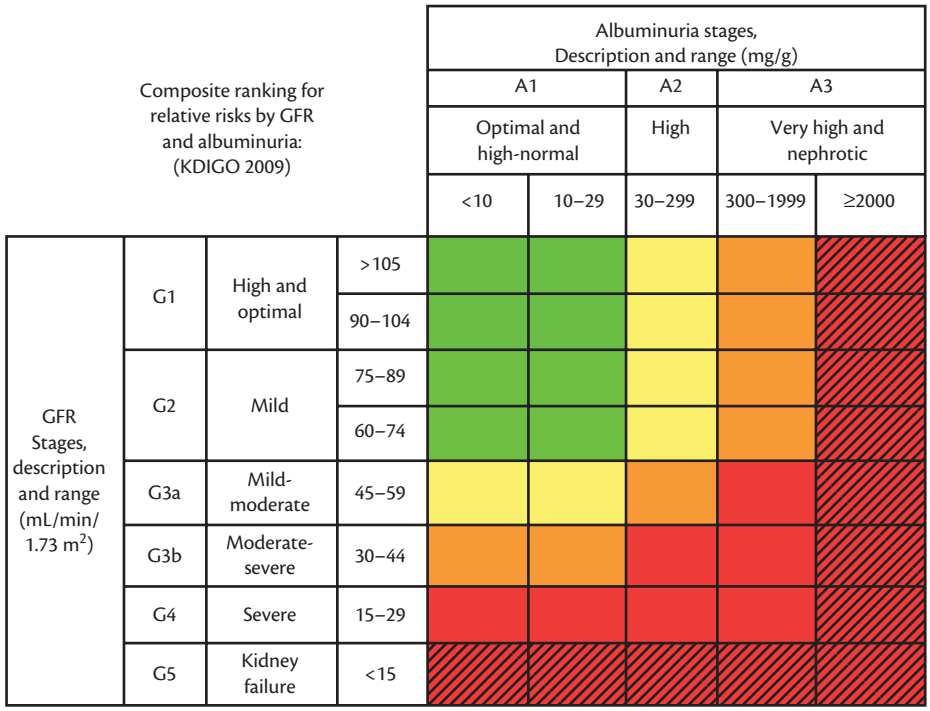

Fig. 94.4 Composite ranking for relative risks by GFR and albuminuria (KDIGO). Composite ranking for relative risks by glomerular filtration rate (GFR) and albuminuria (Kidney Disease: Improving Global Outcomes (KDIGO) 2009). As in Fig. 94.3, colours reflect the ranking of adjusted relative risk. The ranks assigned in Fig. 94.3 were averaged across all five outcomes for the 28 GFR and albuminuria categories. The categories with mean rank numbers 1–8 are green (low risk), mean rank numbers 9–14 are yellow (moderate risk), mean rank numbers 15–21 are orange (high risk), and mean rank numbers 22–28 are red (very high risk). Colour for 12 additional cells with diagonal hash marks is extrapolated based on results from the meta-analysis of chronic kidney disease cohorts. The highest level of albuminuria is termed 'nephrotic' to correspond with nephrotic range albuminuria and is expressed here as > 2000 mg/g. Column and row labels are combined to be consistent with the number of estimated GFR (eGFR) and albuminuria stages agreed on at the conference.

limit of normal usually extends to levels as high as 200–300 mg/day to avoid false-positive results. In addition, persistence of high level of proteinuria for at least 3 months is required to define CKD. Albumin is the predominant urinary protein in most proteinuric kidney diseases, and albuminuria is the earliest sign of kidney disease secondary to diabetes, glomerular diseases, and hypertension. The ratio of albumin or total protein concentration to creatinine concentration in a spot urine specimen has replaced 24-hour excretion rates as the preferred method for quantifying albuminuria and proteinuria. These ratios give an approximate measure of the daily albumin or protein excretion in milligrams (Ginsberg et al., 1983). Although spot ratios are convenient and corrects for variations in urinary albumin or protein concentration due to differences in hydration, they may not accurately estimate 24-hour excretion rates in patients with a urine creatinine excretion that is substantially higher or lower than the normal range. Table 94.6 shows the normal and abnormal values for albuminuria and proteinuria for different types of measurements.

Estimation of GFR

(see also Chapter 7.)

GFR is estimated from a serum creatinine concentration in the standard clinical practice. A number of creatinine-based equations are available for GFR estimation, and most use a combination of age, sex, race, and body size as surrogates to account for the non-GFR determinants of serum creatinine. The Modification of Diet in Renal Disease (MDRD) Study equation is the most widely used estimating equation (Levey et al., 1999). The MDRD Study equation is reasonably accurate for GFR < 60 mL/min/1.73 m^2, but has increased imprecision and bias for higher GFR (Stevens et al., 2007a). The Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation is more accurate and less biased than the MDRD Study equation, particularly at higher levels of GFR (Levey et al., 2009b; Levey and Stevens, 2010; Stevens et al., 2010; Earley et al., 2012), and also is more accurate at predicting risk for future adverse outcomes (Matsushita et al., 2012). The Cockcroft and Gault equation is simpler but its routine use is no longer recommended as its performance is less accurate than the other equations with the use of standardized creatinine assays (Stevens et al., 2007b). The MDRD Study and CKD-EPI equations were both developed in the United States and only have a choice of black (African Americans) or non-black for race. It is therefore not known how these equations fare in all other geographic areas and racial groups, and modifications have been proposed for individuals from China and Japan (Rule and Teo, 2009). All creatinine-based estimating equations may be inaccurate in individuals with unusual body composition, such as in a setting of limb amputation, extreme obesity, or spinal cord injury (Stevens and Levey, 2009). If an accurate estimate of GFR is required, a clearance measurement should be obtained, either a 24-hour urine collection for creatinine clearance or a

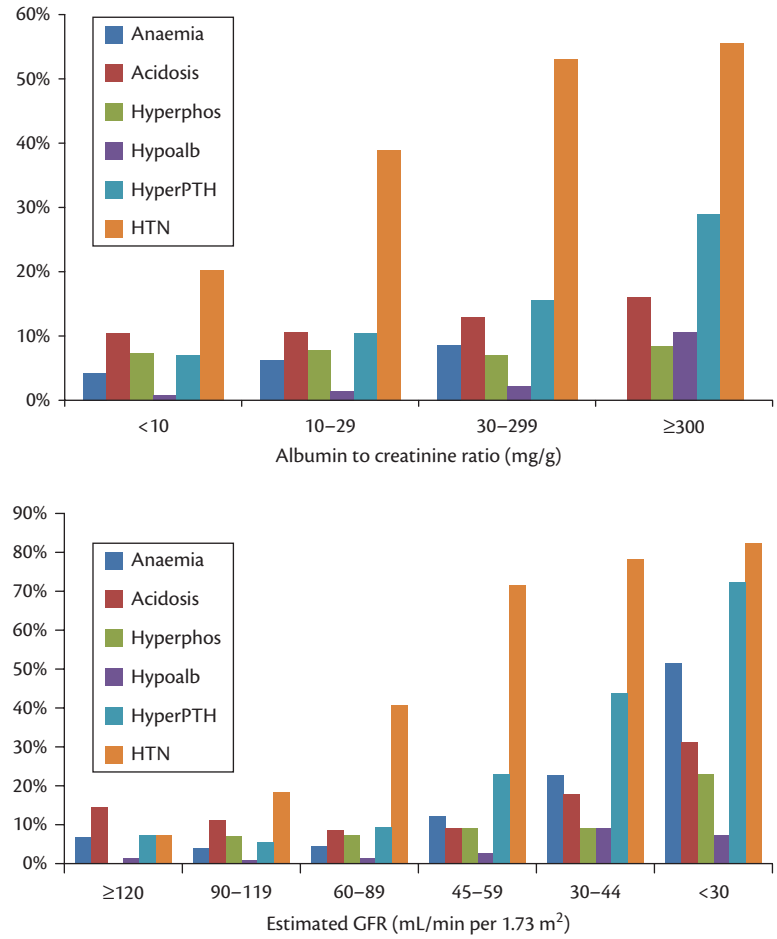

Fig. 94.5 CKD complications by albuminuria and estimated GFR categories. Prevalence rates are unadjusted.
Adapted from Inker et al. (2011).

clearance of an exogenous filtration marker, such as iothalamate or iohexol.

Cystatin C is an endogenous filtration marker that is not routinely used in clinical practice but has been suggested as a possible alternative to serum creatinine. Cystatin C is less affected by race and muscle mass than serum creatinine, but is affected by other non-GFR determinants that are not fully understood (Stevens et al., 2009). While serum cystatin C level alone provides GFR estimates that are nearly as accurate as those estimated from serum creatinine level, estimated GFR from cystatin C is not more accurate than creatinine-based estimating equation (Stevens et al., 2008, Stevens et al., 2011). An equation that includes both serum creatinine and cystatin C provides the most precise and accurate estimates (Inker et al., 2012), and the KDIGO guidelines recommend eGFR based on creatinine and cystatin C as a confirmatory test for decreased GFR in settings where eGFR based on creatinine may be inaccurate (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013). In addition, cystatin C has been shown in some studies to be a better predictor of adverse events than serum creatinine or GFR estimated from serum creatinine, particularly in elderly or patients with CVD (Shlipak et al., 2005; Peralta et al., 2011a, 2011b; Shlipak et al., 2013). It is possible that non-GFR determinants of cystatin C may explain some of this improved risk prediction.

Management

Tables 94.2 and 94.3 describe the clinical action plan for patients with CKD based on the level of GFR and albuminuria. These non-specific recommendations and treatments should be instituted along with specific treatments for the cause of kidney disease, if the cause is known and treatments are available. For both GFR and albuminuria, the main focus of management is on estimating and slowing the progression of CKD, reducing CVD risk, and avoiding exposure to nephrotoxic agents. For GFR, additional focus should be on evaluating and treating complications (Table 94.5), adjusting drug doses on the basis of kidney function, and preparing for kidney replacement therapy (transplantation or dialysis) when GFR falls to < 30 mL/min/1.73 m^2. For albuminuria, slowing progression and treating albuminuria with renin–angiotensin system blockers should be considered. Specialized nephrology care is recommended for severe reduction in GFR or high albuminuria, uncertain diagnosis, or difficult to manage complications.

Referral criteria recommended in major guidelines are enumerated in Table 94.7.

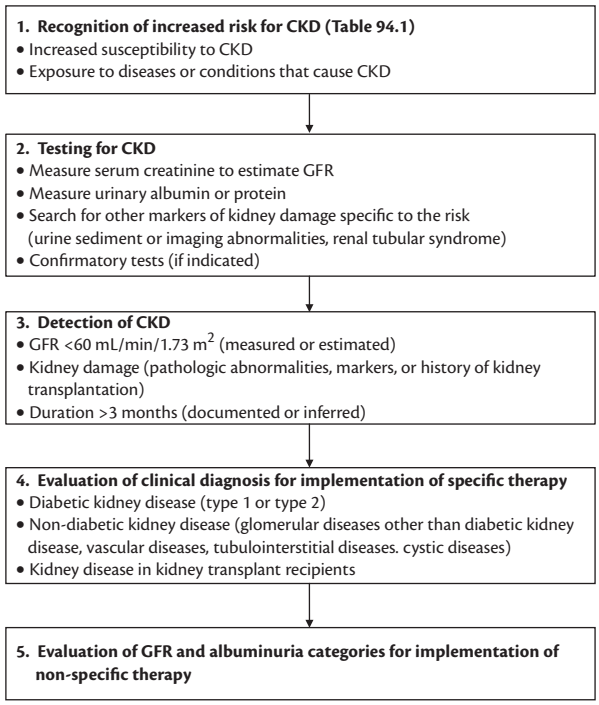

Fig. 94.6 Detection and evaluation of chronic kidney disease.
CVD = cardiovascular disease; GFR = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NSAID = non-steroidal anti-inflammatory drugs.

Table 94.6 Albuminuria and proteinuria measures (see also Chapter 50)

Measure	Categories		
	Normal to mildly increased	Moderately increased	Severely increased
AER (mg/24 hours)	< 30	30–300	> 300
PER (mg/24 hours)	< 150	150–500	> 500
ACR			
(mg/mmol)	< 3	3–30	> 30
(mg/g)	< 30	30–300	> 300
PCR			
(mg/mmol)	< 15	15–50	> 50
(mg/g)	< 150	150–500	> 500
Protein reagent strip	Negative to trace	Negative to +	+ or greater

ACR = albumin-to-creatinine ratio; AER = albumin excretion rate; PCR = protein-to-creatinine ratio; PER = protein excretion rate.

Table 94.7 Criteria for nephrology referral

Guideline group	Referral criteria
National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) (2002, 2004)	Age < 18 eGFR < 30 mL/min/1.73 m^2 ACR > 30 mg/mmol Haematuria not secondary to urological conditions Inability to identify a presumed cause of CKD Increased risk for progression of kidney disease GFR decline > 30% within 4 months without explanation Difficult to manage complications of CKD such as anaemia secondary to CKD requiring erythropoietin stimulating therapy, or abnormalities of bone and mineral metabolism requiring phosphorus binders or vitamin D preparations Hyperkalaemia (serum potassium concentration > 5.5 mEq/L) Resistant hypertension (BP > 130/80 mm Hg despite adherence to a three-drug antihypertensive regimen that includes a diuretic)[a] Difficult-to-manage complications of blood pressure lowering agents[a]
National Institute for Health and Clinical Excellence (NICE) (2008)	eGFR < 30 mL/min/1.73 m^2 Proteinuria (ACR ≥ 70 mg/mmol, PCR ≥ 100 mg/mmol, or 24-hour protein excretion ≥ 1g) unless due to diabetes and already treated Proteinuria (ACR ≥ 30 mg/mmol, PCR ≥ 50 mg/mmol, or 24-hour protein excretion ≥0.5g) with haematuria Rapidly declining eGFR (>5 mL/min/1.73m^2 per year, or >10 mL/min/1.73m^2 per 5 years) People with, or suspected of having, rare or genetic causes of CKD CKD with renal artery stenosis
Caring for Australasians with Renal Impairment (CARI) (Levin et al., 2008; Johnson, 2011)	eGFR <30 mL/min/1.73 m^2 Proteinuria (ACR ≥ 30 mg/mmol, PCR ≥ 50 mg/mmol, or 24-hour protein excretion ≥ 0.5g) Rapidly declining eGFR (> 5 mL/min/1.73 m^2 per 6 months) CKD with difficult to control blood pressure with at least 3 agents CKD with unexplained anaemia (Haemoglobin < 10 g/dL)

(*Continued*)

Table 94.7 Continued

Guideline group	Referral criteria
Canadian Society of Nephrology (Levin et al., 2008)	Persistent eGFR < 30 mL/min/1.73 m^2 Progressive decline in kidney function Proteinuria (ACR ≥ 60 mg/mmol, PCR ≥ 100 mg/mmol, 24-hour protein excretion ≥ 900mg, 24-hour albumin excretion ≥ 500mg) Inability to achieve treatment targets Rapid changes in kidney function
Japanese Society of Nephrology (2009)	eGFR < 50 mL/min/1.73 m^2 Proteinuria (PCR > 0.5 g/g or 2+ by dipstick) Dipstick positive for proteinuria and haematuria Rapidly progressive kidney disease CKD stages 1–3 with difficult to control blood pressure

[a] Kidney disease or hypertension specialist.

ACR = albumin-to-creatinine ratio; eGFR = estimated glomerular filtration rate; PCR = protein-to-creatinine ratio.

References

American Diabetes Association (2011). Standards of medical care in diabetes—2011. *Diabetes Care*, 34 Suppl 1, S11–61.

Astor, B. C., Matsushita, K., Gansevoort, R. T., *et al.* (2011). Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int*, 79, 1331–40.

Chobanian, A. V., Bakris, G. L., Black, H. R., *et al.* (2003). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*, 289, 2560–72.

Chronic Kidney Disease Prognosis Consortium, Matsushita, K., Van Der Velde, M., *et al.* (2010). Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*, 375, 2073–81.

Coresh, J., Selvin, E., Stevens, L. A., *et al.* (2007). Prevalence of chronic kidney disease in the United States. *JAMA*, 298, 2038–47.

Davies, D. F. and Shock, N. W. (1950). Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J Clin Invest*, 29, 496–507.

Earley, A., Miskulin, D., Lamb, E. J., *et al.* (2012). Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. *Ann Intern Med*, 156(11), 785–95.

Eckardt, K. U., Berns, J. S., Rocco, M. V., *et al.* (2009). Definition and classification of CKD: the debate should be about patient prognosis—a position statement from KDOQI and KDIGO. *Am J Kidney Dis*, 53, 915–20.

Gansevoort, R. T., Matsushita, K., Van der Velde, M., *et al.* (2011). Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes in both general and high-risk populations. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int*, 80, 93–104.

Ginsberg, J. M., Chang, B. S., Matarese, R. A., *et al.* (1983). Use of single voided urine samples to estimate quantitative proteinuria. *N Engl J Med*, 309, 1543–6.

Gupta, S. K., Eustace, J. A., Winston, J. A., *et al.* (2005). Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*, 40, 1559–85.

Hemmelgarn, B. R., Manns, B. J., Lloyd, A., *et al.* (2010). Relation between kidney function, proteinuria, and adverse outcomes. *JAMA*, 303, 423–9.

Inker, L. A., Coresh, J., Levey, A. S., *et al.* (2011). Estimated GFR, albuminuria, and complications of chronic kidney disease. *J Am Soc Nephrol*, 22(12), 2322–31.

Inker, L. A., Schmid, C. H., Tighiouart, H., *et al.* (2012). Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*, 367, 20–9.

Ishani, A., Xue, J. L., Himmelfarb, J., *et al.* (2009). Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol*, 20, 223–8.

James, M. T., Hemmelgarn, B. R., and Tonelli, M. (2010). Early recognition and prevention of chronic kidney disease. *Lancet*, 375, 1296–309.

Japanese Society of Nephrology (2009). Chapter 14. Timing for referral of CKD patients to nephrologists. *Clin Exp Nephrol*, 13, 222–3.

Johnson, D. (2011). *When to refer for Specialist Renal Care—The CARI Guidelines Caring for Australasians with Renal Impairment* [Online] <http://www.cari.org.au/DNT%20workshop%202011/6%20Specialist%20Renal%20Care_Early%20CKD_DNT.pdf>

Kidney Disease: Improving Global Outcomes (KDIGO) (2008). KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl*, S1–99.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*, 3, 1–150.

Kidney Disease Outcomes Quality Initiative (K/DOQI) (2002). K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*, 39, S1–266.

Kidney Disease Outcomes Quality Initiative (K/DOQI) (2004). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*, 43, S1–290.

Levey, A. S., Atkins, R., Coresh, J., *et al.* (2007). Chronic kidney disease as a global public health problem: approaches and initiatives—a position statement from Kidney Disease Improving Global Outcomes. *Kidney Int*, 72, 247–59.

Levey, A. S., Bosch, J. P., Lewis, J. B., *et al.* (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*, 130, 461–70.

Levey, A. S. and Coresh, J. (2012). Chronic kidney disease. *Lancet*, 379, 165–80.

Levey, A. S., De Jong, P. E., Coresh, J., *et al.* (2011). The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*, 80, 17–28.

Levey, A. S., Eckardt, K. U., Tsukamoto, Y., *et al.* (2005). Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*, 67, 2089–100.

Levey, A. S. and Stevens, L. A. (2010). Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more

accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis*, 55, 622–7.
Levey, A. S., Stevens, L. A. and Coresh, J. (2009a). Conceptual model of CKD: applications and implications. *Am J Kidney Dis*, 53, S4–16.
Levey, A. S., Stevens, L. A., Schmid, C. H., *et al.* (2009b). A new equation to estimate glomerular filtration rate. *Ann Intern Med*, 150, 604–12.
Levin, A., Hemmelgarn, B., Culleton, B., *et al.* (2008). Guidelines for the management of chronic kidney disease. *CMAJ*, 179, 1154–62.
Lindeman, R. D., Tobin, J., and Shock, N. W. (1985). Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc*, 33, 278–85.
Lo, L. J., Go, A. S., Chertow, G. M., *et al.* (2009). Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. *Kidney Int*, 76, 893–9.
Lysaght, M. J. (2002). Maintenance dialysis population dynamics: current trends and long-term implications. *J Am Soc Nephrol*, 13, S37–40.
Matsushita, K., Mahmoodi, B. K., Woodward, M., *et al.* (2012). Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA*, 307, 1941–51.
National Institute for Health and Clinical Excellence (2008). *Chronic Kidney Disease: National Clinical Guideline for Early Identification and Management in Adults in Primary and Secondary Care*. London: Royal College of Physicians.
Pannu, N., James, M., Hemmelgarn, B. R., *et al.* (2011). Modification of outcomes after acute kidney injury by the presence of CKD. *Am J Kidney Dis*, 58, 206–13.
Peralta, C. A., Katz, R., Sarnak, M. J., *et al.* (2011a). Cystatin C identifies chronic kidney disease patients at higher risk for complications. *J Am Soc Nephrol*, 22, 147–55.
Peralta, C. A., Shlipak, M. G., Judd, S., *et al.* (2011b). Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *JAMA*, 305, 1545–52.
Rettig, R. A., Norris, K., and Nissenson, A. R. (2008). Chronic kidney disease in the United States: a public policy imperative. *Clin J Am Soc Nephrol*, 3, 1902–10.
Rule, A. D., and Teo, B. W. (2009). GFR estimation in Japan and China: what accounts for the difference? *Am J Kidney Dis*, 53, 932–5.
Shlipak, M. G., Matsushita, K., Arnlov, J., *et al.* (2013). Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med*, 369, 932–43.
Shlipak, M. G., Sarnak, M. J., Katz, R., *et al.* (2005). Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med*, 352, 2049–60.
Smith, H. W. (1937). *The Physiology of the Kidney*. New York: Oxford University Press.
Stevens, L. A., Coresh, J., Feldman, H. I., *et al.* (2007a). Evaluation of the modification of diet in renal disease study equation in a large diverse population. *J Am Soc Nephrol*, 18, 2749–57.
Stevens, L. A., Coresh, J., Schmid, C. H., *et al.* (2008). Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis*, 51, 395–406.
Stevens, L. A. and Levey, A. S. (2009). Measured GFR as a confirmatory test for estimated GFR. *J Am Soc Nephrol*, 20, 2305–13.
Stevens, L. A., Li, S., Kurella Tamura, M., *et al.* (2011). Comparison of the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study Equations: Risk Factors for and Complications of CKD and Mortality in the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis*, 57, S9–16.
Stevens, L. A., Manzi, J., Levey, A. S., *et al.* (2007b). Impact of creatinine calibration on performance of GFR estimating equations in a pooled individual patient database. *Am J Kidney Dis*, 50, 21–35.
Stevens, L. A., Schmid, C. H., Greene, T., *et al.* (2009). Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int*, 75, 652–60.
Stevens, L. A., Schmid, C. H., Greene, T., *et al.* (2010). Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m^2. *Am J Kidney Dis*, 56, 486–95.

CHAPTER 95

Chronic kidney disease in the developed world

Morgan E. Grams and Josef Coresh

Overview

Chronic kidney disease (CKD) is an important and increasingly common public health issue within the developed world. Both reduced glomerular filtration rate (GFR) and albuminuria are independently and continuously associated with acute kidney injury (AKI), cardiovascular disease (CVD), end-stage renal disease (ESRD), and death. A disease of multiple aetiologies but most commonly attributed to diabetes and hypertension, CKD rates and progression vary widely by population. Some explanations of the variation are intrinsic to the population studied—the age distribution, the frequency of high-risk genetic alleles (such as those in polycystic kidney disease (*PKD*) and apolipoprotein 1 (*APOL1*), for example), and the burden of chronic conditions such as diabetes and hypertension—but some are extrinsic, such as variation in diagnostic scrutiny and CKD staging, creatinine assay standardization, and GFR estimating equations, as well as the threshold for renal replacement therapy (RRT). For these reasons, comparing CKD rates across countries is a daunting task. Nonetheless, accurate identification and staging of CKD in the developed world is essential to optimal care, including adherence to current guidelines and the development of new and effective interventions.

Introduction

Often asymptomatic until the advanced stages of disease, CKD has been historically under-recognized by both patient and provider. Increased appreciation of CKD-related sequelae, coupled with advances in CKD reporting and staging, may improve CKD detection and treatment. Recent progress includes the standardization of serum creatinine assays (Myers et al., 2006; College of American Pathologists, 2011), the introduction and refinement of GFR estimating equations (Levey et al., 1999, 2009), the issuance of clinical practice guidelines (Kidney Disease Outcomes Quality Initiative (KDOQI)) for CKD staging (Table 95.1) (National Kidney Foundation, 2009), and the incorporation of routine estimated GFR (eGFR) reporting by most laboratory systems (College of American Pathologists, 2011). As a result, CKD identification—even at the population level (e.g. <http://www.cdc.gov/diabetes/projects/kidney.htm>)—is increasingly feasible. A suggested CKD classification system incorporating albuminuria may further improve CKD recognition (Levey et al., 2011); and, once standardized, cystatin C-based determination of CKD should help improve uniformity in national and international evaluations, independent of diet and muscle mass.

Epidemiology of chronic kidney disease

Prevalence of CKD

While many countries maintain registries to track the prevalence and incidence of kidney disease requiring dialysis or transplantation, estimating the rates of earlier stages of kidney disease is more difficult. True and comparable estimates require a population-representative sample, standardized biomarker assays, and uniform estimating equations. For example, using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation tends to result in a lower prevalence of CKD than does the creatinine-based Modification of Diet in Renal Disease (MDRD) Study equation introduced in 1999 (Levey et al., 2009; Stevens et al., 2011). Prevalence determined by the newer biomarker cystatin C is similar to or even greater than that based on serum creatinine (Astor et al., 2009; Peralta et al., 2011). International comparisons are additionally complicated by the use of population-specific GFR estimating equations (e.g. the Japanese eGFR equations (Matsuo et al., 2010; Kitiyakara et al., 2012)).

In the United States, the gold standard for population-based studies may be the National Health and Nutrition Examination Survey (NHANES) (Coresh et al., 2007). In this study, prevalence of CKD stages 3–5 was 7% in the 1999–2004 survey. Estimates of CKD prevalence in other general population cohorts range from 1% to 57% (Matsushita et al., 2012) with variations largely dependent on the age and ethnic distribution of the study participants, as well as the prevalence of chronic conditions—diabetes, hypertension, obesity, and cardiovascular disease—thought to be the primary causes of CKD in the developed world (Table 95.2) (de Boer et al., 2011).

Incidence of CKD

Only limited information exists on the incidence of CKD in the developed world, primarily because the calculation of incidence requires longitudinal follow-up and multiple comparable measures of kidney function within an individual. Hence, the most accurate estimations of CKD incidence stem from long-running prospective cohorts with planned, interval measurement of kidney function. Retrospective analyses of administrative databases are less ideal, as patients at higher risk for CKD may have their

Table 95.1 K/DOQI stages of CKD based on eGFR[a]

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mild reduced GFR	60–89
3	Moderate reduced GFR	30–59
4	Severe reduced GFR	15–29
5	Kidney failure	< 15 or dialysis

Based on data, a consensus statement from the Kidney Disease: Improving Global Outcome (KDIGO) conference suggested adding albuminuria categories (albumin to creatinine ratio of < 30, 30–299, 300+ mg/g) and cause of CKD as additional components of a CKD staging system (Levey et al., 2011).

kidney function measured more often, creating an ascertainment bias, and trends in CKD reporting/assay standardization are difficult to control for. In addition, measures of CKD incidence have not been standardized, with some studies evaluating CKD onset and others requiring a minimal level of change to rule out random variation around the CKD cut-point (e.g. 25% decline in eGFR and eGFR < 60 mL/min/1.73 m^2) (Bash et al., 2009).

In the United States, a few large prospective cohorts have measured incident CKD. The Framingham study, a population-based cohort of predominantly white individuals with a relatively low rate of diabetes (2.7%), found that 9.4% of an initially CKD-free population developed Stage 3 or worse CKD over an 18.5-year follow-up (Fox et al., 2004). A 10-year increase in age more than doubled the odds of developing CKD. The Atherosclerosis Risk in Communities (ARIC) study, a population-based cohort of 45–64-year-old black (25.6%) and white (74.4%) individuals with a much higher rate of diabetes (11.4%), reported 7.3% CKD incidence over 8.8 years, or 10.4 cases per 1000 person-years (Bash et al., 2009). In the Cardiovascular Health Study (CHS), among older adults without baseline CKD, incident CKD was detected at year 7 in 10% using creatinine and 19% using cystatin C (P < 0.001) (Shlipak et al., 2009). Older age was associated with an increased risk of CKD in all of these studies. Consistent results emerged in a retrospective review from the United Kingdom, which found an overall CKD incidence of 1.3 cases per 1000 person-years, ranging from 0.02 in the youngest (< 20 years) to 12 cases per 1000 person years in the oldest (80+) age group (Drey et al., 2003).

Substantial variation in CKD rates by ethnicity has been demonstrated in three long-running US cohorts. The Coronary Artery Risk Development in Young Adults (CARDIA) cohort, a study of black and white individuals aged 18–30 years, reported a 1% incidence of CKD over 20 years of follow-up; however, the risk of CKD among black participants was 2.6 times that among white individuals (Muntner et al., 2012). This was also true in the older

Table 95.2 Prevalence of CKD (eGFR < 60 by CKD-EPI) in the developed world % (Matsushita et al., 2012)

Study name	Study region	Study size	Mean age (years)	% female	% black	% HTN	% DM	% with CKD
Aichi	Japan	4731	48	20	0	26	7	1
ARIC	USA	11,441	63	56	22	48	17	7
AusDiab	Australia	11,179	52	55	0	33	9	6
Beaver Dam	USA	4885	62	56	0	51	10	15
CHS	USA	2988	78	59	17	64	16	21
CIRCS	Japan	11,871	54	61	0	36	5	3
ESTHER	Germany	9641	62	55	0	60	19	14
Framingham	USA	2956	59	53	0	40	10	7
Gubbio	Italy	1682	55	56	0	39	5	1
HUNT	Norway	9659	62	55	0	82	18	11
IPHS	Japan	95,451	59	66	0	50	5	4
MESA	USA	6733	62	53	28	45	13	9
MRC	UK	12,371	81	61	0	34	8	57
NHANESIII	USA	15,563	47	53	28	29	12	7
Ohasama	Japan	1956	63	64	0	41	10	5
PREVEND	Netherlands	8385	49	50	1	33	4	4
Rancho Bernardo	USA	1477	71	60	0	55	12	22
REGARDS	USA	27,306	65	54	40	59	21	11
ULSAM	Sweden	1103	71	0	0	75	19	8

CKD = chronic kidney disease; DM = diabetes mellitus; HTN = hypertension.

Multi-Ethnic Study of Atherosclerosis (MESA) cohort. Here, black people and Hispanics had higher rates of incident CKD than white people and those of Chinese ethnicity, although the effect was not statistically significant after adjustment for baseline hypertension and diabetes (Peralta et al., 2011). In the ARIC study, African Americans had higher incidence rates than white people for CKD hospitalizations and a creatinine rise but not for incidence of eGFR < 60 by the MDRD Study equation (Bash et al., 2009).

Awareness of CKD

Recognition of CKD is low, particularly in the earliest stages of disease. In a survey of US physicians, only 59% of family medicine physicians and 78% of general internal medicine physicians correctly identified stage 3–4 CKD in a hypothetical scenario (Boulware et al., 2006). In clinical practice, physician awareness may be even lower. For example, in an Italian study, general practitioners recognized CKD in only 10.8% of their patients with stage 3 and in 72.6% of those with stage 4–5 (Ravera et al., 2011). Clinical studies of physician awareness should be interpreted cautiously, however: recognition is generally assessed from claims, which represent physician documentation translated to a billing code, a variably sensitive and specific process.

Since CKD diagnosis hinges on laboratory tests, patient awareness of CKD understandably lags that of physicians. In the United States, many studies of patient recognition use the NHANES questionnaire, which asks, 'Have you ever been told you have weak or failing kidneys (excluding kidney stones, bladder infections, or incontinence)?' The proportion of CKD patients answering this question in the affirmative is very low: 5.2% in 1999–2000, compared with 6.7% in 2001–2002, and 6.0% in 2003–2004 (Plantinga et al., 2008). Estimates of awareness are minimally affected by the estimating equation used; in the Kidney Early Evaluation Program (KEEP), 9.5% of participants were aware of MDRD-based CKD, compared with 10.0% of participants aware of CKD-EPI based CKD (Kurella Tamura et al., 2011).

Genetics of CKD

The large variation in CKD rates by ethnicity—more specifically, the strong predisposition to non-diabetic kidney disease among those of African descent—has been the subject of recent intense investigation (Friedman and Pollak, 2011). In 2008, two genome-wide admixture association studies demonstrated a strong link between a locus on chromosome 22 and non-diabetic kidney disease among African Americans (Kao et al., 2008; Kopp et al., 2008). Subsequent studies identified two genetic variants in *APOL1* (a gene in close linkage disequilibrium with myosin heavy chain 9 gene (*MYH9*), the gene originally thought to contain the causal variants) that, in individuals with two risk alleles, confers a 10- to 7-fold increased risk of focal segmental glomerulosclerosis and hypertension-associated ESRD (Genovese et al., 2010; Tzur et al., 2010). Present in 50% of African Americans (and 10–15% have two risk alleles), the G1 and G2 *APOL1* gene variants may be even more strongly linked to HIV-associated nephropathy (Kopp et al., 2011; Fine et al., 2012). In contrast to diabetic nephropathy, which is considered a complex disease with multiple genetic and environmental causes with surprisingly little effect of APOL1, some suggest that APOL1-mediated nephropathy in African-Americans is a predominantly Mendelian disease, with 3 million African Americans carrying the high-risk homozygous genotype (Friedman and Pollak, 2011).

Epidemiology of end-stage renal disease

Prevalence of ESRD

ESRD, or the most advanced stage of CKD, is defined both by the degree of kidney failure and by treatment: kidney disease requiring RRT. This functional definition merits consideration when performing international comparisons and evaluating ESRD trends over time. As countries develop economically, ESRD rates increase, and this chapter covers only the most highly developed countries in the world (20 out of 40 countries included in the United States Renal Data System (USRDS) Annual Data Report) (USRDS, 2010). The threshold for initiating dialysis may vary substantially by country: in 2001, for example, the mean serum creatinine at dialysis initiation was 7.3 mg/dL in the United States compared with 8.5 mg/dL in Australia and New Zealand (Stewart et al., 2004; USRDS, 2010). In addition, there are strong trends towards earlier delivery (i.e. at higher levels of GFR) of RRT in recent years (Rosansky et al., 2009; Grams et al., 2011).

The prevalence of ESRD has grown at a far greater rate (annualized mean, 1998 to 2009, 3.9%) in comparison with ESRD incidence (2.0% over the same period). This is attributable both to the increased numbers of patients initiating RRT and the better survival of patients already on RRT. In absolute terms, the United States has the largest number of ESRD patients (558,239 in 2009), followed by Japan (281,212). Scaled by population, Taiwan (2447 cases per million population), Japan (2205 cases per million population), and the United States (1811 cases per million population) have the highest prevalence rates, followed by Belgium, Canada, France, Greece, and Spain (1141, 1119, 1094, 1065, and 1034, respectively). Luxembourg and Iceland had the lowest prevalence rates. The rate of growth in ESRD prevalence was fairly uniform across developed countries with the exception of Taiwan, in which the prevalence rate averaged a 6.3% increase per year (Fig. 95.1) (USRDS, 2010).

Incidence of ESRD

Data regarding ESRD incidence are more readily available than for CKD incidence for two reasons. First, in contrast to the earlier stages of CKD, the functional definition of ESRD renders it necessarily symptomatic, apparent to both patient and provider. Second, many countries track ESRD patients with national registries. In the United States, for example, the USRDS follows all patients initiated on maintenance haemodialysis and/or receiving kidney transplantation (USRDS, 2010).

The United States and Taiwan have by far the highest rates of ESRD among the developed world, at 371 and 357 incident cases per million population in 2009, respectively (Fig. 95.2). While unadjusted rates have increased steadily over time, rates adjusted for age, sex, and ethnicity have remained fairly stable from 1996 to 2008, with a 1.1% uptick in 2009 (USRDS, 2010). Similar to the ethnic variation seen in CKD rates, ESRD incidence is 3.5 times higher among African Americans than white Americans (USRDS, 2010). Throughout the developed world, only Japan is close to the United States and Taiwanese incidence rates, at 287 new cases per million population. The lowest rates of ESRD were seen in Finland and Iceland (83 and 88 cases per million population, respectively). Greece, Belgium, and Luxembourg presented the highest rates in Europe (204, 201, and 227 cases per million population, respectively). Trends over time were fairly uniform: the unadjusted average annualized increase in incidence rate within developed

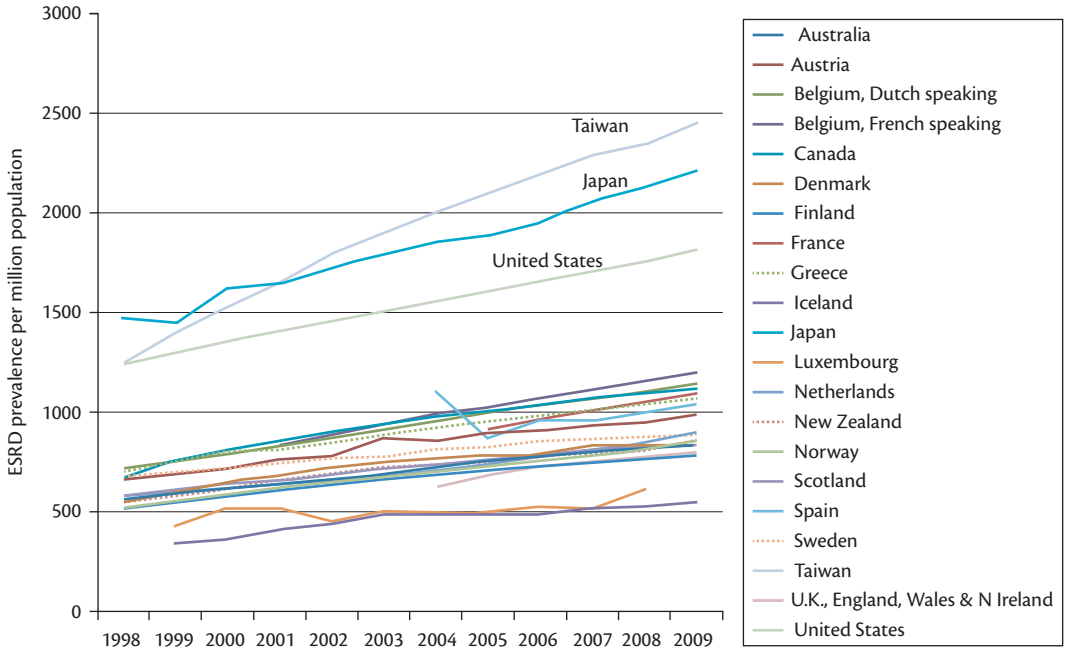

Fig. 95.1 Prevalence rates of ESRD, 1998–2009.

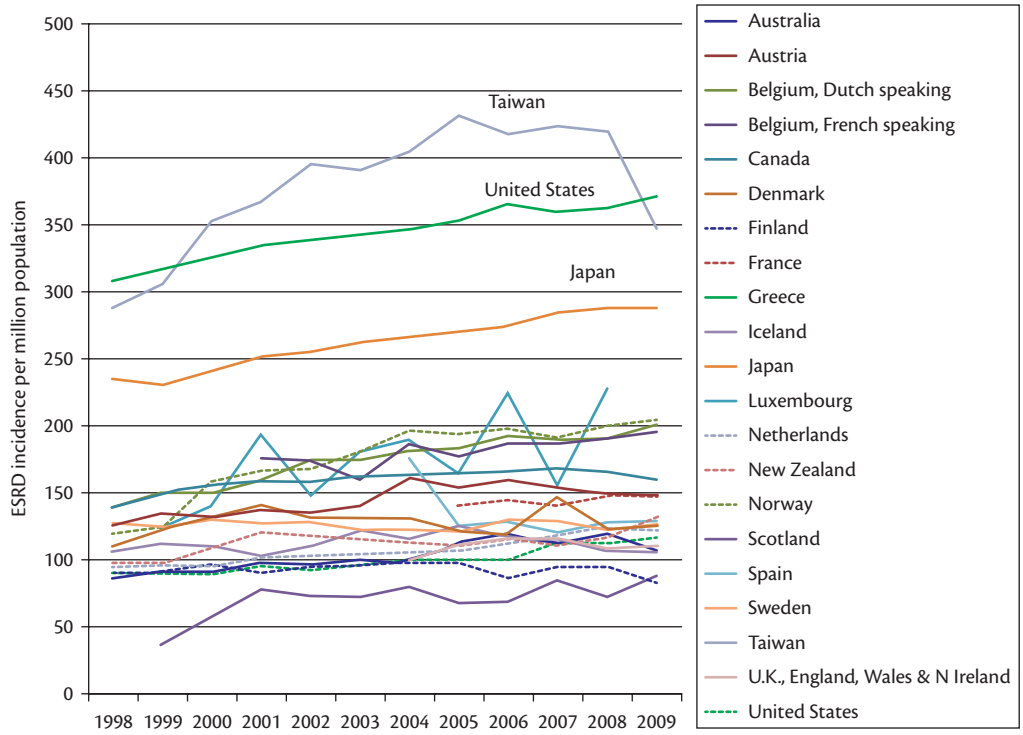

Fig. 95.2 Unadjusted ESRD incidence rates, 1998–2009. Diabetic nephropathy—clearly a term fraught with uncertainty, as the majority of ESRD patients receiving this diagnosis are never biopsied—comprised a differing proportion of incident ESRD cases by country. In 2009, for example, the Netherlands reported that 14.9% of the incident ESRD cases were due to diabetes, whereas Taiwan, Japan, New Zealand, and the United States all attributed > 40% of incident ESRD cases to diabetic nephropathy. Rates of ESRD due to diabetic nephropathy were highest among the 65 to 74-year-old age group; particularly in Taiwan and the United States, where the rates were estimated at 713 and 628 cases per million population, respectively (USRDS, 2010).

Table 95.3 Worldwide distribution of haemodialysis in 2009

Top 5 haemodialysis		Top 5 home haemodialysis		Top 5 peritoneal dialysis	
Country	**% using modality**	**Country**	**% using modality**	**Country**	**% using modality**
Luxembourg[a]	99.0	New Zealand	16.3	New Zealand	35.0
Japan	96.7	Australia	9.3	Sweden	23.6
Greece	92.1	Denmark	4.9	Denmark	21.7
United States	90.9	Finland	3.8	Finland	21.5
Austria	90.6	Canada	3.5	Australia	21.1

[a]2008 figures.

countries was 2.0% from 1998 to 2009, with a median of 1.9%. Spain did experience a declining rate of ESRD (175 cases per million population in 2004 compared with 129 cases per million population in 2009), while Sweden and Scotland remained stable over the 12-year period (USRDS, 2010).

Dialysis modality in ESRD

The distribution of dialysis modality differs by country (Table 95.3). In the United States, for example, there were 113,636 incident dialysis cases in 2009, with 6.9% and 1.1% started on peritoneal dialysis and home haemodialysis, respectively (USRDS, 2010). In contrast, the use of modalities other than in-centre haemodialysis was much more common in New Zealand, Australia, and Finland—perhaps due to their relatively low population densities.

Relationship between CKD prevalence and ESRD incidence

The relationship between CKD prevalence and ESRD incidence is complex. The determinants of ESRD incidence include underlying CKD prevalence, rates of CKD progression, incidence of mortality prior to ESRD, and the rates of acceptance of patients into RRT programmes. National policy and practice patterns may contribute: a country with a lower threshold for RRT initiation (e.g. dialysis is initiated at higher levels of GFR) will have a higher rate of ESRD than a country that forestalls RRT initiation or offers conservative management alternatives to individuals in ill health.

As an example, although CKD prevalence is roughly similar in Europe and the United States, the incidence of ESRD is dramatically different. A comparison of rates between Norway and the United States revealed a similar distribution of patients among CKD stages, but 2.5 times the relative risk of ESRD in US white people versus Norwegians (98% white) (Hallan et al., 2006). Disparities between the countries' ESRD incidence were larger among patients older than 60 (relative risk, 3.0) and women (relative risk, 3.5). Whether this reflects differences in underlying comorbidities or differences in practice patterns is unclear. The proportion of incident ESRD due to diabetic nephropathy was much higher in the United States (41% vs 11% from 1995 to 1997), and the number of pre-dialysis visits with a nephrologist was much lower (41% had five visits or more, compared with 73% in Norway). Other detailed international comparisons have not been done; however, in the United States, there is a strong inverse association between per capita income and incidence rates of ESRD (Young et al., 1994).

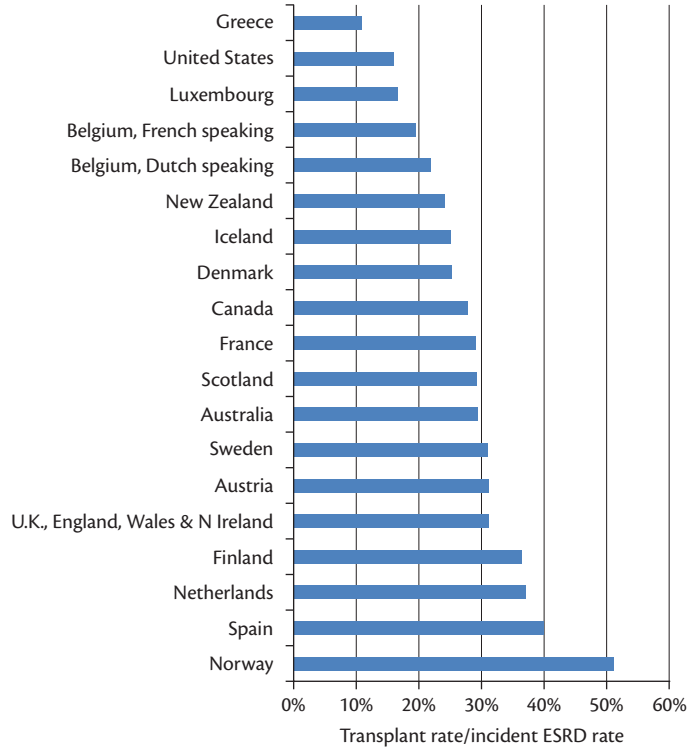

Fig. 95.3 Rates of kidney transplantation per incident ESRD, 1998–2009.

Renal replacement therapy: transplantation

Within the developed world, rates of kidney transplantation ranged from 14.9 (Greece) to 63.1 (Canada) per million population in 2009, or 7.3% (Greece) to 52.1% (Norway) when scaled by ESRD incidence (USRDS, 2010). These rates were similar when averaged over 1998–2009 (Fig. 95.3). The prevalence of kidney transplant recipients with a still-functioning allograft ranged from 215 (Greece) to 562 (United States) per million population in 2009; however, scaled by ESRD prevalence, this ranged from 31% (United States) to 70% (Canada). Transplantation rates in Japan, not available for recent years, have historically ranked among the lowest in the developed world (Satayathum et al., 2005). Internationally, rates of transplantation are consistently highest among young, white, better educated, and wealthier patients, with shorter dialysis vintage (Satayathum et al., 2005).

Prognosis

CKD

CKD is an independent risk factor for multiple adverse outcomes. The two commonly measured components of CKD, reduced GFR and albuminuria, independently contribute to the risk of AKI, ESRD, cardiovascular disease, and mortality (Matsushita et al., 2010; Astor et al., 2011; Gansevoort et al., 2011). Adverse outcomes are interrelated—AKI can be a precursor to ESRD (Hsu et al., 2009), which may in turn increase the risk of cardiovascular disease and death—and the relative incidence of outcomes differs by patient

population. In many studies of renal disease progression, such as the African American Study of Kidney Disease and Hypertension (AASK) (Alves et al., 2010) and the MDRD Study (Menon et al., 2009), the rates of ESRD are greater than that of pre-ESRD death. However, this is likely not true in the general population, where the incidence of CKD far exceeds that of ESRD. Indeed, in a US study using administrative data, the rates of death were consistently higher than those of ESRD in each stage of CKD (e.g. the rates of death and ESRD were 45.7% and 19.9%, respectively, for patients with stage 4 CKD) (Keith et al., 2004). In general, lower GFR, higher proteinuria, and younger age independently increase the relative risk of ESRD versus pre-ESRD death (O'Hare et al., 2007). In contrast, diabetes, vascular disease, and older age confer an increased risk of pre-ESRD death. Among US veterans ages 85 and older, the rate of death exceeded ESRD regardless of level of kidney function (O'Hare et al., 2007).

Dialysis

Mortality rates on dialysis remain exceedingly high. In a recent observational cohort of 32,065 nationally-representative haemodialysis patients in the United States, the mortality rate was 18.6 deaths per 100 person-years (Foley et al., 2011). Certain patient characteristics may predispose to a heightened mortality risk—older age and diabetes, for example, as among the non-ESRD population (Villar et al., 2007)—and ethnicity may modify these relationships (Kucirka et al., 2011). The interval between haemodialysis sessions may play a role: the majority of adverse events may occur on days after the 2-day gap in treatment (Foley et al., 2011). The effect of dialysis modality remains a subject of debate—confounded by selection bias (Quinn et al., 2011) and frequent modality switches—and may vary by patient subgroup (Weinhandl et al., 2010).

Because of the importance of age, ethnicity, and comorbidity distributions, as well as profound differences in local policy and practice, international comparisons of dialysis survival require cautious interpretation. That stated, a striking difference in mortality has been noted across different countries: the 1-year mortality rate reported in 2003 was 6.6% in Japan, 15.6% in Europe, and 21.7% in the United States (Goodkin et al., 2003). Within Europe, the United Kingdom had the highest mortality rate (18.6 deaths per 100 patient-years), followed by Germany (16.3 deaths per 100 patient-years), Spain (15.3 deaths per 100 patient-years), Italy, and France (13.8 and 13.3 deaths per 100 patient-years, respectively) (Rayner et al., 2004). Plausible explanations for these differences include variations in underlying comorbidities (e.g. diabetes and atherosclerotic cardiovascular disease), types of vascular access at initiation of dialysis, delivered dose of dialysis, level of care and education, and nutritional status and supplementation (Foley and Hakim, 2009).

Transplantation

Kidney transplantation is the preferred mode of RRT in ESRD, imparting a significant survival advantage over remaining on dialysis (Wolfe et al., 1999; Oniscu et al., 2005). The survival benefit associated with transplantation varies by recipient age, comorbidities, and quality of the donor organ (Merion et al., 2005). In the United States, post-transplant mortality has improved over time, coinciding with the advent of modern immunosuppressive regimens. As of 2008, the 5-year crude survival rate was 91% for recipients of living donor kidneys and 84% for recipients of standard deceased donor kidneys (Axelrod et al., 2010). Comparisons with other countries are difficult because of differences in allograft quality and the make-up of transplant recipients; however, long-term mortality may be slightly higher in the United States compared with Canada (adjusted hazard ratio, 1.35) (Kim et al., 2006).

References

Alves, T. P., Wang, X., Wright, J. T., Jr., *et al.* (2010). Rate of ESRD exceeds mortality among African Americans with hypertensive nephrosclerosis. *J Am Soc Nephrol*, 21(8), 1361–9.

Astor, B. C., Levey, A. S., Stevens, L. A., *et al.* (2009). Method of glomerular filtration rate estimation affects prediction of mortality risk. *J Am Soc Nephrol*, 20(10), 2214–22.

Astor, B. C., Matsushita, K., Gansevoort, R. T., *et al.* (2011). Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int*, 79(12), 1331–40.

Axelrod, D. A., McCullough, K. P., Brewer, E. D., *et al.* (2010). Kidney and pancreas transplantation in the United States, 1999–2008: the changing face of living donation. *Am J Transplant*, 10(4 Pt 2), 987–1002.

Bash, L. D., Coresh, J., Kottgen, A., *et al.* (2009). Defining incident chronic kidney disease in the research setting: The ARIC Study. *Am J Epidemiol*, 170(4), 414–24.

Boulware, L. E., Troll, M. U., Jaar, B. G., *et al.* (2006). Identification and referral of patients with progressive CKD: a national study. *Am J Kidney Dis*, 48(2), 192–204.

College of American Pathologists (2011). *Current Status of Reporting Estimated Glomerular Filtration Rate (eGFR)*. [Online] <http://www.cap.org/apps/docs/committees/chemistry/current_status_of_reporting_eGFR_2011.pdf>

Coresh, J., Selvin, E., Stevens, L. A., *et al.* (2007). Prevalence of chronic kidney disease in the United States. *JAMA*, 298(17), 2038–47.

De Boer, I. H., Rue, T. C., Hall, Y. N., *et al.* (2011). Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA*, 305(24), 2532–9.

Drey, N., Roderick, P., Mullee, M., *et al.* (2003). A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. *Am J Kidney Dis*, 42(4), 677–84.

Fine, D. M., Wasser, W. G., Estrella, M. M., *et al.* (2012). APOL1 risk variants predict histopathology and progression to ESRD in HIV-related kidney disease. *J Am Soc Nephrol*, 23(2), 343–50.

Foley, R. N., Gilbertson, D. T., Murray, T., *et al.* (2011). Long interdialytic interval and mortality among patients receiving hemodialysis. *N Engl J Med*, 365(12), 1099–107.

Foley, R. N. and Hakim, R. M. (2009). Why is the mortality of dialysis patients in the United States much higher than the rest of the world? *J Am Soc Nephrol*, 20(7), 1432–5.

Fox, C. S., Larson, M. G., Leip, E. P., *et al.* (2004). Predictors of new-onset kidney disease in a community-based population. *JAMA*, 291(7), 844–50.

Friedman, D. J. and Pollak, M. R. (2011). Genetics of kidney failure and the evolving story of APOL1. *J Clin Invest*, 121(9), 3367–74.

Gansevoort, R. T., Matsushita, K., van der Velde, M., *et al.* (2011). Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int*, 80(1), 93–104.

Genovese, G., Friedman, D. J., Ross, M. D., *et al.* (2010). Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science*, 329(5993), 841–5.

Goodkin, D. A., Bragg-Gresham, J. L., Koenig, K. G., *et al.* (2003). Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol*, 14(12), 3270–7.

Grams, M. E., Massie, A. B., Coresh, J., *et al.* (2011). Trends in the timing of pre-emptive kidney transplantation. *J Am Soc Nephrol*, 22(9), 1615–20.

Hallan, S. I., Coresh, J., Astor, B. C., *et al.* (2006). International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol*, 17(8), 2275–84.

Hsu, C. Y., Chertow, G. M., McCulloch, C. E., *et al.* (2009). Nonrecovery of kidney function and death after acute on chronic renal failure. *Clin J Am Soc Nephrol*, 4(5), 891–8.

Kao, W. H., Klag, M. J., Meoni, L. A., *et al.* (2008). MYH9 is associated with nondiabetic end-stage renal disease in African Americans. *Nat Genet*, 40(10), 1185–92.

Keith, D. S., Nichols, G. A., Gullion, C. M., *et al.* (2004). Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med*, 164(6), 659–63.

Kim, S. J., Schaubel, D. E., Fenton, S. S., *et al.* (2006). Mortality after kidney transplantation: a comparison between the United States and Canada. *Am J Transplant*, 6(1), 109–14.

Kitiyakara, C., Yamwong, S., Vathesatogkit, P., *et al.* (2012). The impact of different GFR estimating equations on the prevalence of CKD and risk groups in a Southeast Asian cohort using the new KDIGO guidelines. *BMC Nephrol*, 13, 1.

Kopp, J. B., Nelson, G. W., Sampath, K., *et al.* (2011). APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol*, 22(11), 2129–37.

Kopp, J. B., Smith, M. W., Nelson, G. W., *et al.* (2008). MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. *Nat Genet*, 40(10), 1175–84.

Kucirka, L. M., Grams, M. E., Lessler, J., *et al.* (2011). Association of race and age with survival among patients undergoing dialysis. *JAMA*, 306(6), 620–6.

Kurella Tamura, M., Anand, S., Li, S., *et al.* (2011). Comparison of CKD awareness in a screening population using the Modification of Diet in Renal Disease (MDRD) study and CKD Epidemiology Collaboration (CKD-EPI) equations. *Am J Kidney Dis*, 57(3 Suppl 2), S17–23.

Levey, A. S., Bosch, J. P., Lewis, J. B., *et al.* (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*, 130(6), 461–70.

Levey, A. S., de Jong, P. E., Coresh, J., *et al.* (2011). The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*, 80(1), 17–28.

Levey, A. S., Stevens, L. A., Schmid, C. H., *et al.* (2009). A new equation to estimate glomerular filtration rate. *Ann Intern Med*, 150(9), 604–12.

Matsuo, S., Imai, E., Horio, M., *et al.* (2009). Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*, 53(6), 982–92.

Matsushita, K., Mahmoodi, B. K., Woodward, M., *et al.* (2012). Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA*, 307(18), 1941–51.

Matsushita, K., van der Velde, M., Astor, B. C., *et al.* (2010). Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*, 375(9731), 2073–81.

Menon, V., Kopple, J. D., Wang, X., *et al.* (2009). Effect of a very low-protein diet on outcomes: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. *Am J Kidney Dis*, 53(2), 208–17.

Merion, R. M., Ashby, V. B., Wolfe, R. A., *et al.* (2005). Deceased-donor characteristics and the survival benefit of kidney transplantation. *JAMA*, 294(21), 2726–33.

Muntner, P., Newsome, B., Kramer, H., *et al.* (2012). Racial differences in the incidence of chronic kidney disease. *Clin J Am Soc Nephrol*, 7(1), 101–7.

Myers, G. L., Miller, W. G., Coresh, J., *et al.* (2006). Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem*, 52(1), 5–18.

National Kidney Foundation (2002). K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*, 39(2 Suppl 1), S1–266.

O'Hare, A. M., Choi, A. I., Bertenthal, D., *et al.* (2007). Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol*, 18(10), 2758–65.

Oniscu, G. C., Brown, H., and Forsythe, J. L. (2005). Impact of cadaveric renal transplantation on survival in patients listed for transplantation. *J Am Soc Nephrol*, 16(6), 1859–65.

Peralta, C. A., Katz, R., DeBoer, I., *et al.* (2011). Racial and ethnic differences in kidney function decline among persons without chronic kidney disease. *J Am Soc Nephrol*, 22(7), 1327–34.

Peralta, C. A., Shlipak, M. G., Judd, S., *et al.* (2011). Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *JAMA*, 305(15), 1545–52.

Plantinga, L. C., Boulware, L. E., Coresh, J., *et al.* (2008). Patient awareness of chronic kidney disease: trends and predictors. *Arch Intern Med*, 168(20), 2268–75.

Quinn, R. R., Hux, J. E., Oliver, M. J., *et al.* (2011). Selection bias explains apparent differential mortality between dialysis modalities. *J Am Soc Nephrol*, 22(8), 1534–42.

Ravera, M., Noberasco, G., Weiss, U., *et al.* (2011). CKD awareness and blood pressure control in the primary care hypertensive population. *Am J Kidney Dis*, 57(1), 71–7.

Rayner, H. C., Pisoni, R. L., Bommer, J., *et al.* (2004). Mortality and hospitalization in haemodialysis patients in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*, 19(1), 108–20.

Rosansky, S. J., Clark, W. F., Eggers, P., *et al.* (2009). Initiation of dialysis at higher GFRs: is the apparent rising tide of early dialysis harmful or helpful? *Kidney Int*, 76(3), 257–61.

Satayathum, S., Pisoni, R. L., McCullough, K. P., *et al.* (2005). Kidney transplantation and wait-listing rates from the international Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int*, 68(1), 330–7.

Shlipak, M. G., Katz, R., Kestenbaum, B., *et al.* (2009). Rate of kidney function decline in older adults: a comparison using creatinine and cystatin C. *Am J Nephrol*, 30(3), 171–8.

Stevens, L. A., Li, S., Kurella Tamura, M., *et al.* (2011). Comparison of the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) study equations: risk factors for and complications of CKD and mortality in the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis*, 57(3 Suppl 2), S9–16.

Stewart, J. H., McCredie, M. R., Williams, S. M., *et al.* (2004). Interpreting incidence trends for treated end-stage renal disease: implications for evaluating disease control in Australia. *Nephrology (Carlton)*, 9(4), 238–46.

Tzur, S., Rosset, S., Shemer, R., *et al.* (2010). Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. *Hum Genet*, 128(3), 345–50.

United States Renal Data System (2010). *USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Villar, E., Remontet, L., Labeeuw, M., *et al.* (2007). Effect of age, gender, and diabetes on excess death in end-stage renal failure. *J Am Soc Nephrol*, 18(7), 2125–34.

Weinhandl, E. D., Foley, R. N., Gilbertson, D. T., *et al.* (2010). Propensity-matched mortality comparison of incident hemodialysis and peritoneal dialysis patients. *J Am Soc Nephrol*, 21(3), 499–506.

Wolfe, R. A., Ashby, V. B., Milford, E. L., *et al.* (1999). Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med*, 341(23), 1725–30.

Young, E. W., Mauger, E. A., Jiang, K. H., *et al.* (1994). Socioeconomic status and end-stage renal disease in the United States. *Kidney Int*, 45(3), 907–11.

CHAPTER 96

Chronic kidney disease in developing countries

Luxia Zhang and Haiyan Wang

Introduction

The spread of non-communicable diseases (NCDs) presents a global crisis, which is a barrier to the development of goals including reduction of poverty, health equity, economic stability, and human security (Beaglehole et al., 2011). NCDs accounted for 61% of the estimated 58 million deaths and 46% of the global burden of diseases worldwide in 2005 (Wagner and Brath, 2012). Among NCDs, chronic kidney disease (CKD) is of particular significance. It is recognized that the burden of CKD is not only limited to its impact on demands for renal replacement therapy (RRT) but has equally major impacts on the health of the overall population. For example, it is now well established that among the general population as well as in the diabetic or hypertensive population, the prognosis, especially the mortality and acceleration of cardiovascular events, depends on kidney involvement (Go et al., 2004; Bello et al., 2005; Matsushita et al., 2010). Also, CKD is associated with other major serious consequences including increased risk of acute kidney injury (AKI), increased risk of mineral and bone disease, adverse metabolic and nutritional consequences, infections, and reduced cognitive function. As the consequence of these amplifying effects, the financial expenditure and medical resources consumed for the management of CKD patients is much higher than expected. The burden of CKD is likely to have profound socioeconomic and public health consequences, especially in developing countries. This chapter focuses on the situation of CKD in developing countries.

Prevalence of chronic kidney disease

In 2002, the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation released a practice guideline for CKD (National Kidney Foundation, 2002). Since then, numerous cross-sectional surveys on the prevalence of CKD have been published. For example, results of the National Health and Nutrition Examination Surveys (NHANES) 1988–1994 in the United States revealed a prevalence of 10.0%; this number increased to 13.1% in 1999–2004 (Coresh et al., 2007). Studies from other developed countries reported similar prevalences (Chadban et al., 2003; Hallan et al., 2006).

Data on CKD burden in developing countries is relatively scanty. A recent systematic review of CKD in population-based studies included 26 studies which were published before July 2006 (Zhang and Rothenbacher, 2008). Among them, only four (15.4%) were from developing countries, including Mexico, China, and Thailand (Zhang and Rothenbacher, 2008). Furthermore, data from developing countries provided heterogeneous results, which makes comparisons difficult. There are three major methodological factors that may contribute to this heterogeneity. Firstly, most of the studies did not use a sampling scheme to obtain a representative sample of the general population. For example, in a study from Mexico by Amato et al. (2005), participants were randomly selected from lists of patients assigned to primary care facilities. Other studies involved participants of certain professions (such as government employees (Varma et al., 2010) or employees of the Electric Generation Authority (Domrongkitchaiporn et al., 2005)), or participants from certain areas (such as rural areas (Mani, 2006; O'Donnellet al., 2011) or certain big cities (Agarwal et al., 2005; Zhang et al., 2008; A. Chen et al., 2009; W. Chen et al., 2009b)). The limited representativeness of the study population jeopardizes the generalizability of the results, and also makes it hard to compare between studies. Secondly, the definition of 'renal function decline' is different among studies. Older studies provided estimates based on serum creatinine cut-offs or the Cockroft–Gault (CG) equation to define CKD (Barton et al., 2004; Agarwal et al., 2005; Singh et al., 2009), all of which are proved to be less accurate than the currently recommended creatinine-based estimations of glomerular filtration rate (GFR). Recent studies have employed an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 to define renal function decline; this is now recommended in recently released Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for CKD classification and management (Wheeler et al., 2013). In that guideline, it is also recommended that the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation should be used for estimating GFR. An alternative creatinine-based GFR estimating equation is acceptable only if this equation has a comparable performance. Thirdly, the method of evaluating proteinuria is different among studies. Some earlier studies did not provide information on proteinuria (J. Chen et al., 2005). Hence, the available data are not sufficient to provide the prevalence of CKD in the general population for most developing countries, making between inter-country comparisons difficult.

Among the developing countries, there are two recent national surveys of CKD employing standard protocols recommended by KDOQI guidelines. The first one is the Thai Screening and Early Evaluation of Kidney Disease (SEEK) study (Ingsathit et al., 2010). A stratified-cluster sampling method was used to obtain a sample

of 3459 participants (Ingsathit et al., 2010). eGFR was calculated by using the Modification of Diet in Renal Disease (MDRD) Study equation, and albuminuria was defined by the urinary albumin to creatinine ratio (uACR) of 30 mg/g creatinine or higher (Ingsathit et al., 2010). The prevalence of CKD was reported to be 17.5% (95% confidence interval (CI) 14.6–20.4%) (Ingsathit et al., 2010). The second study is The China National Survey of Chronic Kidney Disease. In this study, a multistage, stratified sampling method was used to obtain a representative sample of people aged 18 years or older in the general population of China (Zhang et al., 20120. eGFR was calculated by the Chinese equation (Ma et al., 2006), and the definition of albuminuria was the same as in the Thai SEEK study. The prevalence of CKD was reported to be 10.8% (95% CI 10.2–11.3%) (Zhang et al., 2012). Both studies revealed a prevalence of CKD comparable to (if not higher than) that of previous reports from developed countries, indicating that CKD has become a leading public health problem in certain developing countries.

As for the prevalence of end-stage renal disease (ESRD), lack of organized ESRD treatment programmes has precluded establishment of ESRD registries in most large developing countries. Some of reported data are rough estimates based on individual experience. According to the 2011 annual data report from the United States Renal Data System (USRDS), the prevalence of ESRD in developing countries varied substantially, from 110 per million population (Philippines) to 1314 per million population (Jalisco, Mexico) (USRDS, 2011). As for the incidence of ESRD in developing countries, it also varied from 13 per million population (Bangladesh) to 597 per million population (Morelos, Mexico). However, the reports from hospital-based data cannot accurately provide prevalence and incidence estimates in developing countries because of incomplete coverage, inability of many patients to reach a hospital, and lack of a proper referral system.

Causes of chronic kidney disease

Diabetes contributes heavily to the burden of CKD in developing countries. One should, however, realize that the term 'diabetic nephropathy' is fraught with uncertainty as the majority of patients with ESRD who receive this diagnosis are not biopsied (see Chapter 149). A study of ESRD patients in a large urban population in India indicated that diabetic kidney disease comprised 40–47% of incident cases between 2002 and 2005 (Modi and Jha, 2006). Several hospital-based studies in India suggested that around 30% of referred CKD cases were diabetic kidney disease (Agarwal and Srivastava, 2009). Reports from Latin America also indicated that diabetes is the leading cause of ESRD (30.3% of incident population) (Cusumano and Gonzalez Bedat, 2008). Furthermore, it is predicted that the proportion of CKD attributable to diabetes will continue to rise in the near future, due to the following facts. Firstly, the rapid surge in diabetes has been observed in almost all developing countries. For example, the prevalence of diabetes in China increased from 1% in 1980 (Zhong, 1982) to 9.7% in 2008 (Yang et al., 2010). In urban Indian adults, diabetes prevalence increased from 3% in the early 1970s to 12% in 2000, with a narrowing rural–urban gradient (Ramachandran, 2005). A similar trend has been observed in other Asian countries such as Bangladesh, Nepal, and Indonesia (Chan et al., 2009), sub-Saharan African (Mbanya et al., 2010), and Latin America (Escobedo et al., 2009). It is speculated that factors including general and abdominal obesity, nutrition transition and changes in diet and lifestyle, and smoking contribute to the increasing number of diabetes in developing countries (Chan et al., 2009). Secondly, the rate of underdiagnosed diabetes is high in developing countries, and a disparity in healthcare is observed between urban and rural areas. In a national survey of diabetes in China, 59.7% of patients were diagnosed through screening (Yang et al., 2010). In South Africa, > 50% of people were aware of their diabetic condition in an urban area (Levitt et al., 1993), compared with only 15% of people who have documented diabetes in rural area (Motala et al., 2008). Finally, the burden of diabetes in some developing countries is disproportionately high or is predicted to escalate in young to middle-aged adults (Chan et al., 2009; Mbanya et al., 2010), which means long disease exposure and therefore more chronic complications, including CKD.

Hypertension is also one of important causes of CKD in developing countries, which leads to 13–21% of ESRD cases (Barsoum, 2006) (see Section 10 of this textbook). The status of hypertension is similar to diabetes, including escalating prevalence, low awareness rate, and suboptimal treatment, especially in rural area. For example, a national survey of hypertension in 1991 suggested that the overall prevalence of hypertension among people aged > 15 years in China was 13.6% (Tao et al., 1995). Ten years later, the number was reported to be 23% in urban areas and 18% in rural areas (Wu et al., 2008). The awareness rate and control rate of hypertension was 24% and 19% (Wu et al., 2008), which is lower than reported from developed countries.

Chronic glomerulonephritis is an import cause of CKD in developing countries, based on the data from dialysis registry and hospital-based data (see Section 3 of this textbook). According to a report from the Dialysis and Transplantation Registration Group of China in 1999 (Dialysis and Transplantation Registration Group, 2001), 49.9% of patients receiving chronic dialysis were diagnosed as chronic glomerulonephritis. A recent report from Beijing, China (Beijing Hemodialysis Quality Control and Improvement Center, 2012) indicated that chronic glomerulonephritis remained the leading cause of haemodialysis in 2011, especially among young patients. However, an increasing tendency of diabetic nephropathy was noticed among incident patients, especially in patients aged > 50 years. Data from Indonesia and Malaysia also revealed similar results (Liu and Hooi, 2007; Prodjosudjadi and Suhardjono, 2009). The histopathological types of glomerulonephritis in the developing countries vary considerably. Immunoglobulin A (IgA) nephropathy predominates in China, Southeast Asia, and the Pacific region. For example, a study involving 5398 consecutive patients receiving a renal biopsy indicated that IgA nephropathy comprised 50.7% of primary glomerulonephritis (Zhou et al., 2009). By contrast, focal segmental glomerulosclerosis is the most common type among the black populations of Africa (15–25%), Saudi Arabia (40%), India (up to 46%), and South America (up to 43%) (Barsoum, 2006).

Infectious diseases also contribute to the burden of CKD in developing countries. The number of people infected with human immunodeficiency virus (HIV) is estimated to be 33 million, and 67% of them are in sub-Saharan Africa (AIDS Foundation, n.d.). Ninety per cent of new HIV infections are in developing countries (Piot and Tezzo, 1990). It is known that infection with HIV and its treatment can produce a variety of kidney diseases, including glomerular (e.g. collapsing focal segmental glomerulosclerosis), vascular (e.g. thrombotic microangiopathy), and tubulointerstitial disorders (Wyatt et al., 2008, 2009) (see also Chapter 187).

In cross-sectional surveys, the prevalence of CKD with HIV infection varied substantially (from 3.5% to 48.5%) (Naicker and Fabian, 2010), partly due to different study populations and different methodologies. Besides HIV infection, other infectious diseases including malaria, schistosomiasis, hepatitis B and hepatitis C also contribute to the burden of CKD in developing countries (Hossain et al., 2009; Nugent et al., 2011) (see also Section 8 in this book).

A significant proportion of the population in developing countries, especially in Asia and Africa, depends on indigenous local medical systems. A longitudinal study from Taiwan indicated that regular users of Chinese herbal medicines have a 20% increased risk of developing CKD (Wen et al., 2008). A recent study (Zhang et al., 2013) using a national representative sample in China indicated that long-term intake of herbs containing aristolochic acid was independently associated with eGFR < 60 mL/min/1.73 m^2 and albuminuria, with an odds ratio of 1.83 (95% CI, 1.22–2.74) and 1.39 (95% CI, 1.03–1.87), respectively. Longitudinal studies from Taiwan revealed that use of aristolochic acid-containing herbs, especially > 60 g of Mu Tong or Fangchi from herbal supplements, is associated with increased risk of developing kidney failure (Lai et al., 2010).

Despite improving maternal and infant mortality rates, a high prevalence of maternal malnutrition and low-birth-weight deliveries is still seen in developing countries. For example, it is reported that 30% of infants are underweight in India (Yajnik et al., 2009). And the percentage of babies not weighed or with unknown birth weight is high in developing countries, due to the absence of scales and trained staff (Goto, 2011). Low birth weight has been associated with later hypertension, congenital low nephron number, and accelerated kidney senescence, which would have an impact on kidney damage in the later adult life (Luyckx and Brenner, 2005; Luyckx et al., 2009). A meta-analysis indicates that low birth weight is associated with subsequent risk of CKD, with an odds ratio of 1.73 (95% CI 1.44–2.08) (White et al., 2009).

The health and economic burden of chronic kidney disease

A recent editorial (The Lancet, 2013) and subsequent series of articles in *The Lancet* between July and August 2013, discuss many aspects related to the global burden of AKI and CKD, in particular low-income countries.

One of the ultimate outcomes of CKD is ESRD, which necessitates ever-growing dialysis and transplantation programmes, and therefore places an unaffordable financial burden on developing countries. A recent national survey in China estimates the number of patients with CKD in China to be 120 million (Zhang et al., 2012). If 1% of them progress to ESRD, the total costs of dialysis would be twice of the current healthcare budget in China. Actually the dialysis rate is quite low in many developing countries compared to that in developed countries, which is limited by the affordability and accessibility of the treatment. A session of haemodialysis costs US$100 in Nigeria, twice the minimum monthly wage paid to federal government workers (Katz et al., 2011). In India, the average cost of haemodialysis per year is around US$9000–14,000, while the average annual income in India is US$8000. Hence, affordability is a major constraint to dialysis treatment. Another obstacle is accessibility of treatment. For example, in China almost all haemodialysis centres are located in cities (Zhang et al., 2009). Nowadays the majority of haemodialysis centres in major cities are believed to be running at capacity. In the last 2 years, peritoneal dialysis (PD) has grown at a rate of 30% annually in China (Zhang et al., 2008), but most of the PD centres are still located in cities. A recent cohort study (Xu et al., 2012) revealed that low personal income was independently associated with all-cause and cardiovascular death, as well as initial peritonitis in patients receiving PD. The situation is similar in India (Agarwal and Srivastava, 2009) and in Africa (Katz et al., 20110, which places a further burden on patients who often have to travel (often with families) to a dialysis centre. Furthermore, health equity (regarding both affordability and accessibility) remains a major challenge to policymakers in developing countries despite the resurgence of interest to promote it. The sheer inadequacy of financial and human resources for health and the progressive undermining of state capacity in many under-resourced settings have made it extremely difficult to promote and achieve significant improvements in equity in health and access to healthcare.

The economic cost associated with milder forms of CKD was even higher. For instance, according to data from USRDS, costs for Medicare patients with CKD reached US$34 billion, and accounted for nearly 16% of total Medicare dollars in 2009 (USRDS, 2012). The expenditures further increased in presence of diabetes and heart failure (USRDS, 2012). Part of the high cost of CKD is driven by its close association with other non-communicable chronic diseases. Cardiovascular disease (CVD) and CKD share common risk factors such as hypertension, diabetes, smoking, obesity, hyperlipidaemia, and ageing as well as some non-traditional risk factors such as vitamin D deficiency, hyperphosphataemia, anaemia, albuminuria, and HIV infection (Sarnak et al., 2003). In a meta-analysis conducted by pooling 45 general population cohorts involving 105,872 individuals, eGFR and ACR are multiplicatively associated with risk of overall and cardiovascular (CV) mortality (Matsushita et al., 2010). Even CKD stages 1 or 2 are associated with an increased risk of adverse overall, CV, and renal outcomes (Matsushita et al., 2010; Gansevoort et al., 2011). Even though the Chinese population is thought to have a relatively lower risk of CVD (Ma et al., 2006; Zhang et al., 2012), a recent study (USRDS, 2011) indicated that individuals with subtle decreased renal function seem much more likely to have multiple CV risk factors and have higher prevalence of CVD than those without CKD. Arterial changes such as elevated carotid artery intima-media thickness were observed in early stage CKD patients (Modi and Jha, 2006). Furthermore, Chinese studies revealed that CKD is associated with high burden of other chronic conditions, including metabolic syndrome (Zhang et al., 2007), cognitive decline (Wang et al., 2010), and ocular fundus pathology (Gao et al., 2011), which all contribute to the adverse patients' outcome and to elevated healthcare costs.

Prevention and early detection of chronic kidney disease

In the developing world, CKD prevention programmes are relatively non-existent. Although CKD shares common risk factors and/or coexists with other NCDs, it has not received the same kind of attention.

Lifestyle intervention for common risk factors for NCDs is important in the prevention of CKD. Several priority interventions were chosen to cope with the global NCD crisis, including

accelerated tobacco control, salt intake reduction, promotion of healthy diets and physical activity, and reduction of harmful alcohol consumption (Beaglehole et al., 2011). Those interventions are cost-effective in countries with a variety range of incomes (Gaziano et al., 2007). Cost-effective lifestyle and behavioural changes can be achieved on a population basis through legislation, government influence, manufacturing changes, mass education campaigns, and bans on negative advertisements (Gaziano et al., 2007). In addition, optimal control of diabetes and hypertension should be pursued (Barsoum et al., 2006).

Based on data from developed countries, screening for CKD among 'high-risk' population (e.g. aged > 60 years or with hypertension or diabetes) is proved to be cost-effective (Boulware et al., 2003). It has been shown that community-based screening programmes in developing countries are feasible (Perico et al., 2009), provided the screening tools are simple and cheap. Even if a urinary dipstick test is a less precise measure of albuminuria, it is still useful for risk stratification and initial screening (Matsushita et al., 2010). Studies in developed countries on the cost-effectiveness of tertiary prevention of CKD by treatment of hypertension, albuminuria, and use of renin–angiotensin system inhibitors have shown that early intervention is more cost-effective than late intervention (Palmer et al., 2000, 2004; Ruggenenti et al., 2001). Therefore, screening for CKD among high-risk populations is warranted, especially considering the low awareness rate of CKD in developing countries (Zhang et al., 2012). Along these lines, the Research and Prevention Committee of the International Society of Nephrology – Global Outreach (ISN-GO) has developed a global early detection and intervention programme for emerging countries that can be implemented according to the peculiar needs and organization facilities of the given country (Perico et al., 2009).

In view of the close linkage and overlapping management strategies, programmes to combat CKD, diabetes, hypertension, and CVD need to be closely integrated in developing countries. As experience from Indian medical society has shown, these integrated early stages of prevention and management could be performed at low cost by medical assistants and nurses. However, in the face of an immature primary care system in developing countries, the involvement of a nephrologist is still needed to train the primary care medical care level and to establish a referral system. Studies are required to analyse successful experiences and to examine the cost-effectiveness of such approaches in different countries.

References

Agarwal, S. K., Dash, S. C., Irshad, M., *et al.* (2005). Prevalence of chronic renal failure in adults in Delhi, India. *Nephrol Dial Transplant*, 20(8), 1638–42.

Agarwal, S. K. and Srivastava, R. K. (2009). Chronic kidney disease in India: challenges and solutions. *Nephron Clin Pract*, 111(3), c197–203.

AIDS Foundation (n.d.). *HIV/AIDS in South Africa*. [Online] <http://www.aids.org.za/hivaids-in-south-africa/>

Amato, D., Alvarez-Aguilar, C., Castaneda-Limones, R., *et al.* (2005). Prevalence of chronic kidney disease in an urban Mexican population. *Kidney Int Suppl*, 97, S11–17.

Barsoum, R. S. (2006). Chronic kidney disease in the developing world. *N Engl J Med*, 354(10), 997–9.

Barton, E. N., Sargeant, L. A., Samuels, D., *et al.* (2004). A survey of chronic renal failure in Jamaica. *West Indian Med J*, 53(2), 81–4.

Beaglehole, R., Bonita, R., Horton, R., *et al.* (2011). Priority actions for the non-communicable disease crisis. *Lancet*, 377(9775), 1438–47.

Beijing Hemodialysis Quality Control and Improvement Center (2012). The Annual Data Report of Beijing Hemodialysis Quality Control and Improvement Center, 2012. *Chinese Journal of Blood Purification*, z1, 42.

Bello, A. K., Nwankwo, E., and El Nahas, A. M. (2005). Prevention of chronic kidney disease: a global challenge. *Kidney Int Suppl*, 98, S11–17.

Boulware, L. E., Jaar, B. G., Tarver-Carr, M. E., *et al.* (2003). Screening for proteinuria in US adults: a cost-effectiveness analysis. *JAMA*, 290(23), 3101–14.

Chadban, S. J., Briganti, E. M., Kerr, P. G., *et al.* (2003). Prevalence of kidney damage in Australian adults: The AusDiab kidney study. *J Am Soc Nephrol*, 14(7 Suppl 2), S131–8.

Chan, J. C., Malik, V., Jia, W., *et al.* (2009). Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA*, 301(20), 2129–40.

Chen, J., Wildman, R. P., Gu, D., *et al.* (2005). Prevalence of decreased kidney function in Chinese adults aged 35 to 74 years. *Kidney Int*, 68(6), 2837–45.

Chen, N., Wang, W., Huang, Y., *et al.* (2009). Community-based study on CKD subjects and the associated risk factors. *Nephrol Dial Transplant*, 24(7), 2117–23.

Chen, W., Wang, H., Dong, X., *et al.* (2009). Prevalence and risk factors associated with chronic kidney disease in an adult population from southern China. *Nephrol Dial Transplant*, 24(4), 1205–12.

Coresh, J., Selvin, E., Stevens, L. A., *et al.* (2007). Prevalence of chronic kidney disease in the United States. *JAMA*, 298(17), 2038–47.

Cusumano, A. M. and Gonzalez Bedat, M. C. (2008). Chronic kidney disease in Latin America: time to improve screening and detection. *Clin J Am Soc Nephrol*, 3(2), 594–600.

Dialysis and Transplantation Registration Group (2001). The report about the registration of dialysis and transplantation in China 1999. *Chin J Nephrol*, 17, 77–9.

Domrongkitchaiporn, S., Sritara, P., Kitiyakara, C., *et al.* (2005). Risk factors for development of decreased kidney function in a southeast Asian population: a 12-year cohort study. *J Am Soc Nephrol*, 16(3), 791–9.

Escobedo, J., Buitron, L. V., Velasco, M. F., *et al.* (2009). High prevalence of diabetes and impaired fasting glucose in urban Latin America: the CARMELA Study. *Diabet Med*, 26(9), 864–71.

Gansevoort, R. T., Matsushita, K., van der Velde, M., *et al.* (2011). Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes in both general and high-risk populations. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int*, 80(1), 93–104.

Gao, B., Zhu, L., Pan, Y., *et al.* (2011). Ocular fundus pathology and chronic kidney disease in a Chinese population. *BMC Nephrol*, 12, 62.

Gaziano, T. A., Galea, G., and Reddy, K. S. (2007). Scaling up interventions for chronic disease prevention: the evidence. *Lancet*, 370(9603), 1939–46.

Go, A. S., Chertow, G. M., Fan, D., *et al.* (2004). Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*, 351(13), 1296–305.

Goto, E. (2011). Meta-analysis: identification of low birthweight by other anthropometric measurements at birth in developing countries. *J Epidemiol*, 21(5), 354–62.

Hallan, S. I., Coresh, J., Astor, B. C., *et al.* (2006). International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol*, 17(8), 2275–84.

Hossain, M. P., Goyder, E. C., Rigby, J. E., *et al.* (2009). CKD and poverty: a growing global challenge. *Am J Kidney Dis*, 53(1), 166–74.

Ingsathit, A., Thakkinstian, A., Chaiprasert, A., *et al.* (2010). Prevalence and risk factors of chronic kidney disease in the Thai adult population: Thai SEEK study. *Nephrol Dial Transplant*, 25(5), 1567–75.

Katz, I. J., Gerntholtz, T., and Naicker, S. (2011). Africa and nephrology: the forgotten continent. *Nephron Clin Pract*, 117(4), c320–7.

Lai, M. N., Lai, J. N., Chen, P. C., *et al.* (2010). Risks of kidney failure associated with consumption of herbal products containing Mu Tong or Fangchi: a population-based case-control study. *Am J Kidney Dis*, 55(3), 507–18.

Levitt, N. S., Katzenellenbogen, J. M., Bradshaw, D., *et al.* (1993). The prevalence and identification of risk factors for NIDDM in urban Africans in Cape Town, South Africa. *Diabetes Care*, 16(4), 601–7.

Liu, W. J. and Hooi, L. S. (2007). Patients with end stage renal disease: a registry at Sultanah Aminah Hospital, Johor Bahru, Malaysia. *Med J Malaysia*, 62(3), 197–200.

Luyckx, V. A. and Brenner, B. M. (2005). Low birth weight, nephron number, and kidney disease. *Kidney Int Suppl*, 97, S68–77.

Luyckx, V. A., Compston, C. A., Simmen, T., *et al.* (2009). Accelerated senescence in kidneys of low-birth-weight rats after catch-up growth. *Am J Physiol Renal Physiol*, 297(6), F1697–705.

Ma, Y. C., Zuo, L., Chen, J. H., *et al.* (2006). Modified glomerular filtration rate estimating equation for chinese patients with chronic kidney disease. *J Am Soc Nephrol*, (10), 2937–44.

Mani, M. K. (2006). Nephrologists sans frontieres: preventing chronic kidney disease on a shoestring. *Kidney Int*, 70(5), 821–3.

Matsushita, K., van der Velde, M., Astor, B. C., *et al.* (2010). Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*, 375(9731), 2073–81.

Mbanya, J. C., Motala, A. A., Sobngwi, E., *et al.* (2010). Diabetes in sub-Saharan Africa. *Lancet*, 375(9733), 2254–66.

Modi, G. K. and Jha, V. (2006). The incidence of end-stage renal disease in India: a population-based study. *Kidney Int*, 70(12), 2131–3.

Motala, A. A., Esterhuizen, T., Gouws, E., *et al.* (2008). Diabetes and other disorders of glycemia in a rural South African community: prevalence and associated risk factors. *Diabetes Care*, 31(9), 1783–8.

Naicker, S. and Fabian, J. (2010). Risk factors for the development of chronic kidney disease with HIV/AIDS. *Clin Nephrol*, 74 Suppl 1, S51–6.

National Kidney Foundation (2002). K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*, 39(2 Suppl 1), S1–266.

Nugent, R. A., Fathima, S. F., Feigl, A. B., *et al.* (2011). The burden of chronic kidney disease on developing nations: a 21st century challenge in global health. *Nephron Clin Pract*, 118(3), c269–c277.

O'Donnell, J. K., Tobey, M., Weiner, D. E., *et al.* (2011). Prevalence of and risk factors for chronic kidney disease in rural Nicaragua. *Nephrol Dial Transplant*, 26(9), 2798–805.

Palmer, A. J., Annemans, L., Roze, S., *et al.* (2004). An economic evaluation of the Irbesartan in Diabetic Nephropathy Trial (IDNT) in a UK setting. *J Hum Hypertens*, 18(10), 733–8.

Palmer, A. J., Weiss, C., Sendi, P. P., *et al.* (2000). The cost-effectiveness of different management strategies for type I diabetes: a Swiss perspective. *Diabetologia*, 43(1), 13–26.

Perico, N., Bravo, R. F., De Leon, F. R., *et al.* (2009). Screening for chronic kidney disease in emerging countries: feasibility and hurdles. *Nephrol Dial Transplant*, 24(5), 1355–8.

Piot, P. and Tezzo, R. (1990). The epidemiology of HIV and other sexually transmitted infections in the developing world. *Scand J Infect Dis Suppl*, 69, 89–97.

Prodjosudjadi, W. and Suhardjono, A. (2009). End-stage renal disease in Indonesia: treatment development. *Ethn Dis*, 19(1 Suppl 1), S1-33–36.

Ramachandran, A. (2005). Epidemiology of diabetes in India–three decades of research. *J Assoc Physicians India*, 53, 34–8.

Ruggenenti, P., Pagano, E., Tammuzzo, L., *et al.* (2001). Ramipril prolongs life and is cost effective in chronic proteinuric nephropathies. *Kidney Int*, 59(1), 286–94.

Sarnak, M. J., Levey, A. S., Schoolwerth, A. C., *et al.* (2003). Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*, 108(17), 2154–69.

Singh, N. P., Ingle, G. K., Saini, V. K., *et al.* (2009). Prevalence of low glomerular filtration rate, proteinuria and associated risk factors in North India using Cockcroft-Gault and Modification of Diet in Renal Disease equation: an observational, cross-sectional study. *BMC Nephrol*, 10, 4.

Tao, S., Wu, X., Duan, X., *et al.* (1995). Hypertension prevalence and status of awareness, treatment and control in China. *Chin Med J (Engl)*, 108(7), 483–9.

The Lancet (2013). The global issue of kidney disease. *Lancet*, 382 (9887), 101.

United States Renal Data System (2012). *USRDS 2011 Annual Data Report*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Varma, P. P., Raman, D. K., Ramakrishnan, T. S., *et al.* (2010). Prevalence of early stages of chronic kidney disease in apparently healthy central government employees in India. *Nephrol Dial Transplant*, 25(9), 3011–17.

Wagner, K. H. and Brath, H. (2012). A global view on the development of non-communicable diseases. *Prev Med*, 54 Suppl, S38–41.

Wang, F., Zhang, L., Liu, L., *et al.* (2010). Level of kidney function correlates with cognitive decline. *Am J Nephrol*, 32(2), 117–21.

Wen, C. P., Cheng, T. Y., Tsai, M. K., *et al.* (2008). All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. *Lancet*, 371(9631), 2173–82.

Wheeler, D. C. and Becker, G. J. (2013). Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease? *Kidney Int*, 83(3), 377–83.

White, S. L., Perkovic, V., Cass, A., *et al.* (2009). Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. *Am J Kidney Dis*, 54(2), 248–61.

Wu, Y., Huxley, R., Li, L., *et al.* (2008). Prevalence, awareness, treatment, and control of hypertension in China: data from the China National Nutrition and Health Survey 2002. *Circulation*, 118(25), 2679–86.

Wyatt, C. M., Morgello, S., Katz-Malamed, R., *et al.* (2009). The spectrum of kidney disease in patients with AIDS in the era of antiretroviral therapy. *Kidney Int*, 75(4), 428–34.

Wyatt, C. M., Rosenstiel, P. E., and Klotman, P. E. (2008). HIV-associated nephropathy. *Contrib Nephrol*, 159, 151–61.

Xu, R., Han, Q. F., Zhu, T. Y., *et al.* (2012). Impact of individual and environmental socioeconomic status on peritoneal dialysis outcomes: a retrospective multicenter cohort study. *PLoS One*, 7(11), e50766.

Yajnik, C. S. (2009). Nutrient-mediated teratogenesis and fuel-mediated teratogenesis: two pathways of intrauterine programming of diabetes. *Int J Gynaecol Obstet*, 104 Suppl 1, S27–31.

Yang, W., Lu, J., Weng, J., *et al.* (2010). Prevalence of diabetes among men and women in China. *N Engl J Med*, 362(12), 1090–101.

Zhang, J., Zhang, L., Wang, W., *et al.* (2013). Association between aristolochic acid and CKD: a cross-sectional survey in China. *Am J Kidney Dis*, 61(6), 918–22.

Zhang, L., Wang, F., Wang, L., *et al.* (2012). Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet*, 379(9818), 815–22.

Zhang, L. and Wang, H. (2009). Chronic kidney disease epidemic: cost and health care implications in China. *Semin Nephrol*, 29(5), 483–6.

Zhang, L., Zhang, P., Wang, F., *et al.* (2008). Prevalence and factors associated with CKD: a population study from Beijing. *Am J Kidney Dis*, 51(3), 373–84.

Zhang, L., Zuo, L., Wang, F., *et al.* (2007). Metabolic syndrome and chronic kidney disease in a Chinese population aged 40 years and older. *Mayo Clin Proc*, 82(7), 822–7.

Zhang, Q. L. and Rothenbacher, D. (2008). Prevalence of chronic kidney disease in population-based studies: systematic review. *BMC Public Health*, 8, 117.

Zhong, X. L. (1982). Diabetes mellitus survey in China. *Chin Med J (Engl)*, 95(6), 423–30.

Zhou, F. D., Zhao, M. H., Zou, W. Z., *et al.* (2009). The changing spectrum of primary glomerular diseases within 15 years: a survey of 3331 patients in a single Chinese centre. *Nephrol Dial Transplant*, 24(3), 870–6.

CHAPTER 97

Chronic kidney disease long-term outcomes: progression, death, cardiovascular disease, infections, and hospitalizations

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Progression to end-stage renal disease (dialysis or transplantation)

Data describing progression to renal replacement therapy (RRT) comes from large observational cohort studies in Australia, Canada, the United Kingdom, and the United States (Hsu et al., 2002; Iseki et al., 1996; Wen et al., 2008; Jafar et al., 2009; White et al., 2010; McDonald et al., 2010; Jolly et al., 2011; Hallan et al., 2012). Of note, in general or non-referred cohorts, the progression to end-stage renal disease (ESRD) is much lower than in those patients known to nephrologists. It is important to consider the patient population in describing the probability of progression. The Chronic Kidney Disease Prognosis Consortium (CKD-PC) has described the probability of ESRD in general populations, high-risk populations, and CKD populations (Matsushita et al., 2010; Astor et al., 2011; Gansevoort et al., 2011; Levey et al., 2011; Nitsch et al., 2013). On aggregate, there is the highest probability of progression in the CKD group, with the expected dose–response reduced risk in those in high-risk and general populations, respectively. The CKD-PC has used the parameters of proteinuria and estimated glomerular filtration rate (eGFR) to develop risk ratios for important outcomes, including progression to ESRD (Matsushita et al., 2010; Van der Velde et al., 2011) in 45 different cohorts obtained from clinical trials, clinical databases, and administrative datasets. The findings therein have been corroborated in multiple other studies: those with the highest levels of proteinuria are at greatest risk for progression, irrespective of eGFR, those with lower eGFR values are also at risk, but those with intermediate values of eGFR and little or no proteinuria do not appear to be at risk for progression (Iseki et al., 2003; Halbesma et al., 2006; Hemmelgarn et al., 2006, 2010).

In referred cohorts, those known to nephrologists, it appears that approximately 70% of patients demonstrate some rate of decline in eGFR, of which a much lesser number end up on dialysis in any given year (Keith et al., 2004; Levin et al., 2008; Astor et al., 2011). Over the long term, predictors of progression include male gender, younger age, heavy proteinuria, lower eGFR, diabetes, and hypertension. Recent prediction models published have included additional laboratory variables such as phosphate, bicarbonate, and albumin to improve the precision of the model, but from a clinical standpoint, the first six clinical variables are easily incorporated into clinical decision-making as simple parameters (Hunsicker et al., 1997; Keane et al., 2006; Halbesma et al., 2011; Tangri et al., 2011). The search for additional and better prediction models and refinement of existing ones is ongoing.

There are ethnic differences in progression rates, whereby African Americans, Asians, Aboriginal peoples, and Hispanics all appear to have faster rates of decline than Caucasians. While this may be confounded by socioeconomic factors and access to care, there is accruing data that true genetic factors play an important role (Hallan et al., 2006; Barbour et al., 2008, 2010; Pakov et al., 2008; Bui et al., 2009; Chen et al., 2009; Sood et al., 2010; Conley et al., 2012).

The diversity of outcomes of people with CKD cannot be overstated. There is remarkable variability in outcomes of patients at each stage of CKD, and the trajectories of progression are not linear. This leads to confusion among patients and care providers, and difficulties in decision-making and planning. The trajectories can be impacted by hospitalizations, episodes of acute kidney injury (AKI) which often but not necessarily occur in the context of hospitalizations, infections, and cardiovascular (CV) events (either natural or investigation related). Thus, the complexity of the prediction of progression to ESRD is underscored by the events that occur to people with CKD, which impact both the trajectory as well as the probability of surviving to 'achieve' that outcome. Li et al. describe a number of different trajectories, as a function of time of follow-up, in that the longer people are followed, the more variable is the trajectory over time; O'Hare et al. describe four trajectories using dialysis within 2 years as the outcome; others have described non-progression over time (John et al., 2004; Imai et al., 2008; Li et al., 2012; O'Hare et al., 2012) (see Figs 97.1 and 97.2).

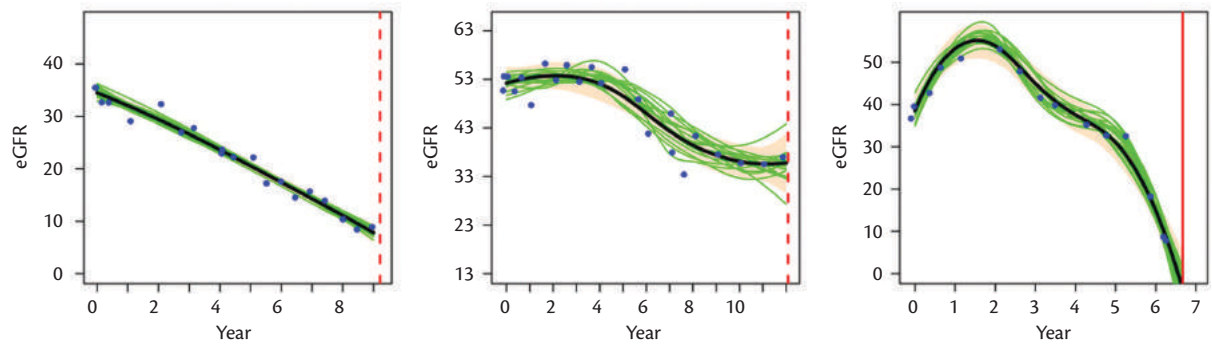

Fig. 97.1 Variability in trajectories of change in renal function over time.
From Li et al. (2012).

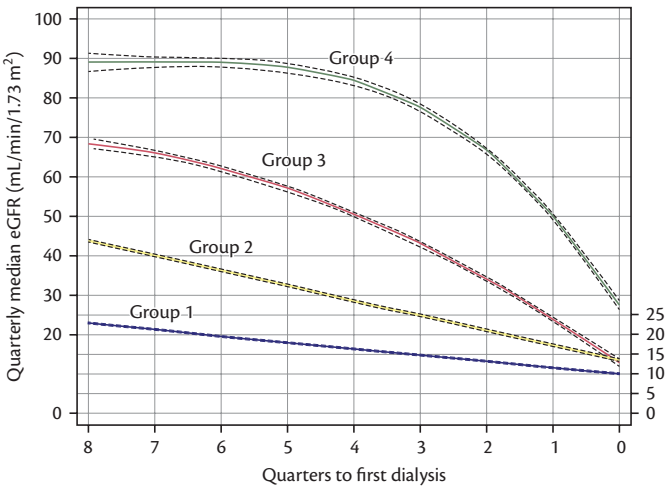

Fig. 97.2 Different trajectories in those who achieved dialysis within 2 years.
From O'Hare et al. (2012).

In the following sections, the probability of these outcomes, their predictors, and interactions with other factors are described in more detail.

Markers of progression

While progression has long been thought to be associated with age, it is better understood as a consequence of the comorbidities that accrue as a function of ageing, and thus markers of 'true progression' have been sought (Lindeman, 1984; Fliser et al., 1997; Lindeman et al., 1998). As has been discussed above, the rate at which this decline occurs varies according to the underlying population, presence of albuminuria/proteinuria, comorbidities, and exposures to nephrotoxins or AKI events (Coca et al., 2009; La France et al., 2010; James et al., 2011). Nonetheless, there is accruing data which helps clinicians and researchers to identify true progression, within individuals, as opposed to biological variability or simple, slow 'age'-related decline.

In a general population study, Prevention of Renal and Vascular End-Stage Disease (PREVEND), decline in kidney function at the population level is described and reports eGFR decline which is variable as a function of proteinuria (Halbesma et al., 2006). The variability in rates of progression was closely linked to the amount of proteinuria: those with no proteinuria experienced a loss in eGFR of 0.2 mL/min/1.73 m^2 over 4 years whereas those with an elevated urinary albumin to creatinine ratio (UACR) experienced a much faster rate of 2.3–7.2 mL/min/1.73m^2 over 4 years. In a Japanese general population, followed for > 10 years, the decline was less at 0.36 mL/min/1.73m^2 (Imai et al., 2008). Proteinuria is recognized as an important marker of progression, as has been demonstrated in numerous studies (Halbesma et al., 2006; Imai et al., 2008; Hemmelgarn et al., 2010). In general, the studies suggest progression rates of approximately 0.3–1 mL/min/1.73m^2 per year among participants without proteinuria or co-morbidity, with much higher rates (two to three times) in those with any degree of with proteinuria or co-morbidity. There are some population-based studies, identifying those with impaired kidney function, but in the absence of proteinuria measurements, which describe similarly low rates of renal decline (John et al., 2004; Halbesma et al., 2006). This apparent paradox is best understood in the context of the populations studied (i.e. general populations versus referred cohorts).

Additional predictors of progression, above and beyond the aetiology of CKD, include the presence of hyperphosphataemia, hyperuricaemia, dyslipidaemia, and acidosis. Many of these would be considered to be markers of severity of CKD, and thus it is potentially difficult to sort what is 'chicken and egg' with respect to marker of severity versus marker of progression per se. Nonetheless, biological and experimental data do support these metabolic and laboratory abnormalities in the context of progression (Krowlewski et al., 1994; Ravid et al., 1998; Iseki et al., 2001; Obermayr et al., 2008; Kovedsky et al., 2009; Menon et al., 2010; Tangri et al., 2011). Cohort studies have described more rapid progression in those with hyperuricaemia and acidosis, and small studies of interventions for these two abnormalities, either alone or together, have demonstrated promising results to attenuate reduction in GFR (Siu et al., 2006; Goicoechea et al., 2010). Larger studies will improve our understanding of both predictors of CKD progression and effective interventions.

Markers of oxidative stress, inflammation, and fibrosis have been examined in the context of predicting progression, but are not yet appropriate for use in clinical care. They do, however, serve to inform pathological mechanisms and thus avenues for clinical interventions. For a comprehensive overview of biomarkers important in progression of CKD, the reader is referred to an excellent review (Fassett et al., 2011). N-terminal pro-brain natriuretic peptide (NT-pro-BNP) and troponin I have also been identified as predictive of progression (Desai et al., 2011). The role of specific molecules like asymmetric dimethylarginine (ADMA),

transforming growth factor beta (TGF-β), and interleukin 6 (IL-6) remain areas of active study (Roberts et al., 2006; Young et al., 2009; Baretto et al., 2010).

Progressive kidney disease remains problematic for clinicians and researchers alike. Improved understanding of the predictors of progression, best interventions to slow rates of progression, and the impact of progressive disease on resource utilization and patient outcomes remain active areas of investigation.

Chronic kidney disease and risk of death

CKD can lead to a significant reduction in lifespan. Most of this reduction is due to the increased burden of cardiovascular disease (CVD), but it has been increasingly recognized that CKD increases risk of non-cardiac death as well.

The mortality rates on maintenance dialysis have been the most extensively reported but recent research has helped to quantify the increased risk of mortality attributed to CKD in patients not on dialysis (CKD-ND). In addition, the presence of albuminuria, and episodes of AKI have also been shown to impact mortality. This section will highlight what is currently known with respect to the increased risk of mortality due to kidney disease.

Risk of death in CKD patients not on dialysis

The risk of death attributed to a reduced eGFR has been evaluated in several population-based studies (Garg et al., 2002; Muntner et al., 2002; Go et al., 2004; Nitsch et al., 2013).

In a large American study, > 1.1 million community-based adults with CKD-ND (eGFR < 60 mL/min/1.73 m^2) were followed for a median of 2.84 years (Go et al., 2004). An independent, graded association was noted between a reduced eGFR and the risk of death. As eGFR declined, the risk of death from any cause increased sharply. The adjusted hazard ratios (HRs) for death were 1.2, 1.8, 3.2, and 5.9 for eGFR 45–59, 30–44, 15–29, and < 15 mL/min/1.73 m^2, respectively. This translates to a mortality risk increase from 17% at an eGFR of 45–59 mL/min to a staggering 343% at an eGFR of < 15 mL/min.

In 2006, a systematic review of the association between CKD-ND and the risk for all-cause and CV mortality was conducted (Tonelli et al., 2006). Thirty-nine studies that followed > 1.3 million participants were included. The unadjusted relative risk for mortality in those with CKD versus those without, ranged from 0.94 to 5.0. The absolute risk for death increased exponentially with decreasing function. Adjusting for common associated patient factors such as diabetes and hypertension reduced, but did not negate the increased risk of death. In this meta-analysis, CV deaths (representing 58% of deaths) were the largest driver for the increased risk of death.

In 2010, the results of a large global collaborative meta-analysis were reported. Results of the CKD-PC highlighted that both lower eGFR and the presence of albuminuria independently predicted mortality in the general population independent of cardiac risk factors (Matsushita et al., 2010). In a collaborative meta-analysis of > 1 million patients in the general population cohort, the consortium found that lower eGFR and higher albuminuria were risk factors for all-cause and CV mortality, independent of each other and of CV risk factors. The HRs for all-cause mortality at eGFRs of 60, 45, and 15 mL/min/1.73 m^2 were 1.18, 1.57, and 3.14 respectively when compared to an eGFR of 95 mL/min/1.73 m^2. The presence of albuminuria also carried an increased risk of mortality. Compared with UACR of 0.6 mg/mmol, adjusted HRs for all-cause mortality were 1.2, 1.63, and 2.22 for UACR 1.1, 3.4, and 33.9 mg/mmol respectively. Subsequently, the analysis of cohorts at risk for CKD (Astor et al., 2011) or with CKD (van der Velde et al., 2011) has demonstrated similar associations. In addition, a recent meta-analysis of these cohorts assessed for the presence of a sex interaction in the associations of eGFR and UACR with all-cause mortality, CV mortality, and ESRD (Nitsch et al., 2013). This study demonstrated that both sexes face an increased risk of all-cause mortality, CV mortality, and ESRD with reduced eGFR and increasing UACR.

Importantly, the association of kidney disease measures, eGFR, and albuminuria with mortality or ESRD has also been consistently found in those with or without hypertension (Mahmoodi et al., 2012), diabetes (Fox et al., 2012), and also regardless of age (Hallan et al., 2012).

There are multiple possible explanations for the increased risk of death for patients with CKD. Prior CVD and known risk factors for CVD represent some of the risk. However, when adjusted for these known risks, CKD still carries a strong, independent, and graded risk of death. Several possible explanations have been given including endothelial dysfunction, inflammation, pro-coagulability, anaemia, left ventricular hypertrophy, arterial stiffness, and calcification (Levin et al., 1999; Hsu et al., 2002; Raggi et al., 2002; Shiplak et al., 2003, 2005; Muntner et al., 2004). The answer probably lies in a combination of some, if not all of the above factors. The mechanism by which this multitude of factors leads to increased mortality in CKD is still poorly elucidated.

Risk of death in CKD patients on dialysis

Although dialysis is a life-saving treatment for patients with ESRD, the mortality rate for those on dialysis remains exceedingly high. In general, becoming dialysis dependent carries a prognosis worse than most cancers. Although many factors must be taken into consideration, the lifespan of a 60–64-year-old starting dialysis in the United States is approximately 4.5 years and 8 years for a 40–44-year-old patient (United States Renal Data System (USRDS), 2009). Factors that have been associated with decreased survival on dialysis include burden of co-morbidities, length of time on dialysis (Chertow et al., 2000), and either low or high pre-dialysis potassium levels (Kovesdy et al., 2007).

In terms of specific modality of dialysis (haemodialysis (HD) or peritoneal dialysis (PD)), data is still conflicting regarding whether one modality has improved long-term outcomes over another. After several trials to address this question, we do know that there is no large survival advantage between modalities of dialysis as conventionally prescribed. However, there is currently a significant amount of research looking at outcomes with short daily and nocturnal HD (Nesrallah et al., 2004; Nesrallah et al., 2006). Preliminary results have been encouraging, with studies showing an improved survival among patients using nocturnal and short daily compared to conventional dialysis in one recent study (Johansen et al., 2009). Another study showed that patients on nocturnal HD had a similar survival to patients who received a deceased donor transplant (Pauly et al., 2009). However, recent randomized trials investigating whether more frequent HD sessions compared to the conventional three-times-weekly regimen showed some clinical and/or biochemical advantages, but none of these trials could give answers to the question of whether frequent dialysis ameliorates long-term dialysis patient survival; none of them was indeed

designed for addressing this most important outcome parameter (Lameire et al., 2012).

CVD remains the major cause of death in this population, accounting for up to half of all deaths. Of the cardiac causes, sudden cardiac death (SCD), most commonly due to ventricular arrhythmias, is the most common specific cause of death, representing close to 27% of all-cause mortality in dialysis patients (USRDS 2010). It is well known that obstructive coronary artery disease is not the only contributor to SCD in dialysis patients. Other myocardial abnormalities, including left ventricular hypertrophy, endothelial dysfunction, and myocardial perfusion abnormalities are also thought to be factors (Young, 2011).

Studies have also shown an enhanced risk of SCD in the first HD session of the week after a 2-day dialysis-free interval (Bleyer et al., 1999). This study compared the risk of SCD on Monday (for patients dialysing Monday, Wednesday, and Friday) or on Tuesday (for patients dialysing Tuesday, Thursday, and Saturday) and found a 50% higher risk on the Monday or Tuesday.

An increased risk of SCD has also been shown in patients using a low potassium dialysate (<2 mEq/L), low calcium dialysate, and increased ultrafiltration volumes (Pun et al., 2011), therefore, these may be modifiable changes that can be made to the HD prescription to reduce the risk of SCD.

The majority of literature has focused on HD patients and few studies assess these outcomes in PD. However, SCD is also the leading cause of death in PD patients noted in a prospective 5-year observational study from Hong Kong that reported 24% of the deaths in the cohort were attributed to SCD, similar to HD cohorts (Wang et al., 2010).

After CVD, infections and withdrawal of dialysis (either due to patient request, or the inability to provide dialysis to the patient) are the next most frequent causes of death in dialysis patients. Infections in CKD are detailed extensively in the 'Infections' section of this chapter.

Risk of mortality following acute kidney injury

It has been shown in several studies that in-hospital AKI increases in-hospital mortality for a variety of conditions (Uchino et al., 2005). Logically, if an individual survives a period of AKI but is left with CKD, their mortality will be increased as well, as has been demonstrated (Coca et al., 2009). Recent literature also suggests that in patients with normal pre-hospitalization kidney function, those with an episode of resolved hospital-acquired AKI have an increased subsequent risk of CKD and death compared to those that did not have AKI in hospital (Lafrance et al., 2010; Bucaloiu et al., 2011). This highlights the need for active surveillance of patients with AKI in hospital, regardless of whether it resolves prior to discharge. (See Chapter 237 for more details.)

Conclusion/implications for future research

The risk of death is increased in CKD regardless of severity of kidney disease. The risk increases significantly as kidney function declines. Despite modest improvements over the last 40 years, the prognosis of patients on dialysis is still poor.

Increased CV mortality represents an important factor but is not the only cause of increased death in CKD patients. Further prospective studies that aim to understand the causes and mechanisms of the increased risk of mortality in people with CKD, irrespective of dialysis status, are required.

Current treatment strategies mirror the risk factor modification of the non-CKD population. Further prospective research is required to determine the most useful interventions. In addition, randomized controlled trials (RCTs) with modification to current methods of dialysis are required to ensure advances in dialysis technology and prescriptions lead to a reduction in mortality.

Cardiovascular disease and events

CVD is the major cause of death for people with CKD (Go et al., 2004). CVD in CKD is characterized by accelerated atherosclerosis, arteriosclerosis, vascular calcification, and cardiomyopathy (predominantly left ventricular hypertrophy). At the time of CKD diagnosis, a significant proportion of patients have established CVD, and CVD prevalence increases as renal function declines (Martínez-Castelao et al., 2011; Foster et al., 2013). In the National Health and Nutrition Survey (NHANES) 2007–2010, the prevalence of CVD was 29.6% with CKD stages 3–5 and 13.0% with stages 1 and 2, compared to 5.5% of those without CKD after controlling for age, sex, and race (Foster et al., 2013).

In CKD patients without established CVD, expert groups advocate that they be considered in the highest risk category for future CV events (Sarnak et al., 2003). Whether this statement applies uniformly to all groups with CKD is unknown, as large population-based studies show conflicting results. In the Women's Health Study, an eGFR < 60 mL/min/1.73 m^2 was associated with an increased risk of CVD death but not other CVD events or non-CVD mortality (Kurth et al., 2009). Similarly, both men and women with moderate CKD in NHANES did not have an increased risk of CVD (Garg et al., 2002). In contrast, a population-based study in Iceland demonstrated that all stages of CKD are associated with coronary heart disease (Di Angelantonio et al., 2010). By evaluating both urinary protein excretion (urine dipstick or UACR) and GFR, the ability to predict future CVD events is improved. A meta-analysis from the CKD-PC evaluating 1.2 million individuals from 21 general population cohorts found that eGFR < 60 mL/min/1.73 m^2 and UACR ≥ 1.1 mg/mmol are independent predictors of all-cause and CV mortality (Matsushita et al., 2010). Similar findings were observed in a high-risk population cohort with hypertension, diabetes, and established CVD (van der Velde et al., 2011).

The rate of decline in kidney function also predicts CV events. A cohort study in older individuals defined rapid decline as > 3 mL/min/1.73 m^2 based on cystatin C measurements found after adjustment for demographics, CVD risk factors, and baseline kidney function, that rapid kidney function decline was significantly associated with heart failure (HR 1.32), myocardial infarction (HR 1.48), and peripheral arterial disease (PAD) (HR 1.67), and did not differ by the presence or absence of CKD at baseline (Shlipak et al., 2009).

Both traditional and non-traditional risk factors likely contribute to the increased CV risk observed in CKD. Hypertension, smoking, diabetes, dyslipidaemia, and older age are highly prevalent in CKD populations (Abboud and Henrich, 2010). While they do not entirely explain the increased CV risk, they do appear to be the most important contributors in this population (Muntner et al., 2005; Shlipak et al., 2005). In a large population-based cohort, traditional risk factors had an area under the curve (AUC) of 0.73 to explain CV mortality among older patients with eGFR < 60 mL/min/1.73 m^2; adding novel risk factors to the model only increased

the AUC to 0.74 (Shlipak et al., 2005). The relationship between certain risk markers and CV events in CKD stage 5D often differs from that in the general population, a phenomenon termed reverse epidemiology; whether the same is true in non-dialysis CKD remains unknown.

Atherosclerotic disease may not follow the same pathways in people with CKD as compared to those with normal renal function, and there are several non-traditional risk factors unique to CKD that may contribute to or accelerate the CV risk. There is a multitude of observational data linking these non-traditional risk factors to poor CV outcomes throughout the spectrum of CKD; however, none have been proven a necessary cause in CVD. Purported non-traditional risk factors include uric acid, sympathetic over-activity, bone mineral metabolism (serum phosphate concentration, calcium loading, and more recently FGF23 (Isakova et al., 2011)), anaemia, arterial stiffness, chronic overhydration, inflammatory markers (especially ADMA and IL-6), uraemic toxins, and oxidative stress.

Outcomes after an acute coronary syndrome (unstable angina and myocardial infarction) in CKD patients are worse compared to the non-CKD population. Observational studies and a large meta-analysis in the general population demonstrate that in those with a cardiac event, short- and long-term CV morbidity and mortality are inversely and independently associated with kidney function, especially at eGFR < 15 mL/min/1.73 m^2 (Shlipak et al., 2002; Anavekar et al., 2004; Cardinal et al., 2010; Campbell et al., 2012). Observational data also consistently shows increased risk of serious operative complications in CKD patients. The incidence of postoperative death after coronary artery bypass grafting is three- to sevenfold higher in CKD stages 4–5ND than in non-CKD patients (Cooper et al., 2006).

Non-atherosclerotic CVD considerations in CKD

Congestive heart failure (CHF) is very common in CKD patients (USRDS, 2004). The mechanisms that lead to CHF are pressure overload, volume overload, and CKD-associated non-haemodynamic factors that affect the myocardium (Ronco et al., 2009). CKD is associated with increased mortality in heart failure (Smith et al., 2006), with a higher mortality observed in diastolic compared to systolic heart failure in CKD patients (Ahmed 2007).

An increased risk of stroke is observed in CKD patients (USRDS, 2009). A large meta-analysis found that an eGFR < 60 mL/min/1.73 m^2 was associated with an increased risk of incident stroke (pooled relative risk 1.43) compared to those with eGFR > 90 mL/min/1.73 m^2 (Lee et al., 2010). Proteinuria or albuminuria also increases stroke risk. CKD also portends a worse prognosis after stroke; the risk of fatal stroke is higher than overall stroke risk in those with eGFR <60 mL/min/1.73 m^2 (Lee, BMJ 2010).

Atrial fibrillation is common in individuals with CKD-ND, with prevalence rates of approximately 20%. CKD is an independent risk factor for development of this arrhythmia, the risk increasing as GFR declines. A community-based study found the age-adjusted risk of incident atrial fibrillation of 2.2, 5.1, and 6.6 per 1000 person years for eGFR ≥ 60, 30–59, and < 30 mL/min/1.73 m^2, respectively (Watanabe et al., 2009). The presence of CKD and proteinuria predict adverse outcomes (stroke and peripheral thromboembolism) (Fang et al., 2011).

There is a high prevalence of PAD in CKD. The Chronic Renal Insufficiency Cohort Study shows a PAD prevalence of 7% in CKD-ND patients. In general, the weight of evidence points to worse outcomes after percutaneous or surgical management of PAD in CKD patients.

There are several limitations and knowledge gaps in our current understanding of CVD in CKD. Firstly, the most important limitation is the lack of inclusion of patients with significant CKD from CV trials. Certainly, a uniform, accurate definition of CKD incorporating albuminuria cut-offs (possibly standardized for age) is important to categorize patients appropriately according to CV risk in trials. Longitudinal studies evaluating clinical, standard laboratory parameters and biomarkers in CKD patients are underway, and will hopefully improve prediction of adverse events in this population, and may identify other contributing factors to CVD in CKD. Finally, (large-scale) intervention trials for traditional and purported non-traditional CV risk factors are needed to elucidate if intervention decreases adverse outcomes in this population.

Infections

Risk of infection

Infection is an often underappreciated source of morbidity and mortality in CKD. In CKD-ND populations, a graded increase in the risk of hospitalization and death due to infection is observed as kidney function declines (James et al. 2008, 2009; USRDS, 2011; Dalrymple et al., 2012). Infection is also a major cause of hospitalization in CKD-D patients on dialysis (CKD-D), with rates peaking within the first 3 months following dialysis initiation, particularly in HD (Collins et al. 2009). Furthermore, infection consistently ranks as a leading cause of mortality in CKD-D, accounting for about 20% of deaths in the United Kingdom (Caskey et al. 2010).

Studies of infections in CKD focus mainly on episodes requiring hospitalization or causing death. Since many infections (including those requiring intravenous and intraperitoneal antibiotics) are treated on an outpatient basis particularly in dialysis patients, existing epidemiological data can be considered to underestimate the true burden of infectious diseases in all stages of CKD (Dalrymple and Go, 2008).

Risk factors

Risk factors for infections causing hospitalization or death have mainly been described in CKD-D. These include advanced age, comorbidities (diabetes mellitus, heart failure, ischaemic heart disease, stroke, chronic lung disease, malignancy, inability to ambulate), nutritional compromise (low body mass index, low albumin), and use of immunosuppressive medications (Powe et al., 1999; Allon et al., 2005; Slinin et al., 2006; Dalrymple and Go, 2008; Guo et al., 2008; Dalrymple et al., 2010).

In HD, central venous catheter use is a major risk factor for infection. In addition, both HD and PD result in the potential for repeated infectious exposures due to the nature of the procedures themselves (e.g. interruption of intact skin). Finally, uraemia is associated with abnormalities in both innate and adaptive immunity that increase susceptibility to infection and result in hyporesponsiveness to vaccines. These abnormalities are discussed in detail in Chapter 128.

A lower risk of sepsis requiring hospitalization was reported in one observational study of individuals on dialysis prescribed statin medications (Gupta et al., 2007). Mixed results have been reported in similar studies in the general population. RCTs are required to determine whether or not statins have a role in preventing infection.

Infections in CKD patients not on dialysis

The risk of hospital admission and death due to various infections in CKD-ND has been described recently. The risk is graded and rises with advancing CKD. These findings are consistent for the majority of serious infections.

Risk of bloodstream infection-related hospitalization and death was quantified retrospectively in an elderly (aged 65 or greater with at least one measure of creatinine available in 2001) cohort of > 25,000 (27% with CKD) from Canada. Over a median follow-up of 3.2 years, 3.1% were hospitalized with bloodstream infection. Compared to those with Modification of Diet in Renal Disease (MDRD; MDRD Study Group, 1991) formula-estimated GFR ≥ 60 mL/min/1.73 m^2, the adjusted HRs for death were 1.34, 1.61, and 4.1 for GFR 45–59, 30–44, and < 30 mL/min/1.73 m^2, respectively. Results for hospitalization were very similar (James et al., 2008).

Risk of pneumonia-related hospitalization and death increased with declining MDRD formula-estimated GFR in a second retrospective cohort study from Canada of > 250,000 adults (aged 18 or greater with at least one measure of creatinine available in 2003 or 2004) followed for a median of 2.5 years. Not unexpectedly, the elderly accounted for the greatest absolute number of hospital admissions and deaths; however, the relative risk of these outcomes was greatest in younger individuals (James et al., 2009).

Rates of all infection-related hospitalizations have been reported in US cohorts where CKD was defined using diagnosis codes. For elderly US Medicare beneficiaries (aged 66 or greater) in 2009, the adjusted hospital admission rate due to any infection was 1.5 times greater in those with CKD (56 per 1000 patient-years in the non-CKD population versus 82 per 1000 patient-years in non-dialysis-dependent CKD). Hospitalization rates increased as CKD worsened: from 69 per 1000 patient-years in stages 1 and 2 CKD, to 78 per 1000 patient-years in stage 3 CKD, to 107 per 1000 patient-years in stages 4 and 5 (non-dialysis) CKD. Similar trends were observed regardless of the site of primary infection (skin, circulatory, lung, genitourinary, musculoskeletal, and abdominal) (USRDS, 2011).

Two recent reports have reinforced these findings. In an analysis of the Cardiovascular Health Study participants (5142 people aged 65 years or greater, excluding GFR < 15 mL/min/1.73 m^2), 30% were hospitalized at least once for infection over a median follow-up period of 11.5 years. Reduced kidney function, in this study estimated using a cystatin C-based method, was again associated with a graded increase in adjusted risk of all infectious hospitalizations, including pulmonary and genitourinary infections (Dalrymple et al., 2012). Examination of infection-related mortality among NHANES III participants yielded very similar results. In addition, heavier proteinuria was a risk factor for hospitalization due to infection in this study (Wang et al. 2011).

Infections in CKD patients on dialysis

Infection is often listed as the second leading cause of mortality in CKD-D (Foley, 2007). It accounted for about 20% of deaths in dialysis patients in the United Kingdom in 2009 (Caskey et al. 2010). The first few months following dialysis initiation appear to be a particularly high-risk period for infectious hospitalizations, especially for HD patients (Collins et al., 2009).

The risk of septicaemia or bacteraemia varies by dialysis and vascular access type. In HD, they occur more frequently when temporary or cuffed catheters are used than when an arteriovenous graft of fistula (AVG or AVF) is used. Rates of sepsis and bacteraemia in PD are similar to those reported in HD with an AVF (Ishani et al., 2005).

Reported rates of catheter-related bacteraemia in HD vary between and within countries, but range from < 1 to 4 per 1000 catheter days in most reports. While catheter use for HD remains a concern in certain countries, it should be remembered that that the majority of septic events are accounted for by non-vascular access-related causes. For example, among the 1846 participants in the prospective HEMO Study, only one-fifth of all infection-related first hospitalizations were felt to be related to vascular access (Allon et al., 2003).

Vascular access-related infections in HD are discussed in detail elsewhere (see Chapter 269).

In comparison to the general population, mortality rates from sepsis in dialysis are alarmingly high. In the United States for the years 1994–1996, the adjusted annual mortality was between 100 and 300 times that observed from sepsis in the general population. The impact is especially significant in younger individuals (Sarnak and Jaber, 2000).

Peritonitis is a major infectious complication of PD, and is discussed in detail elsewhere (see Chapter 266). Reported rates of PD-associated peritonitis vary by jurisdiction. In a large North American survey, peritonitis occurred at a rate of about one episode per 30 patient-months (Mujais, 2006). Mortality from an episode of peritonitis is < 4%, and peritonitis accounts for about 20% of infection-related deaths on PD (Li et al., 2010). The significance of this finding is highlighted in Australia and New Zealand, where the risk of infection-related death was found to be greater in PD than in HD, largely due to an excess of deaths from bacterial and fungal peritonitis episodes (Johnson et al., 2009).

Pneumonia (inpatient and outpatient) is common in dialysis-dependent CKD, with a reported incidence of 21% (27.9 per 100 patient-years) within the first year of dialysis initiation in US Medicare beneficiaries starting dialysis between 1996 and 2001 (hospitalization rate 6.1 per 100 patient-years). The cumulative 1-year survival following pneumonia was only 51% at 1 year. Interestingly, the risk of pneumonia was higher in HD than PD patients (29.0 compared to 18.2 per 100 patient-years, respectively) in this report (Guo et al., 2008). In contrast, no difference in pneumonia rates between modalities was reported in Australia and New Zealand (Johnson et al., 2009).

In a US study comparing pulmonary infectious mortality in dialysis to the general population, the annual mortality rate in all age groups combined was reported to be 14–16 times greater in those on dialysis (Sarnak and Jaber, 2001).

Long-term implications of serious infections in CKD

In addition to the immediate risks posed by infections, these events also portend a poor longer-term prognosis in the subsequent months and years. In US dialysis patients, increased risks of CV morbidity (including heart failure, myocardial infarction, and stroke) and death have been reported up to 5 years following an infectious event (Ishani et al., 2005; Guo et al., 2008). Inflammatory pathways may be the pathophysiologic link between infections and adverse CV outcomes (Foley, 2007).

Opportunities for prevention of infections in CKD

In view of the high risk of infectious events in CKD and the associated poor outcomes, efforts to prevent infections are extremely

important. This includes addressing modifiable individual risk factors (e.g. nutrition), reducing pathogen exposure (e.g. reducing central venous catheter use in HD, avoiding hospitalization and procedures where possible) and vaccination (e.g. influenza, pneumococcus, and hepatitis B) (Dalrymple and Go, 2008).

The topic of vaccination in CKD is discussed in Chapter 128.

Hospitalizations

Risk of hospitalization

Given the multitude of complications associated with CKD, it is not surprising that hospitalization rates are high in this population, especially dialysis patients. The most common reason for hospital admission is CVD, followed by infection (USRDS, 2011). Hospitalization represents a major source of morbidity and healthcare expenditure throughout the entire CKD spectrum.

Hospitalization in CKD patients not on dialysis

The increased risk of hospitalization with declining kidney function in CKD-ND has been described recently in several cohorts in the United States, Canada, and the United Kingdom. It has been consistently reported that the risk of hospital admission increases as GFR declines. Proteinuria is also an important independent risk factor for hospitalization.

In an American study of > 1.1 million adults (mean age 52 years) in the Kaiser Permanente Renal Registry in California with at least one serum creatinine measured between 1996 and 2000 and followed for a median of 2.8 years, the adjusted HRs for any hospital admission were 1.1, 1.5, 2.1, and 3.1 for MDRD formula-estimated GFR 45–59, 30–44, 15–29, and < 15 (non-dialysis dependent) mL/min/1.73 m^2 compared to ≥ 60 mL/min/1.73 m^2, respectively (Go et al., 2004).

Findings were similar in a report from the USRDS of elderly Medicare beneficiaries (age 66 years or greater). Overall hospital admission rates were three to five times higher in CKD (defined using diagnosis codes) than in those without a CKD diagnosis; however, with adjustment for disease severity (including comorbidities and prior hospitalization) the risk was 1.4 times greater. In 2009, the adjusted hospital admission rate for non-dialysis dependent CKD was 444 per 1000 patient-years compared to 318 per 1000 patient-years in those without CKD. Rates increased as CKD worsened (407 per 1000 patient-years in stages 1 and 2, 438 per 1000 patient-years in stage 3, 560 per 1000 patient-years in stage 4 and stage 5 (non-dialysis) CKD). The most common reasons for hospital admission were CVD (about 30%) and infections (about 20%) (USRDS, 2011).

A series of studies of a community-based cohort from Alberta, Canada used a province-wide laboratory registry to determine the associations between MDRD formula-estimated GFR and proteinuria with the risk of hospitalization for various CV events and with AKI. About 1 million adults were included with a median follow-up of 35 months. Risk of hospitalization with AKI increased with declining kidney function, as did the risk of hospitalization for myocardial infarction, congestive heart failure, peripheral vascular disease, and transient ischaemic attack/cerebrovascular attack. Worsening proteinuria was also consistently and independently associated with increased risk of these outcomes, highlighting its importance as a risk factor for adverse events in CKD (Hemmelgarn et al., 2010; James et al., 2010; Bello et al., 2011).

A recent analysis including > 10,000 community-dwelling elderly individuals (aged 75 years or greater) from 53 general practices in the United Kingdom supports the findings in the previous studies. Those with CKD-Epidemiology Collaboration formula-estimated GFR < 30 mL/min/1.73 m^2 were at increased risk of hospitalization. Dipstick positivity for proteinuria was also independently associated with hospital admission over a 2-year follow-up period (Nitsch et al., 2011).

Hospitalization in CKD patients on dialysis

Among individuals with CKD, the hospitalization risk is highest for those on dialysis. The first 3 months after initiation of dialysis are a particularly high-risk period for hospitalization (Collins et al., 2009). This has been attributed in part to the high frequency of catheter use in incident HD patients. As in the non-dialysis-dependent CKD population, the most common reason for hospital admission is CVD, followed by infection (USRDS, 2011).

In US prevalent dialysis patients, the adjusted all-cause hospitalization rate has remained fairly stable over the past decade, at about 1.9 per patient-year, although the infectious hospitalization rate has been steadily increasing. In 2009, the adjusted hospital admission rate for CVD was 0.55 per patient-year, and for infections was 0.47 per patient-year. Rehospitalization occurred in 36% within 30 days of discharge, indicating that this is a major cause of morbidity in dialysis patients. Overall, PD patients had fewer hospitalizations than their HD counterparts matched for various comorbidities and indicators of disease severity (USRDS, 2011).

Hospital admission and readmission rates have recently been reported in the United Kingdom. In a retrospective, 5-year observational study in Northern Ireland, the median number of hospital admissions was three per HD patient. Similar to the observations reported by the USRDS, hospital admissions were especially common within the first 100 days of dialysis initiation, accounting for just over 50% of all hospital admissions. Importantly, duration of hospital stay was also noted to be far longer in HD patients by a factor of 3.75 (Quinn et al., 2011).

Summary: chronic kidney disease long-term outcomes

CKD, defined as reduction in kidney function or evidence of kidney damage present for a duration of 3 months or longer, has been definitively associated with poor long-term outcomes in numerous populations. While heterogeneity within populations is appreciated, the fact remains that those with CKD are at risk for progression of CKD, AKI, hospitalizations, infections, CVD (atherosclerotic and non-atherosclerotic), and death. Increasingly data have become available which identify both traditional and non-traditional risk factors for these adverse outcomes but few intervention trials have been conducted with help to guide therapy. Of note, an increasing commitment is observed within the international renal community to conduct large RCTs to answer important questions relevant for patients. Examples include the SHARP study (Study of Heart and Renal Protection), which determined that use of a combined lipid-lowering strategy of simvastatin and ezetimibe does reduce atherosclerotic events in those with CKD, with little adverse effects; the IDEAL study which determined that early start of dialysis was not associated with benefits and may have associated increased costs; and the TREAT study which determined that higher target

haemoglobins using erythropoietic-stimulating agents in diabetic CKD-ND patients did not result in improved mortality and was associated with harm (Pfeffer et al., 2009; Baigent et al., 2011; Cooper et al., 2011).

Thus, while we continue to better define high-risk populations, best interventions for delaying CKD progression, and complications such as infections, hospitalizations, and death, it would behove the community to review and apply results of well-conducted RCTs, and design future studies to address important clinical questions. These collaborative efforts will serve to improve understanding and outcomes in years to come.

References

Abboud, H. and Henrich, W. L. (2010). Stage IV chronic kidney disease. *N Engl J Med*, 362, 56–65.

Ahmed, A., Rich, M. W., Sanders, P. W., *et al.* (2007). Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. *Am J Cardiol*. 99, 393–8.

Allon, M., Depner, T. A., Radeva, M., *et al.* (2003). Impact of dialysis dose and membrane on infection-related hospitalization and death: results of the HEMO Study. *J Am Soc Nephrol*, 14(7), 1863–70.

Allon, M., Radeva, M., Bailey, J., *et al.* (2005). The spectrum of infection-related morbidity in hospitalized haemodialysis patients. *Nephrol Dial Transplant*, 20(6), 1180–6.

Anavekar, N. S., McMurray, J. J., Velazquez, E. J., *et al.* (2004). Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*, 351, 1285–95.

Astor, B. C., Matsushita, K., Gansevoort, R. T., *et al.* (2011). Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int*, 79(12), 1331–40.

Baigent, C., Landray, M. J., Reith, C., *et al.* (2011). The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): randomised placebo-controlled trial. *Lancet*, 377 (9784), 2181–92.

Barbour, S. J., Er, L., Djurdjev, O., *et al.* (2008). The prevalence of hematologic and metabolic abnormalities during chronic kidney disease stages in different ethnic groups. *Kidney Int*, 74(1), 108–14.

Barbour, S. J., Er, L., Djurdjev, O., *et al.* (2010). Differences in progression of CKD and mortality amongst Caucasian, Oriental Asian and South Asian CKD patients. *Nephrol Dial Transplant*, 25(11), 3663–72.

Bello, A. K., Hemmelgarn, B., Lloyd, A., *et al.* (2011). Associations among estimated glomerular filtration rate, proteinuria, and adverse cardiovascular outcomes. *Clin J Am Soc Nephrol*, 6(6), 1418–26.

Bleyer, A. J., Russell, G. P., and Satko, S. G. (1999). Sudden and cardiac death rates in hemodialysis patients. *Kidney Int*, 55(4), 1553–9.

Bucaloiu, I. D., Kirchner, H. L., Norfolk, E. R., *et al.* (2011). Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. *Kidney Int*, 81(5), 477–85.

Bui, A. L., Katz, R., Kestenbaum, B., *et al.* (2009). Cystatin C and carotid intima-media thickness in asymptomatic adults: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Kidney Dis*, 53(3), 389–98.

Campbell, N. G., Varagunam, M., Sawhney, V., *et al.* (2012). Mild chronic kidney disease is an independent predictor of long-term mortality after emergency angiography and primary percutaneous intervention in patients with ST-elevation myocardial infarction. *Heart*, 98, 42–7.

Cardinal, H., Bogaty, P., Madore, F. *et al.* (2010). Therapeutic management in patients with renal failure who experience an acute coronary syndrome. *Clin J Am Soc Nephrol*, 5, 87–94.

Caskey, F., Dawnay, A., Farrington, K., *et al.* (2011). UK Renal Registry, Bristol, UK. UK Renal Registry 2010. 13th Annual Report of the Renal Association. *Nephron Clin Pract*, 119, Suppl 2.

Chen, N., Wang, W., Huang, Y., *et al.* (2009). Community based study on CKD subjects and associated risk factors. *Nephrol Dial Transplant*, 24, 2117–23.

Chen, Y. C., Su, C. T., Wang, S. T., *et al.* (2009). A preliminary investigation of the association between serum uric acid and impaired renal function. *Chang Gung Med J*, 32, 66–71.

Chertow, G. M., Johansen, K. L., Lew, M., *et al.* (2000). Vintage, nutritional status and survival in hemodialysis patients. *Kidney Int*, 57(3), 1176–81.

Coca, S. G., Yusuf, B., Shlipak, M. G., *et al.* (2009). Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis*, 53(6), 961–73.

Collins, A. J., Foley, R. N., Gilbertson, D. T., *et al.* (2009). The state of chronic kidney disease, ESRD, and morbidity and mortality in the first year of dialysis. *Clin J Am Soc Nephrol*, 4 Suppl 1, S5–11.

Cooper, B. A., Branley, P., Bulfone, L., *et al.* (2010). A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med*, 363, 609–19.

Cooper, W. A., O'Brien, S. M., Thourani, V. H., *et al.* (2006). Impact of renal dysfunction on outcomes of coronary artery bypass surgery: results from the Society of Thoracic Surgeons National Adult Cardiac Database. *Circulation*, 113, 1063–70.

Dalrymple, L. S. and Go, A. S. (2008). Epidemiology of acute infections among patients with chronic kidney disease. *Clin J Am Soc Nephrol*, 3(5), 1487–93.

Dalrymple, L. S., Johansen, K. L., Chertow, G. M., *et al.* (2010). Infection-related hospitalizations in older patients with ESRD. *Am J Kidney Dis*, 56(3), 522–30.

Dalrymple, L. S., Katz, R., Kestenbaum, B., *et al.* (2012). The risk of infection-related hospitalization with decreased kidney function. *Am J Kidney Dis*, 59(3), 356–63.

Desai, A. S., Toto, R., Jarolim, P., *et al.* (2011). Association between cardiac biomarkers and the development of ESRD in patients with type 2 diabetes mellitus, anemia, and CKD. *Am J Kidney Dis*, 58(5), 717–28.

Di Angelantonio, E., Chowdhury, R., Sarwar, N., *et al.* (2010). Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. *BMJ*, 341, c4986.

Fang, M. C., Go, A. S., Chang, Y., *et al.* (2011). A new risk scheme to predict warfarin-associated hemorrhage—The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol*, 58, 395–401.

Fassett, R. G., Venuthurupalli, S. K., Gobe, G. C., *et al.* (2011). Biomarkers in chronic kidney disease: a review. *Kidney Int*, 80, 806–21.

Fliser, D., Franek, E., Joest, M., *et al.* (1997). Renal function in the elderly: impact of hypertension and cardiac function. *Kidney Int*, 51, 1196–204.

Foley, R. N. (2007). Infections in patients with chronic kidney disease. *Infect Dis Clin North Am*, 21(3), 659–72, viii.

Foster, M. C., Rawlings, A. M., Marrett, E., *et al.* (2013). Cardiovascular risk factor burden, treatment, and control among adults with chronic kidney disease in the United States. *Am Heart J*, 166, 150–6.

Fox, C., Matsushita, K., Woodward, M., *et al.* (2012). Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*, 380, 1662–73.

Gansevoort, R. T., Matsushita, K., van der Velde, M., *et al.* (2011). Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes in both general population and high risk cohorts. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int*, 80(1), 93–104.

Garg, A. X., Clark, W. F., Haynes, R. B., *et al.* (2002). Moderate renal insufficiency and the risk of cardiovascular mortality: results from the NHANES I. *Kidney Int*, 61, 1486–94.

Go, A. S., Chertow, G. M., Fan, D., *et al.* (2004). Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*, 351, 1296–305.

Goicoechea, M., Garcia de Vinuesa, S., and Verdalles, U. (2010). Effect of allopurinol in CKD progression and cardiovascular risk. *Clin J Am Soc Nephrol*, 5, 1388–93.

Guo, H., Liu, J., Collins, A. J., *et al.* (2008). Pneumonia in incident dialysis patients—the United States Renal Data System. *Nephrol Dial Transplant*, 23(2), 680–6.

Gupta, R., Plantinga, L. C., Fink, N. E., *et al.* (2007). Statin use and sepsis events [corrected] in patients with chronic kidney disease. *JAMA*, 297(13), 1455–64.

Halbesma, N., Jansen, D. F., Heymans, M. W., *et al.* (2011). Development and validation of a general population risk score. *Clin J Am Soc Nephrol*, 6, 1731–8.

Halbesma, N., Kuiken, D. S., Brantsma, A. H., *et al.* (2006). Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. *JAMA*, 17, 2582–90.

Hallan, S. I., Coresh, J., Astor, B. C., *et al.* (2006). International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol*, 17, 2275–84.

Hallan, S. I., Matsushita, K., Sang, Y., *et al.* (2012). Age and association of kidney measures with mortality and end-stage renal disease. *JAMA*, 308(22), 2349–60.

Hemmelgarn, B. R., Manns, B. J., Lloyd, A., *et al.* (2010). Relation between kidney function, proteinuria, and adverse outcomes. *JAMA*, 303, 423–9.

Hemmelgarn, B. R., Zhang, J., Manns, B. J., *et al.* (2006). Progression of kidney dysfunction in the community-dwelling elderly. *Kidney Int*, 69, 2155–61.

Hsu, C. Y., Iribarren, C., McCulloch, C. E., *et al.* (2009). Risk factors for end stage renal disease: 25 year follow up. *Arch Intern Med*, 169, 342–50.

Hsu, C. Y., McCulloch, C. E., and Curhan, G. C. (2002). Epidemiology of anemia associated with chronic renal insufficiency among adults in the US; results from the Third NHANES. *J Am Soc Nephrol*, 13, 504–10.

Hunsicker, L. G., Adler, S., Caggiula, A., *et al.* (1997). Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. *Kidney Int*, 51(6), 1908–19.

Imai, E., Horio, M., Yamagata, K., *et al.* (2008). Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. *Hypertens Res*, 31, 433–41.

Isakova, T., Xie, H., Yang, W., *et al.* (2011). Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *JAMA*, 305, 2432–9.

Iseki, K., Ikemiya, Y., Iseki, C., *et al.* (2003). Proteinuria and the risk of developing end stage renal disease. *Kidney Int*, 63, 1468–74.

Iseki, K., Iseki, C., Ikemiya, Y., *et al.* (1996). Risk of developing end-stage renal disease in a cohort of mass screening. *Kidney Int*, 49, 800–5.

Iseki, K., Oshiro, S., Tozawa, M., *et al.* (2001). Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. *Hypertens Res*, 24, 691–7.

Ishani, A., Collins, A. J., Herzog, C. A., *et al.* (2005). Septicemia, access and cardiovascular disease in dialysis patients: the USRDS Wave 2 study. *Kidney Int*, 68(1), 311–18.

Jafar, T. H., Qadri, Z., and Hashmi, S. (2009). Prevalence of microalbuminuria and associated electrocardiographia abnormalities in an Indo-Asian population. *Nephrol Dial Transplant*, 24(7), 2111–16.

James, M. T., Hemmelgarn, B. R., Wiebe, N., *et al.* (2010). Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. *Lancet*, 376(9758), 2096–103.

James, M. T., Laupland, K. B., Tonelli, M., *et al.* (2008). Risk of bloodstream infection in patients with chronic kidney disease not treated with dialysis. *Arch Intern Med*, 168(21), 2333–9.

James, M. T., Quan, H., Tonelli, M., *et al.* (2009). CKD and risk of hospitalization and death with pneumonia. *Am J Kidney Dis*, 54(1), 24–32.

John, R., Webb, M., Young, A., *et al.* (2004). Unreferred chronic kidney disease: a longitudinal study. *Am J Kidney Dis*, 43, 825–35.

Johansen, K. L., Zhang, R., Huang, Y., *et al.* (2009). Survival and hospitalization among patients using nocturnal and short daily compared to conventional hemodialysis: a USRDS study. *Kidney Int*, 76(9), 984–90.

Johnson, D. W., Dent, H., Hawley, C. M., *et al.* (2009). Associations of dialysis modality and infectious mortality in incident dialysis patients in Australia and New Zealand. *Am J Kidney Dis*, 53(2), 290–7.

Keane, W. F., Zhang, Z., Lyle, P. A., *et al.* (2006). Risk scores for predicting outcomes in patients with type 2 diabetes and nephropathy: the RENAAL study. *Clin J Am Soc Nephrol*, 1, 761–7.

Keith, D. S., Nichols, G. A., Gullion, C. M., *et al.* (2004). Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med*, 164, 659–63.

Kovesdy, C. P., Anderson, J. E., Kalantar-Zadeh, K. (2009). Association of serum bicarbonate levels with mortality in patients with non-dialysis dependent CKD. *Nephrol Dial Transplant*, 24, 1232–7.

Kovesdy, C. P., Regidor, D. L., Mehrotra, R. *et al.* (2007). Serum and dialysate potassium concentrations and survival in hemodialysis patients. *Clin J Am Soc Nephrol*, 2(5), 999–1007.

Kurth, T., de Jong, P. E., Cook, N. R., *et al.* (2009). Kidney function and risk of cardiovascular disease and mortality in women: a prospective cohort study. *BMJ*, 338, b2392.

Lafrance, J. P., Djurdjev, O., and Levin, A. (2010). Incidence and outcomes of acute kidney injury in a referred chronic kidney disease cohort. *Nephrol Dial Transplant*, 25(7), 2203–9.

Lameire, N., Eloot, S., Van Biesen, W., *et al.* (2012). Ongoing controversies on the role of frequent hemodialysis and its benefits in patients with ESRD. *NephSAP*, 11, 1–6.

Lee, M., Saver, J. L., Chang, K. H., *et al.* (2010). Low glomerular filtration rate and risk of stroke: meta-analysis. *BMJ*, 341, c4249.

Levey, A. S., de Jong, P. E., Coresh, J., *et al.* (2011). The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*, 80, 17–28.

Levin, A., Djurdjev, O., Beaulieu, M., *et al.* (2008). Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. *Am J Kidney Dis*, 52(4), 661–71.

Levin, A., Thompson, C. R., Ethier, J., *et al.* (1999). Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis*, 34, 125–34.

Li, L., Astor, B., Lewis, J., *et al.* (2012). Longitudinal progression trajectory of GFR among patients with CKD. *Am J Kidney Dis*, 59(4), 504–12.

Li, P. K., Szeto, C. C., Piraino, B., *et al.* (2010). Peritoneal dialysis-related infections recommendations: 2010 update. *Perit Dial Int*, 30(4), 393–423.

Lindeman, R. D. (1998). Is the decline in renal function with normal aging inevitable? *Geriatr Nephrol Urol*, 8, 7–9.

Lindeman, R. D., Tobin, J. D., and Shock, N. W. (1984). Association between blood pressure and the rate of decline in renal function with age. *Kidney Int*, 26, 861–8.

Mahmoodi, B. K., Matsushita, K., Woodward, M., *et al.* (2012). Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. *Lancet*, 380, 1649–61.

Martínez-Castelao, A., Górriz, J., Portolés, J. M., *et al.* (2011). Baseline characteristics of patients with chronic kidney disease stage 3 and stage 4 in Spain: the MERENA observational cohort study. *BMC Nephrol*, 12, 53.

Matsushita, K., van der Velde, M., Astor, B. C., *et al.* (2010). Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*, 375, 2073–81.

McDonald, S., Excell, L., and Livingston, B. (eds.) (2010). *ANZDATA Registry Report 2010*. Adelaide: Australia and New Zealand Dialysis and Transplant Registry.

MDRD Study Group (1991). Assessing the progression of renal disease in clinical studies: effects of duration of follow-up and regression to the mean. *J Am Society Nephrol*, 1, 1087–94.

Menon, V., Tighiouart, H., Smith Vaughn, N., *et al.* (2010). Serum bicarbonate and long term outcomes in CKD. *Am J Kidney Dis*, 56, 907–14.

Mujais, S. (2006). Microbiology and outcomes of peritonitis in North America. *Kidney Int Suppl*, 103, S55–62.

Muntner, P., Hamm, L., Kusek, J. W., *et al.* (2004). The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. *Ann Intern Med*, 140, 9–17.

Muntner, P., He, J., Astor, B. C., *et al.* (2005). Traditional and non-traditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. *J Am Soc Nephrol*, 16, 529–38.

Muntner, P., He, J., Hamm, L., *et al.* (2002). Renal insufficiency and subsequent death resulting from cardiovascualr disease in the United States. *J Am Soc Nephrol*, 13, 45–53.

Nesrallah, G. E., Moist, L. M., Awaraji, C. *et al.* (2004). An international registry to compare quotidian dialysis regimen with conventional thrice weekly hemodialysis: why, how, and potential pitfalls. *Sem Dial*, 17, 131–135.

Nesrallah, G. E., Suri, R. S., Zoller, R. *et al.* (2006). The international quotidian dialysis registry. Annual Reporst 2006. *Hemodial Int*, 10, 219–24.

Nitsch, D., Grams, M., Sang, Y., *et al.* (2013). Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. Chronic Kidney Disease Prognosis Consortium. *BMJ*, 346, f324.

Nitsch, D., Nonyane, B. A., Smeeth, L., *et al.* (2011). CKD and hospitalization in the elderly: a community-based cohort study in the United Kingdom. *Am J Kidney Dis*, 57(5), 664–72.

O'Hare, A. M., Batten, A., Ríos Burrows, N., *et al.* (2012). Trajectories of kidney function decline in the 2 years before initiation of long-term dialysis. *Am J Kidney Dis*, 59(4), 513–22.

Obermayr, R. P., Temml, C., Gutjahr, G., *et al.* (2008). Elevated uric acid increases the risk for kidney disease. *J Am Soc Nephrol*, 19, 2407–13.

Pauly, R. P., Gill, J. S., Rose, C. L., *et al.* (2009). Survival among nocturnal home haemodialysis patients compared to kidney transplant recipients. *Nephrol Dial Transplant*, 24(9), 2915–19.

Pfeffer, M., Burdmann, E. A., Chen, C. Y., *et al.* (2009). The TREAT Investigators. A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease. *N Engl J Med*, 361, 2019–32.

Powe, N. R., Jaar, B., Furth, S. L., *et al.* (1999). Septicemia in dialysis patients: incidence, risk factors, and prognosis. *Kidney Int*, 55(3), 1081–90.

Pun, P. H., Lehrich, R. W., Honeycutt, E. F., *et al.* (2011). Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. *Kidney Int*, 79(2), 218–27.

Quinn, M. P., Cardwell, C. R., Rainey, A., *et al.* (2011). Patterns of hospitalisation before and following initiation of haemodialysis: a 5 year single centre study. *Postgrad Med J*, 87(1028), 389–93.

Raggi, P., Boulay, A., Chasan-Taber, S., *et al.* (2002). Cardiac calcification in adult hemodialysis patients: a link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol*, 39, 695–701.

Ravid, M., Broshd, D., Ravid-Safran, D., *et al.* (1998). Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure and hyperglycemia. *Arch Intern Med*, 158, 998–1004.

Roberts, M. A., Hare, D. L., Ratnaike, S., *et al.* (2006). Cardiovascular biomarkers in CKD: pathophysiology and implications for clinical management of cardiac disease. *Am J Kidney Dis*, 48(3), 341–60.

Ronco, C., Chionh, C. Y., Haapio, M., *et al.* (2009). The cardiorenal syndrome. *Blood Purif*, 27, 114–26.

Sarnak, M. J. and Jaber, B. L. (2000). Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. *Kidney Int*, 58(4), 1758–64.

Sarnak, M. J. and Jaber, B. L. (2001). Pulmonary infectious mortality among patients with end-stage renal disease. *Chest*, 120(6), 1883–7.

Sarnak, M. J., Levey, A. S., Schoolwerth, A. C., *et al.* (2003). Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*, 108, 2154–69.

Shlipak, M. G., Fired, L. F., Crump, C., *et al.* (2003). Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation*, 107, 87–92.

Shiplak, M. G., Fired, L. F., Cushman, M., *et al.* (2005). Cardiovascular mortality risk in chronic kidney disease—comparison of traditional and novel risk factors. *JAMA*, 293, 1737–45.

Shlipak, M. G., Heidenreich, P. A., Noguchi, H., *et al.* (2002). Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med*, 137, 555–62.

Shlipak, M. G., Katz, R., Kestenbaum, B., *et al.* (2009). Rapid decline of kidney function increases cardiovascular risk in the elderly. *J Am Soc Nephrol*, 20(12), 2625–30.

Siu, Y. P., Leung, K. T., Tong, M. K., *et al.* (2006). Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *Am J Kidney Dis*, 47, 51–9.

Slinin, Y., Foley, R. N., Collins, A. J. (2006). Clinical epidemiology of pneumonia in hemodialysis patients: the USRDS waves 1, 3, and 4 study. *Kidney Int*, 70(6), 1135–41.

Smith, G. L., Lichtman, J. H., Bracken, M. B., *et al.* (2006). Renal impairment and outcomes in heart failure: systematic review and meta-analysis. *J Am Coll Cardiol*, 47, 1987–96.

Sood, M. M., Komenda, P., Sood, A. R., *et al.* (2010). Adverse outcomes among Aboriginal patients receiving peritoneal dialysis. *CMAJ*, 182(13), 1433–9.

Tangri, N., Stevens, L. A., Griffith, J., *et al.* (2011). A predictive model for progression of chronic kidney disease to kidney failure. *JAMA*, 305(15), 1553–7.

Tonelli, M., Wiebe, N., Culleton, B., *et al.* (2006). Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol*, 17, 2034–47.

Uchino, S., Kellum, J. A., Bellomo, R., *et al.* (2005). Acute renal failure in critically ill patients: a multinational, multicentre study. *JAMA*, 294(7), 813–18.

United States Renal Data System (2004). *USRDS 2004 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

United States Renal Data System (2009). *USRDS 2009 Annual Data Report: Volume One: Atlas of Chronic Kidney Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

United States Renal Data System (2010). Excerpts from USRDS 2009 Annual Data Report. US. Department of Health and Human Services. *Am J Kidney Dis*, 55(Suppl 1), S1.

United States Renal Data System (2011). *USRDS 2011 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Van der Velde, N., Matsushita, K., Coresh, J., *et al.* (2011). Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high risk population cohorts. *Kidney Int*, 79(12), 1341–52.

Wang, A. Y., Lam, C. W., Chan, I. H., *et al.* (2010). Sudden cardiac death in end-stage renal disease patients: a 5-year prospective analysis. *Hypertension*, 56, 210–16.

Wang, H. E., Gamboa, C., Warnock, D. G., *et al.* (2011). Chronic kidney disease and risk of death from infection. *Am J Nephrol*, 34(4), 330–6.

Watanabe, H., Watanabe, T., Sasaki, S., *et al.* (2009). Bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. *Am Heart J*, 158, 629–36.

Wen, C. P., Cheng, T. Y., Tsai, M. K., *et al.* (2008). All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. *Lancet*, 371(9631), 2173–82.

Wen, C. P., David Cheng, T. Y., Chan, H. T., *et al.* (2010). Is high serum uric acid a risk marker or a target for treatment? Examination of its independent effect in a large cohort with low cardiovascular risk. *Am J Kidney Dis*, 56, 273–88.

White, S. L., Polkinghorne, K. R., Atkins, R. C., *et al.* (2010). Comparison of the Prevalence and Mortality Risk of CKD in Australia Using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR Estimating Equations: The AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. *Am J Kidney Dis*, 55(4), 660–70.

Young, B. A. (2011). Prevention of sudden cardiac arrest in dialysis patients: can we do more to improve outcomes? *Kidney Int*, 79, 147–9.

Young, J. M., Terrin, N., Wang, X., *et al.* (2009). Asymmetric dimethylarginine and mortality in stages 3 to 4 chronic kidney disease. *Clin J Am Soc Nephrol*, 4(6), 1115–22.

CHAPTER 98

Cardiovascular disease and chronic kidney disease: overview

David J. Goldsmith

Introduction

Many studies in various populations have reported that reduced estimated glomerular filtration rate (eGFR) and raised albuminuria are associated with cardiovascular disease (CVD). Data from 31 published and unpublished cohort studies involving > 1.4 million individuals were assessed in meta-analyses. After adjustment for traditional cardiovascular risk factors and albuminuria, the risk gradient for cardiovascular mortality changed little when eGFR was > 75 mL/min/1.73 m^2 but increased linearly once < 75 mL/min/1.73 m^2.

Cardiovascular mortality was about twice as high in patients with stage 3 chronic kidney disease (CKD) and three times higher at stage 4 than that in individuals with normal kidney function. In contrast to the non-linear risk relationship for eGFR, the association of albuminuria with cardiovascular risk has no threshold effect, even after adjustment for traditional cardiovascular risk factors and eGFR. The adjusted risk of cardiovascular mortality is more than doubled at the upper end of the microalbuminuria category (3–30 mg/mmol, 30–300 mg/g), compared with the risk in individuals with normal albuminuria.

This lack of threshold effect indicates that albuminuria even at the upper end of the normal range (threshold 3 mg/mmol, 30 mg/g) confers cardiovascular risk. This is independent of, but additive to, diabetes and raised blood pressure (BP) (Fig. 98.1) (see Chapter 97).

The proportion of deaths from CVD increases as eGFR declines. In a Canadian cohort, when adjusted for age and sex, CVD accounted for 27.5% of deaths in individuals with normal kidney function versus 58.0% in those with kidney failure. A similar increase in the proportion of deaths due to CVD is observed among people with raised albuminuria.

When adjusted for gender, life expectancy due to CVD is shortened by 1.3, 7.0, 12.5, and 16.7 years, respectively, in patients aged 30 years with eGFR stages 3A, 3B, 4, and 5 (45–59, 30–44, 15–29, and < 15 mL/min/1.73 m^2, respectively), compared with that in individuals with normal kidney function. Kidney transplantation does not completely correct this deficit in longevity.

Pathophysiology

Increased cardiovascular risk in individuals with CKD is due partly to the high prevalence of traditional risk factors, such as raised BP and diabetes. Smoking too has a most malign influence on both the heart and the kidney in CKD (see Chapter 103).

Raised blood pressure

Raised BP is both a familiar and strong risk factor for development of CKD. Even in its earliest manifestations, CKD tends to raise BP, which is likely to increase cardiovascular risk in affected patients (see Chapter 100). Data from cohort studies suggest that antihypertensive therapy would more effectively reduce cardiovascular risk in patients with CKD than in those without this disorder. Few prospective studies, however, support this assumption. A target BP of < 140/90 mmHg is considered appropriate to prevent CVD in patients with CKD, but a BP target of < 130/80 mmHg is now widely recommended for albuminuric patients (see Chapter 99).

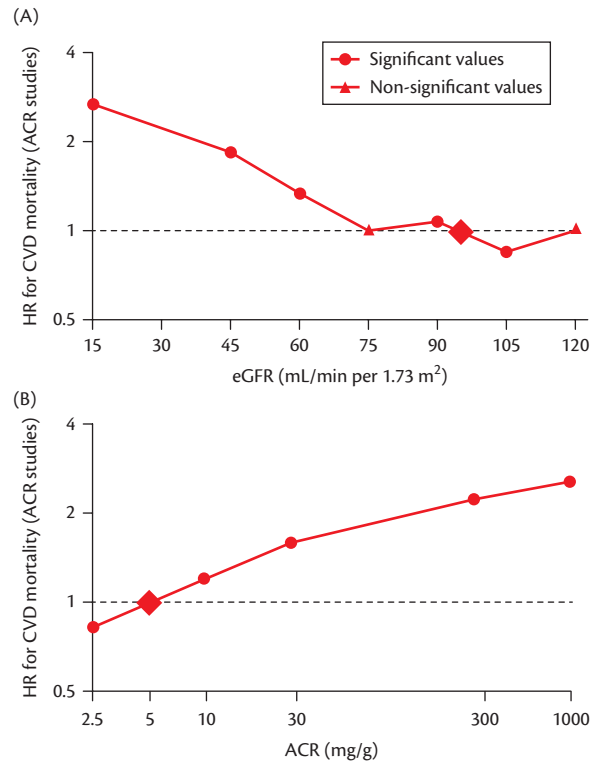

Fig. 98.1 The proportion of deaths from cardiovascular disease increases as eGFR declines.
From Gansevoort et al. (2013).

Left ventricular hypertrophy, sudden cardiac death, and cardiomyopathy

In patients with early or advancing CKD, the prevalence of left ventricular hypertrophy (LVH) (see Chapter 107) is strikingly increased. When eGFR is < 30 mL/min/1.73 m^2, around 50% of patients develop LVH, of which most is concentric hypertrophy. Apart from hypertension, renal anaemia (see Chapter 123) and increased vascular stiffness (see Chapter 111) seem to have pivotal roles in development of LVH and thus reduced coronary reserve. The latter could be aggravated by reduced cardiac capillary density in CKD and impaired coronary dilatory responses. Expression of endothelial nitric-oxide synthase is downregulated, which suggests a possible mechanism for coronary endothelial dysfunction in early stages of CKD. Histologically, LVH in CKD is characterized by myocardial fibrosis that is thought to impair contractility when severe. The high prevalence of LVH, with its associated risk of cardiac-rhythm disturbances, could at least partly explain why the prevalence of sudden cardiac death (see Chapter 108) is increased in people with CKD. In the general population, sudden cardiac death accounts for roughly one death per 1000 person-years and for around 5–10% of all deaths, whereas among individuals with kidney failure, the rates are around 50–60 deaths per 1000 person-years and 25% of total mortality (nearly half of all CV mortality). Besides the high prevalence of LVH, abnormal electrolyte concentrations and increased prevalence of coronary artery disease are predisposing factors for sudden cardiac death in patients with CKD.

Atherosclerosis and valvular heart disease are frequently seen in patients with kidney failure, but also occur in those with early CKD. The key modulators in this field have not been elucidated in intervention trials, but seem likely to include calcification inhibitors (e.g. fetuin-A and matrix Gla protein), promoters (e.g. hyperphosphataemia), and calcium-phosphate product, parathyroid hormone, and leptin. (See Chapters 115 and 120).

Distinguishing heart failure from volume overload in patients with advanced CKD can be difficult, but there seems little doubt that volume control is important in preventing heart failure as well as in treating it (see Chapters 107 and 268).

Cardiorenal syndrome (CRS) is a group of diagnoses defined as disorders of the heart and kidney, whereby dysfunction in one organ may induce dysfunction in the other. The umbrella term and discrete subtypes (Table 98.1) were developed by the Acute Dialysis Quality Initiative (ADQI) to emphasize the bidirectional pathways and to provide context for identification of the complex pathophysiological interactions occurring in different types of combined heart and kidney disorders (House et al., 2010).

The value of a concept of a specific (or several) cardiorenal syndromes is not clear.

Table 98.1 Discrete subtypes of cardiorenal syndrome as defined by the ADQI

Name		Description
Acute cardiorenal syndrome	Type 1	Acute worsening of cardiac function leading to renal dysfunction
Chronic cardiorenal syndrome	Type 2	Chronic abnormalities in cardiac function leading to renal dysfunction
Acute renocardiac syndrome	Type 3	Acute worsening of renal function causing cardiac dysfunction
Chronic renocardiac syndrome	Type 4	Chronic abnormalities in renal function leading to cardiac disease
Secondary cardiorenal syndromes	Type 5	Systemic conditions causing simultaneous dysfunction of the heart and kidney

ADQI: Acute Dialysis Quality Initiative.

Lipids, oxidative stress, inflammation, endothelial function, and advanced glycation end products

Dyslipidaemia and low-grade inflammation are also caused by CKD (see Chapters 102 and 110). In patients with impaired kidney function and high albuminuria, lipid profiles become atherogenic, owing partly to defective high-density lipoprotein cholesterol function and excessive oxidation of low-density lipoprotein cholesterol. Mechanisms of increased systemic inflammation in CKD are unclear, but increased production of inflammatory mediators has been attributed to raised oxidative stress (see Chapter 112) and accumulation of postsynthetically modified proteins and toxins that are cleared with normal renal function. Advanced glycation end products (AGEs) and receptors for AGEs (RAGEs) are much studied in CKD and may be both markers and drivers of CVD.

Renin–angiotensin system, renalase, and asymmetric dimethylarginine

Other factors that raise cardiovascular risk in patients with CKD include increased activity of the renin–angiotensin system and sympathetic nerve activity in CKD. Angiotensin stimulates production of superoxide, interleukin 6, and other cytokines (see Chapter 110). Bioavailability of nitric oxide, which is involved with vascular smooth-muscle contraction and growth, platelet aggregation, and leucocyte adhesion to the endothelium, becomes decreased (see Chapter 113). Activity of renalase is lowered in individuals with CKD. This enzyme is produced by the kidney and inactivates catecholamines. All these vasoactive factors impinge on endothelial function (see Chapter 113). Another key factor for endothelial function seems to be asymmetric dimethylarginine (ADMA). Plasma ADMA concentrations increase with decreasing kidney function and predict mortality and cardiovascular complications in CKD patients (see Chapter 113). ADMA inhibits generation of nitric oxide, reduces cardiac output, and raises both systemic vascular resistance and BP. Increased concentrations of ADMA and sympathetic overactivity are strongly associated with concentric LVH.

Mineral and bone metabolites

Patients with impaired kidney function frequently develop deficiency of active vitamin D because of a lack of its precursor, impaired activity of the kidney enzyme 1 α-hydroxylase, which converts this precursor to the active hormone, or both. Observational studies in patients with CKD have shown associations between vitamin D deficiency and increased risk of cardiovascular events, and experimental data suggest that the vitamin D pathway is involved in modifying cardiac structure and function. Elevated serum phosphate, fibroblast growth factor 23, and calcium concentrations have both been associated with the development of future CVD in CKD, and also in the general, populations—as yet no interventional study has tested whether these associations are causal. (See Chapter 115.)

Conclusions

Too few randomized controlled trials have been conducted into prevention of CVD in this most susceptible CKD population; indeed, much effort has been expended to exclude CKD patients from the majority of CVD trials. Until this ends, while we can make long lists of associations and risk factors, we can make comparatively much shorter lists of useful, practical, proven interventions.

Further reading

Blood Pressure Lowering Treatment Trialists' Collaboration, Ninomiya, T., Perkovic, V., *et al.* (2013). Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. *BMJ*, 347, f5680.

Block, G. A., Ix, J. H., Ketteler, M., *et al.* (2013). Phosphate homeostasis in CKD: report of a scientific symposium sponsored by the National Kidney Foundation. *Am J Kidney Dis*, 62(3), 457–73.

Clementi, A., Virzì, G. M., Goh, C. Y., *et al.* (2013). Cardiorenal syndrome type 4: a review. *Cardiorenal Med*, 3(1), 63–70.

Gustafsson, D. and Unwin, R. (2013). The pathophysiology of hyperuricaemia and its possible relationship to cardiovascular disease, morbidity and mortality. *BMC Nephrol*, 14, 164.

Huang, Y., Cai, X., Zhang, J., *et al.* (2014). Prehypertension and Incidence of ESRD: a Systematic Review and Meta-analysis. *Am J Kidney Dis*, 63(1), 76–83.

Jain, G. and Jaimes, E. A. (2013). Nicotine signaling and progression of chronic kidney disease in smokers. *Biochem Pharmacol*, 86(8), 1215–23.

Khan, U. A., Garg, A. X., Parikh, C. R., *et al.* (2013). Prevention of chronic kidney disease and subsequent effect on mortality: a systematic review and meta-analysis. *PLoS One*, 8(8), e71784.

Lambers Heerspink, H. J. and de Zeeuw, D. (2013). Novel drugs and intervention strategies for the treatment of chronic kidney disease. *Br J Clin Pharmacol*, 76(4), 536–50.

Lv, J., Ehteshami, P., Sarnak, M. J., *et al.* (2013). Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. *CMAJ*, 185(11), 949–57.

Moradi, H., Sica, D. A., and Kalantar-Zadeh, K. (2013). Cardiovascular burden associated with uremic toxins in patients with chronic kidney disease. *Am J Nephrol*, 38(2), 136–48.

Waheed, A. A., Pedraza, F., Lenz, O., *et al.* (2013). Phosphate control in end-stage renal disease: barriers and opportunities. *Nephrol Dial Transplant*, 28(12), 2961–8.

References

Gansevoort, R. T., Correa-Rotter, R., Hemmelgarn, B. R., *et al.* (2013). Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet*, 382(9889), 339–52.

House, A. A., Anand, I., Bellomo, R., *et al.* (2010). Definition and classification of Cardio-Renal Syndromes: workgroup statements from the 7th ADQI Consensus Conference. *Nephrol Dial Transplant*, 25(5), 1416–20.

CHAPTER 99

Recommendations for management of high renal risk chronic kidney disease

Charles J. Ferro and Khai Ping Ng

Introduction

Worsening chronic kidney disease (CKD) is associated with increasing morbidity and mortality, mainly as a consequence of cardiovascular disease (Fig. 99.1) (Matsushita et al., 2010). Population studies have consistently shown that people with CKD identified by screening have a far greater likelihood of cardiovascular death than progression to end-stage renal disease (ESRD) (Keith et al., 2008). Preventing further deterioration of renal function and reducing the cardiovascular risk in this population is essential to improve the clinical outcomes of CKD patients.

The concept that CKD is a single entity with generic treatment is clearly a huge oversimplification and requires that CKD be viewed as a single process despite a range of primary diseases. Nevertheless it is a useful concept and is supported by the effectiveness of some generic therapies and on data suggesting final common physiological pathways underlie the progression of CKD irrespective of the initiating causation (Turner et al., 2012) (see Chapter 136). Indeed, extensive studies have shown that the rate of loss of renal function may be largely due to common secondary factors often unrelated to the original renal disease. These factors are often also cardiovascular risk factors and so preventing the progression of CKD and reducing cardiovascular risk often are not mutually exclusive but indeed complementary.

Even though the risk of progressive kidney disease and cardiovascular disease increases with even minimal renal impairment and microalbuminuria (Fig. 99.1), there is a much higher risk when the estimated glomerular filtration rate (eGFR) falls significantly below 60 mL/min/1.73 m^2 especially in the presence of proteinuria (Levey et al., 2011; Turner et al., 2012). This chapter will focus on the management of these high-risk patients. Given that many local, national, and international societies produce their own, often frequently updated, guidelines on the management of CKD a selection of useful websites is given in Box 99.1.

The increasing use of treatments to attenuate CKD progression has coincided with a plateau of ESRD incidence in the United States and United Kingdom in the last few years (Byrne et al., 2010). However, incidence is still high and the field has not seen a truly new preventative therapy in over a decade. Nevertheless there is a growing literature that multidisciplinary programmes including patient education and using evidence-based guidelines can slow down the progression of CKD, decrease hospitalizations, improve arteriovenous fistula creation before haemodialysis, and decrease mortality both before and after the initiation of dialysis (Lee et al., 2007; Snyder et al., 2009). These programmes have been found to be cost-effective.

Interventions influencing prognosis

Hypertension

Whereas the evidence that blood pressure lowering confers renal and cardiovascular protection is clear, the optimal level of blood pressure control is less well established. The MDRD Study showed that the level of proteinuria significantly modulates the effect of blood pressure lowering such that a lower blood pressure target (≤ 125/75 mmHg vs ≤ 140/90 mmHg) was associated with a slower rate of GFR decline among patients with > 1 g/day of proteinuria. Secondary analysis revealed significant correlations between rate of GFR decline and achieved blood pressure and long-term follow-up showed lower mortality and incidence of ESRD randomized to the low blood pressure target (Peterson et al., 1995). The African American Study of Kidney Disease and Hypertension (AASK) study did not show any additional benefit in targeting a blood pressure lower than 140/90 mmHg although there was a trend for this in patients with proteinuria consistent with the MDRD study (Wright et al., 2002).

Several studies have suggested worse patient and renal outcomes with low achieved blood pressure (systolic 110–120 mmHg) (Cushman et al., 2010) There is therefore no evidence to support lowering blood pressure to below a systolic pressure of 120 mmHg and caution should be exercised particularly in patients who may suffer harm from excessive lowering of blood pressure such as patients with autonomic neuropathy or postural hypotension.

The inherent difficulty associated with setting specific numeric targets for blood pressure control as well as the limited nature of the supporting evidence has recently been discussed in detail (Lewis, 2010). On balance, systolic blood pressure should be controlled to < 140 mmHg and the diastolic blood pressure to < 90 mmHg. For patients with significant proteinuria (urine albumin:creatinine ratio > 70 mg/mmol; urine protein:creatinine ratio > 100 mg/mmol; 24-hour urinary protein excretion > 1 g) or diabetes and CKD, a lower blood pressure (< 130/80 mmHg) is desirable. Lowering

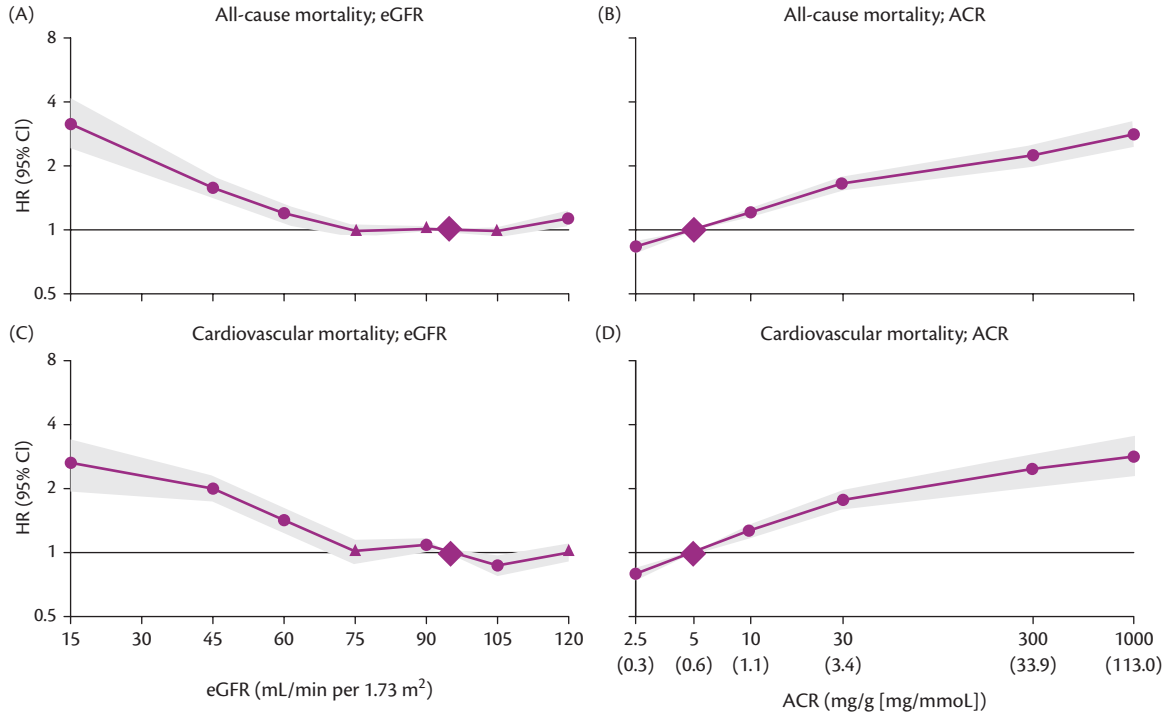

Fig. 99.1 Hazard ratios and 95% confidence intervals (CIs) for all-cause and cardiovascular mortality according to spline estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR). Hazard ratios and 95% CIs (shaded areas) according to eGFR (A, C) and ACR (B, D) adjusted for each other, age, sex, ethnic origin, history of cardiovascular disease, systolic blood pressure, diabetes, smoking, and total cholesterol. The reference (diamond) was eGFR 95 mL/min/1.73 m^2 and ACR 5 mg/g (0.6 mg/mmol), respectively. Circles represent statistically significant and triangles represent not significant. ACR plotted in mg/g. To convert ACR in mg/g to mg/mmol multiply by 0.113. Approximate conversions to mg/mmol are shown in parentheses. From Gansevoort et al. (2013).

systolic blood pressure to < 120 mmHg should be avoided according to some guidance. However, this probably should not apply to teenagers or young adults and on occasion it may be useful to relate blood pressures to age norms. In the major paediatric study on control of blood pressure in CKD, a target of below the median for age was used rather than an absolute value (Escape Trial Group, 2009).

Use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers

Several large prospective randomized controlled trials among different groups of patients with CKD provide evidence that angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) afford significant renal protection in addition to that attributable to blood pressure lowering. Specifically, ACEI treatment reduces CKD progression in patients with diabetic nephropathy (Lewis et al., 1993) and in non-diabetic patients with proteinuria > 1 g/day (Wright et al., 2002). Treatment with ACEIs, compared with other antihypertensive drugs, significantly lowers the incidence of ESRD after adjustment for differences in level of blood pressure control. However, the benefit appears to be confined to patients with proteinuria > 0.5g/day (Casas et al., 2005). ARB treatment has also been shown to afford significant renal protection in patients with established diabetic nephropathy (Brenner et al., 2001; Lewis et al., 2001).

Microalbuminuria is strongly positively associated with an increased risk of cardiovascular morbidity and mortality (Fig. 99.1). ACEIs and ARBs appear to be superior to more conventional antihypertensive therapies at reducing urinary albumin excretion in diabetic, non-diabetic, and hypertensive populations (Brenner et al., 2001; Lewis et al., 2001). There is also a large body of evidence indicating that ACEI or ARB treatment reduces or delays progression from microalbuminuria to overt nephropathy and reduces cardiovascular risk in diabetic patients with microalbuminuria (Jafar et al., 2003).

A number of small studies have suggested that using higher doses of an ACEI or ARB or indeed using a combination of these agents might result in superior outcomes, especially in reducing progression of kidney disease, compared to using conventional doses of single agents. This approach has, however, recently been called into question by both the withdrawal of the COOPERATE study (Kunz et al., 2008) and the publication of the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) (Mann et al., 2008). This large-scale trial found that using a fixed dose combination of an ACEI and ARB resulted in worse renal outcomes (Mann et al., 2008). The injudicious use of ACEIs and ARBs in patients with CKD has further been called into question by investigators suggesting that they may increase the rate of progression in some patient groups, especially those with advanced CKD (Goncalves et al., 2011). Current evidence does not support the use of ACEI or ARB treatment for all patients with CKD.

Large prospective randomized controlled studies have reported significant reductions in cardiovascular morbidity and mortality associated with ACEI treatment (Yusuf et al., 2000; Fox, 2003). Interestingly, secondary analysis of the Prevention of Events with ACEI (PEACE) trial found a significant reduction in all-cause

Box 99.1 Online sources of guidelines

Nephrology guidelines

Kidney Disease: Improving Global Outcome (KDIGO)
<http://www.kdigo.org>
European Renal Best Practice (ERBP)
<http://www.era-edta.org/page-8-38-0-38-erbpeuropeanrenalbestpractice.html>
Renal Association Guidelines (United Kingdom)
<http://www.renal.org/Clinical/GuidelinesSection/Guidelines.aspx>
National Institute for Health and Care Excellence (NICE) guidelines on CKD
<http://www.nice.org.uk/CG73>
National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF KDOQI) (United States)
<http://www.kidney.org/professionals/kdoqi/guidelines_commentaries.cfm>
Caring for Australasians with Renal Impairment (CARI) guidelines (Australia)
<http://www.cari.org.au/guidelines.php>

Cardiovascular guidelines

World Health Organization cardiovascular guidelines
<http://www.who.int/cardiovascular_diseases/guidelines/Pocket_GL_information/en/index.html>
National Institute for Health and Care Excellence (NICE) guidelines on cardiovascular disease
<http://www.nice.org.uk/guidance/index.jsp?action=byTopic&o=7195>
American College of Cardiology/American Heart Association (ACC/AHA) joint guidelines
<http://my.americanheart.org/professional/StatementsGuidelines/ACCAHA-Joint-Guidelines_UCM_321694_Article.jsp>
National Heart Lung and Blood Institute guidelines (United States)
<http://www.nhlbi.nih.gov/guidelines/current.htm>

Hypertension guidelines

World Health Organization/International Society of Hypertension guidelines
<http://www.who.int/cardiovascular_diseases/guidelines/hypertension/en/>
British Hypertension Society guidelines
<http://www.bhsoc.org/>
America Society of Hypertension guidelines
<http://www.ash-us.org/For-Professionals/Position-Papers.aspx>
National Heart Lung and Blood Institute guidelines (United States)
<http://www.nhlbi.nih.gov/guidelines/current.htm>

mortality associated with ACEI treatment in the CKD subgroup but not in patients with normal renal function (Solomon et al., 2006). It would, therefore, seem reasonable to use ACEI or ARB treatment for reduction of cardiovascular risk as well as slowing of CKD progression.

Direct renin inhibitors and mineralocorticoid receptor inhibitors have shown some promise when combined with ACEIs or ARBs in small studies looking at surrogate endpoints (Parving et al., 2008; Edwards et al., 2009). However, larger hard outcome studies are needed before these agents are recommended for routine use in CKD patients. Indeed, the recent ALTITUDE trial examined the use of a direct renin inhibitor (DRI) combined with ARB therapy in patients with diabetic nephropathy was terminated early due to safety concerns in view of the elevated incidence adverse events.

In summary, ACEI or ARB treatment should form part of the antihypertensive therapy of patients with CKD and urinary protein excretion of > 0.5 g/day unless there is a specific contraindication. Patients with CKD and proteinuria > 0.5 g/day should have their ACEI or ARB and other antihypertensive treatment escalated to achieve the lowest possible level of proteinuria. Similarly, patients with diabetes mellitus and microalbuminuria should be treated with an ACEI or ARB, unless there is a specific contraindication. The use of 'dual-blockade' with various combinations of ACEI/ARB/DRI has so far been proven disappointing.

Hyperlipidaemia

Despite prior evidence to suggest that lipid-lowering with statins had a small but significant effect on CKD progression by reducing annual decline by 1.22 mL/min/year compared with placebo (Sandhu et al., 2006) as well as reducing proteinuria (Douglas et al., 2006), the largest study of lipid-lowering in CKD patients (SHARP; Study of Heart and Renal Protection) failed to demonstrate benefit in terms of slowing CKD progression (Baigent et al., 2011). The study did however show cardiovascular benefits. Lipids in CKD are discussed in Chapter 102.

Statins are a well-established treatment to reduce cardiovascular risk in a wide range of populations for both primary and secondary prevention. The benefits are effective regardless of baseline cholesterol levels, with an approximate 20% reduction in the 5-year risk of cardiovascular events per 1 mmol/L reduction in serum cholesterol.

Post hoc analysis and meta-analysis of studies, which included some patients with CKD, demonstrated that statins remained effective at reducing cardiovascular risk and mortality (Strippoli et al., 2008). The CKD patients included in these studies had relatively mild CKD and most were included in these trials because of other cardiovascular risk factors and not because of CKD per se. In general, CKD patients have a very similar reduction (~ 20%) in cardiovascular mortality to the general population with a 1 mmol/L reduction in low-density lipoprotein cholesterol (Strippoli et al., 2008). These findings have been confirmed by the SHARP study (Baigent et al., 2011).

To justify primary prevention with lipid-lowering therapy, an estimate of cardiovascular risk is required. Available tools to assess cardiovascular risk do not adequately incorporate the impact of reduced GFR or increased proteinuria. Until such revised tools are available, and given the lack of specific evidence for intervention in the CKD population, the standard tools should probably continue to be used despite the expected higher risk. See also Chapter 102.

Dietary protein

Dietary protein restriction was one of the earliest treatments used in CKD and it is reviewed in Chapter 101. In summary, while protein restriction has been shown to ameliorate symptoms associated with advanced CKD its effects on progression of earlier CKD are less clear-cut. It lowers phosphate and uric acid intake, as well as improving metabolic acidosis (Turner et al., 2012). Protein restriction has been shown in many animal studies to reduce CKD progression possibly by lowering glomerular hyperfiltration and fibrosis (Turner et al., 2012). However, clinical trials have been much less clear as to its efficacy, perhaps because blood pressure and other factors were better controlled. The largest and best study so far, the MDRD Study showed no effect (Klahr et al., 1994). A meta-analysis did find a reduced requirement for dialysis associated with restricted protein diets in non-diabetic CKD (Fouque et al., 2009) but this is difficult to interpret when the best study produced a different result. In the meta-analysis, because of study heterogeneity an optimum level of protein intake could not be suggested.

While most agree that high-protein diets are likely to be hazardous (Chapter 101) substantial protein restriction requires a significant amount of effort from physicians, dieticians, and patients if it is also to be safe. Careful monitoring of nutritional status is required to avoid malnutrition. Provided the burden is acceptable to the patient and malnutrition is avoided, a target of 0.8 g of protein per kg body weight per day seems reasonable (Turner et al., 2012). See also Chapter 101.

Dietary salt

Western populations consume substantially higher amounts of sodium than is necessary, and this is associated with a higher prevalence of hypertension and cardiovascular disease (Bibbins-Domingo et al., 2010). There is relatively little evidence on whether a high sodium intake is specifically associated with poorer renal outcomes, or whether reducing sodium intake improves renal outcomes. However, given the impact of sodium reduction on blood pressure (Vollmer et al., 2001), and the known impact of high blood pressure on renal function and proteinuria, it seems sensible to adopt the general population recommendation of maintaining dietary sodium at < 2.4 g/day (100 mmol/day or < 6 g/day of salt). See also Chapter 101.

Acidosis

The concentration of hydrogen ions is normally managed by several buffering and elimination systems, including the kidney. Lower blood pH and reduced plasma bicarbonate levels thus accompany deterioration of renal function, especially when the GFR falls below 20mL/min/1.73 m^2 (Hsu et al., 2002). Some experimental evidence as well as small studies in humans have suggested that lightening the acid load could stabilize or temporarily improve renal function. A randomized controlled trial in 134 patients with CKD demonstrated improvements in the rate of decline of renal function as well as a decrease in the need for dialysis in patients treated with sodium bicarbonate (de Brito-Ashurst et al., 2009). While further larger and confirmatory studies are awaited it would seem reasonable to treat patients with evidence of acidosis on blood tests with oral sodium bicarbonate given its simplicity, safety, and low cost. This is described further in Chapter 148.

Smoking

Smoking has been identified as a risk factor for the development and progression of CKD (Yoshida et al., 2008) (Chapter 103). A small study has also intriguingly suggested that stopping smoking may slow down the rate of renal function deterioration (Schiffl et al., 2002). Regardless, the clear evidence of smoking as a risk factor for cardiovascular and respiratory disease makes smoking cessation a critical intervention for improving survival in CKD patients. See also Chapter 103.

Interventions with uncertain or no effect on prognosis

Chronic kidney disease–mineral and bone disorder

Although there are strong associations between markers of mineral bone disease in CKD (CKD-MBD), including associations of mortality with serum phosphate levels in the general population as well as in patients with advanced CKD (Fig. 99.2) (Chue et al., 2010, 2011), it has been hard to prove that any interventions benefit progression of CKD or mortality, even in patients on dialysis. This is discussed further in Chapters 109, 117, and 118.

Anaemia

Renal anaemia is considered in detail in Chapter 123. Anaemia was hypothesized to play a role in the early development of cardiovascular disease but the publication of several trials including CREATE (Drueke et al., 2006), CHOIR (Singh et al., 2006), and in particular the placebo-controlled TREAT (Pfeffer et al., 2009) have challenged the 'cardiovascular' rationale behind anaemia correction to higher targets. It is now recognized that complete anaemia correction is not advisable but partial correction may still be important, with different targets applying to different subgroups (Locatelli et al., 2009).

Uric acid

Hyperuricaemia increases as GFR declines. Uric acid is clearly toxic to the kidney in very high concentrations such as in tumour lysis. However, whether more modest elevations are detrimental is much less clear (Filiopoulos et al., 2012), although there is evidence from small trials that lowering uric acid concentrations with allopurinol is associated with improvements in surrogate markers of cardiovascular disease (Filiopoulos et al., 2012). The little evidence available

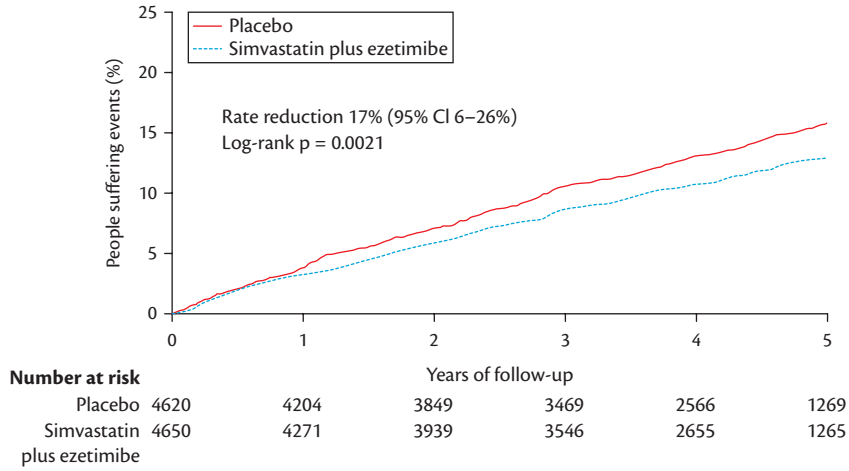

Fig. 99.2 Life-table plot of effects of allocation to simvastatin plus ezetimibe versus placebo on major atherosclerotic events. Numbers remaining at risk of a first major atherosclerotic event at the beginning of each year are shown for both treatment groups. From Baigent et al. (2011).

together with the occasional risk of severe allergic reactions to allopurinol make recommending routine lowering of uric acid difficult except in the context of recurrent gout.

Obesity

Obesity is associated with a number of conditions known to increase the risk of CKD including hypertension, diabetes mellitus, and heart failure (Guh et al., 2009), and its impact on CKD is considered in detail in Chapter 106. However, the evidence that obesity is an independent risk factor for CKD or associated with increased rate of progression is limited. Intriguingly, small studies in patients after bariatric surgery show improvements in blood pressure control, proteinuria, and inflammatory markers as well as in GFR although this last parameter needs to be interpreted with caution and confirmed in larger studies with harder endpoints (Navaneethan et al., 2009). Nevertheless, given the negative impact of obesity on general and cardiovascular health it makes sense to recommend weight loss using lifestyle modification, in patients with CKD.

Exercise

Patients with CKD have reduced exercise capacity and muscle strength which can improve with the introduction of an exercise programme (Kosmadakis et al., 2012). Regular, moderate exercise reduces cardiovascular risk in the general population (Paffenbarger, 2000). Although there is no solid evidence that regular exercise improves cardiovascular or renal outcomes in patients with CKD, the positive impact exercise has on general health and as part of a weight-loss programme makes it seem reasonable to recommend regular moderate exercise to CKD patients.

Glycaemic control in diabetes mellitus

Observational studies suggest that HbA1C influences cardiovascular event rates and survival (Coresh et al., 2007). There is also strong evidence that improved glycaemic control prevents the development of microalbuminuria, progression of renal dysfunction, and microvascular complications in patients with both type 1 and 2 diabetes mellitus as well as reducing cardiovascular events and improving overall survival (de Boer et al., 2011).

The precise level of glycaemic control to be achieved remains somewhat controversial. Recent randomized trials have indicated that aiming for more intensive glycaemic control may be associated with adverse events, mainly hypoglycaemia, and increased overall mortality (Gerstein et al., 2011). Whereas the benefits of good glycaemic control are well established, the potential risks should also be considered and therapeutic targets should therefore be individualized and agreed with the patient.

Hyperhomocystinuria, vitamin B_{12}, and folate deficiency

Higher homocysteine levels are associated with increased mortality and vascular disease in the general population and in patients with CKD (Zoccali et al., 2007). Homocysteine levels are higher in patients with all levels of renal impairment (Ganji et al., 2003), and are approximately three times higher in patients with ESRD (Heinz et al., 2009). Homocysteine levels can be reduced by supplementation with folic acid by approximately 25%, and vitamin B_{12} by approximately 7%. Trials of folate supplementation in both the general and CKD population, however, have failed to show any benefit (Lonn et al., 2006; Vianna et al., 2007).

There are of course sound haematopoietic rationales for the use of folate supplements if there is anaemia or macrocytosis which can be attributed to folate deficiency. Indeed, correction of folate deficiency is generally good clinical practice irrespective of putative effects on homocysteine levels or vascular disease risk.

References

Baigent, C., Landray, M. J., Reith, C., *et al.* (2011). The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*, 377, 2181–92.

Bibbins-Domingo, K., Chertow, G. M., Coxson, P. G., *et al.* (2010). Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med*, 362, 590–9.

Brenner, B. M., Cooper, M. E., de Zeeuw, D., *et al.* (2001). Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*, 345, 861–9.

Byrne, C., Ford, D., Gilg, J., *et al.* (2010). UK Renal Registry 12th Annual Report (December 2009): chapter 3: UK ESRD incident rates in 2008: national and centre-specific analyses. *Nephron Clin Pract*, 115 Suppl 1, c9–39.

Casas, J. P., Chua, W., Loukogeorgakis, S., *et al.* (2005). Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet*, 366, 2026–33.

Chue, C.D., Edwards, N.C., Davis, L.J., *et al.* (2011). Serum phosphate but not pulse wave velocity predicts decline in renal function in

patients with early chronic kidney disease. *Nephrol Dial Transplant*, 26, 2576–82.
Chue, C. D., Townend, J. N., Steeds, R. P., or delete from list. (2010). Arterial stiffness in chronic kidney disease: causes and consequences. *Heart*, 96, 817–23.
Coresh, J., Selvin, E., Stevens, L. A., *et al.* (2007). Prevalence of chronic kidney disease in the United States. *JAMA*, 298, 2038–47.
Cushman, W. C., Evans, G. W., Byington, R. P., *et al.* (2010). Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*, 362, 1575–85.
De Boer, I. H., Rue, T. C., Cleary, P. A., *et al.* (2011). Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. *Arch Intern Med*, 171, 412–20.
De Brito-Ashurst, I., Varagunam, M., Raftery, M. J., *et al.* (2009). Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol*, 20, 2075–84.
Douglas, K., O'Malley, P. G., and Jackson, J. L. (2006). Meta-analysis: the effect of statins on albuminuria. *Ann Intern Med*, 145, 117–24.
Drueke, T. B., Locatelli, F., Clyne, N., *et al.* (2006). Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*, 355, 2071–84.
Edwards, N. C., Steeds, R. P., Stewart, P. M., *et al.* (2009). Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease: a randomized controlled trial. *J Am Coll Cardiol*, 54, 505–12.
Escape Trial Group (2009). Strict blood-pressure control and progression of renal failure in children. *N Engl J Med*, 361, 1639–50.
Filiopoulos, V., Hadjiyannakos, D. and Vlassopoulos, D. (2012). New insights into uric acid effects on the progression and prognosis of chronic kidney disease. *Ren Fail*, 34(4), 510–20.
Fouque, D. and Laville, M. (2009). Low protein diets for chronic kidney disease in non diabetic adults. *Cochrane Database Syst Rev*, 3, CD001892.
Fox, K. M. (2003). Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*, 362, 782–8.
Ganji, V. and Kafai, M. R. (2003). Demographic, health, lifestyle, and blood vitamin determinants of serum total homocysteine concentrations in the third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr*, 77, 826–33.
Gansevoort, R. T., Correa-Rotter, R., Hemmelgarn, B. R., *et a*l. (2013). Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet*, 382(9889), 339–52.
Gerstein, H. C., Miller, M. E., Genuth, S., *et al.* (2011). Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med*, 364, 818–28.
Goncalves, A. R., Khwaja, A., Ahmed, A. K., *et al.* (2011). Stopping renin-angiotensin system inhibitors in chronic kidney disease: predictors of response. *Nephron Clin Pract*, 119, c348–54.
Guh, D. P., Zhang, W., Bansback, N., *et al.* (2009). The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health*, 9, 88.
Heinz, J., Domrose, U., Luley, C., *et al.* (2009). Influence of a supplementation with vitamins on cardiovascular morbidity and mortality in patients with end-stage renal disease: design and baseline data of a randomized clinical trial. *Clin Nephrol*, 71, 363–5.
Hsu, C. Y. and Chertow, G. M. (2002). Elevations of serum phosphorus and potassium in mild to moderate chronic renal insufficiency. *Nephrol Dial Transplant*, 17, 1419–25.
Jafar, T. H., Stark, P. C., Schmid, C. H., *et al.* (2003). Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med*, 139, 244–52.
Keith, D., Ashby, V. B., Port, F. K., *et al.* (2008). Insurance type and minority status associated with large disparities in prelisting dialysis among candidates for kidney transplantation. *Clin J Am Soc Nephrol*, 3, 463–70.
Klahr, S., Levey, A. S., and Beck, G. J. (1994). The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med*, 330, 877–84.
Kosmadakis, G. C., John, S. G., Clapp, E. L., *et al.* (2012). Benefits of regular walking exercise in advanced pre-dialysis chronic kidney disease. *Nephrol Dial Transplant*, 27, 997–1004.
Kunz, R., Wolbers, M., Glass, T., *et al.* (2008). The COOPERATE trial: a letter of concern. *Lancet*, 371, 1575–6.
Lee, W., Campoy, S., Smits, G., *et al.* (2007). Effectiveness of a chronic kidney disease clinic in achieving K/DOQI guideline targets at initiation of dialysis—a single-centre experience. *Nephrol Dial Transplant*, 22, 833–8.
Levey, A. S., de Jong, P. E., Coresh, J., *et al.* (2011). The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*, 80, 17–28.
Lewis, E. J., Hunsicker, L. G., Bain, R. P., *et al.* (1993). The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med*, 329, 1456–62.
Lewis, E. J., Hunsicker, L. G., Clarke, W. R., *et al.* (2001). Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*, 345, 851–60.
Lewis, J. B. (2010). Blood pressure control in chronic kidney disease: is less really more? *J Am Soc Nephrol*, 21, 1086–92.
Locatelli, F., Covic, A., Eckardt, K. U., *et al.* (2009). Anaemia management in patients with chronic kidney disease: a position statement by the Anaemia Working Group of European Renal Best Practice (ERBP). *Nephrol Dial Transplant*, 24, 348–54.
Lonn, E., Yusuf, S., Arnold, M. J., *et al.* (2006). Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med*, 354, 1567–77.
Mann, J. F., Schmieder, R. E., McQueen, M., *et al.* (2008). Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet*, 372, 547–53.
Matsushita, K., van der Velde, M., Astor, B. C., *et al.* (2010). Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*, 375, 2073–81.
Menon, V., Kopple, J. D., Wang, X., *et al.* (2009) Effect of a very low protein diet on outcomes: long-term follow-up of the MDRD study. *Am J Kidney Dis*, 53, 208–17.
Navaneethan, S. D. and Yehnert, H. (2009). Bariatric surgery and progression of chronic kidney disease. *Surg Obes Relat Dis*, 5, 662–5.
Paffenbarger, R. (2000). Physical exercise to reduce cardiovascular disease risk. *Proc Nutr Soc*, 59, 421–2.
Parving, H. H., Persson, F., Lewis, J. B., *et al.* (2008). Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med*, 358, 2433–46.
Peterson, J. C., Adler, S., Burkart, J. M., *et al.* (1995). Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med*, 123, 754–62.
Pfeffer, M. A., Burdmann, E. A., Chen, C. Y., *et al.* (2009). A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*, 361, 2019–32.
Sandhu, S., Wiebe, N., Fried, L. F., *et al.* (2006). Statins for improving renal outcomes: a meta-analysis. *J Am Soc Nephrol*, 17, 2006–16.
Schiffl, H., Lang, S. M. and Fischer, R. (2002). Stopping smoking slows accelerated progression of renal failure in primary renal disease. *J Nephrol*, 15, 270–4.
Singh, A. K., Szczech, L., Tang, K. L., *et al.* (2006). Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*, 355, 2085–98.
Snyder, J. J. and Collins, A. J. (2009). Association of preventive health care with atherosclerotic heart disease and mortality in CKD. *J Am Soc Nephrol*, 20, 1614–22.
Solomon, S. D., Rice, M. M., Jablonski, J. A., *et al.* (2006). Renal function and effectiveness of angiotensin-converting enzyme inhibitor therapy in patients with chronic stable coronary disease in the Prevention of Events with ACE inhibition (PEACE) trial. *Circulation*, 114, 26–31.

Strippoli, G. F., Navaneethan, S. D., Johnson, D. W., *et al*. (2008). Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. *BMJ*, 336, 645–51.

Turner, J. M., Bauer, C., Abramowitz, M. K., *et al*. (2012). Treatment of chronic kidney disease. *Kidney Int*, 81, 351–62.

Vianna, A. C., Mocelin, A. J., Matsuo, T., *et al*. (2007). Uremic hyperhomocysteinemia: a randomized trial of folate treatment for the prevention of cardiovascular events. *Hemodial Int*, 11, 210–16.

Vollmer, W. M., Sacks, F. M., Ard, J., *et al*. (2001). Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. *Ann Intern Med*, 135, 1019–28.

Wright, J. T., Jr., Bakris, G., Greene, T., *et al*. (2002). Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*, 288, 2421–31.

Yoshida, T., Takei, T., Shirota, S., *et al*. (2008). Risk factors for progression in patients with early-stage chronic kidney disease in the Japanese population. *Intern Med*, 47, 1859–64.

Yusuf, S., Sleight, P., Pogue, J., *et al*. (2000). Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*, 342, 145–53.

Zoccali, C., Mallamaci, F. and Tripepi, G. (2007). It is important to lower homocysteine in dialysis patients. *Semin Dial*, 20, 530–3.

CHAPTER 100

Hypertension as a cause of chronic kidney disease: what is the evidence?

Teena Tandon and Rajiv Agarwal

Introduction

Hypertension is a major public health problem worldwide. In the United States, it is estimated that one out of every three people has hypertension (Centers for Disease Prevention, 2013). After diabetes, hypertension is the second most common cause of end-stage renal disease (ESRD) (United States Renal Data System, 2013). But is it? Or is the hypertension in many of these patients caused by subclinical renal disease?

To insinuate hypertension as a cause of chronic kidney disease (CKD), there are two levels of evidence—observational and interventional. First, the observational data are reviewed. Next, we review those randomized trials that have targeted blood pressure lowering to different levels in people with CKD to evaluate whether such interventions have any effect on CKD progression or cardiovascular disease. Finally, there is emerging evidence that specific genes may confer susceptibility to CKD rather than hypertension per se.

Observational data associate hypertension with end-stage renal disease

Several large observational studies associate hypertension with CKD. Those that have used ESRD as an endpoint are discussed further.

The Multiple Risk Factor Intervention Trial (MRFIT) (Klag et al., 1996) was a randomized primary prevention trial to test the effect of a multifactor intervention programme such as blood pressure control, diet modification for reducing blood cholesterol, and cessation of smoking on mortality from coronary heart disease in 12,866 high-risk men aged 35–57 years. In this trial, 332,544 men screened from 1973 to 1975 were followed prospectively over 16 years. Over this time, 814 cases of ESRD were identified. A continual and progressive increase in risk of ESRD was noted with increasing level of blood pressure. With optimal blood pressure (systolic blood pressure < 120 mmHg) as reference, stage 1 hypertension (systolic 140–159 mmHg or diastolic 90–99 mmHg) was associated with adjusted relative risk (RR) for ESRD of 3.1, stage 2 hypertension (systolic 160–179 mmHg or diastolic 100–109 mmHg) with adjusted RR of 6.0, stage 3 hypertension (systolic 180–209 mmHg or diastolic 110–119 mmHg) with adjusted RR 11.0, and stage 4 (systolic ≥ 210 mmHg or diastolic ≥ 120 mmHg) hypertension with even a higher adjusted RR for ESRD of 20 (Table 100.1). These data suggest that risk for CKD increases above systolic blood pressure >140 mmHg. Systolic blood pressure higher by 1 standard deviation (SD) was associated with a doubling of the risk of ESRD ($P < 0.001$) whereas diastolic blood pressure higher by 1 SD was associated with a 2.5-fold increase in the risk of ESRD ($P < 0.001$).

Although MRFIT was limited to men, the Okinawa study (Tozawa et al., 2003) in Japan followed both men and women. Unlike the MRFIT study, the Okinawa study was without interventions. An observational cohort of 46,881 men and 51,878 women in Okinawa, Japan were evaluated at baseline and followed over 17 years. In both men and women, there was a significant positive association between systolic and diastolic blood pressure and the risk of development of ESRD. The RR for ESRD with each 10 mmHg increase in systolic blood pressure was 1.29 among men and 1.34 among women; for each 10 mmHg increase in diastolic blood pressure, the RR for ESRD was 1.56 in men and 1.69 in women. This study also concluded that in both men and women, high-normal blood pressure and hypertension are independent risk factors for ESRD.

Jafar et al. (2001, 2003) performed a meta-analysis that included 11 randomized trials in 1860 patients with non-diabetic renal disease to evaluate the effect of achieved systolic blood pressure on renal outcome. Achieved systolic blood pressure of 110–129 mmHg and urine protein excretion < 2.0 g/day were associated with the lowest risk for CKD progression. Higher levels of systolic blood pressure were associated with a steep increase in the risk of CKD progression. Furthermore, achieved systolic blood pressure < 110 mmHg was also associated with increased risk of CKD progression. Although this meta-analysis included randomized trials, most of these trials did not randomize patients to two different blood pressure goals. In fact, all the trials in this meta-analysis tested the notion whether angiotensin converting enzyme inhibitor (ACEI) use can slow the progression of CKD. Thus, a cause and effect relationship is difficult to establish. Given this limitation, the authors appropriately concluded that 'reverse causation cannot be excluded with certainty'. Moreover, although achieved systolic blood pressure of 110–129 mmHg was ideal, the adjusted RR for CKD progression was not statistically significant in when systolic blood pressure during follow-up was between 120–129 mmHg (adjusted RR 1.23; 95% confidence interval

Table 100.1 MRFIT trial showed that risk of ESRD increases with stage of hypertension

Stage of hypertension	Systolic blood pressure	Diastolic blood pressure	Adjusted RR of ESRD
Stage 1	140–159 mmHg	90–99 mmHg	3.1
Stage 2	160–179 mmHg	100–109 mmHg	6.0
Stage 3	180–209 mmHg	110–119 mmHg	11.0
Stage 4	>210 mmHg	>120 mmHg	20.0

(CI) 0.63–2.40) or between 130–139 mmHg (adjusted RR 1.83; 95% CI 0.97–3.44). Thus, achieved blood pressure of 140 mmHg or more was associated with increased CKD progression.

Thus, high blood pressure is strongly associated with ESRD. This risk for ESRD is present even when hypertension is mild and occurs in the absence of history of diabetes or any other identifiable cause of ESRD. Nonetheless, association of blood pressure with ESRD does not establish causation. To insinuate that blood pressure is a cause of progressive CKD and therefore ESRD, randomized controlled data will be reviewed.

Randomized trials linking hypertension to chronic kidney disease

Most of the evidence evaluating the level to which blood pressure should be lowered to has emerged from observational studies and post hoc analyses of randomized controlled trials that did not lower blood pressure to pre-specified goals. There are only three prospective randomized multicentre trials that have asked the question of how far blood pressure should be lowered to prevent the occurrence of ESRD and slow the progression of CKD. These trials were the Modification of Diet in Renal Disease (MDRD) Study, the African American Study of Kidney Disease (AASK), and the Ramipril Efficacy in Nephropathy (REIN-2) trial.

The MDRD Study (Klahr et al., 1994) was a randomized controlled trial that tested the interventions of dietary modification and blood pressure lowering among 840 patients with CKD. Two studies were performed. In study 1, 585 patients with glomerular filtration rates (GFRs) of 25–55 mL/min/1.73 m^2 body surface area were randomly assigned using a 2 × 2 factorial design to dietary or blood pressure modifications. The diets were either a usual-protein diet or a low-protein diet and blood pressure levels were usual- or a low-blood pressure group. Blood pressure assignments were by mean arterial pressure, 107 or 92 mmHg respectively in the two groups. In study 2, 255 patients with GFRs of 13–24 mL/min/1.73 m^2 body surface area were randomly assigned to the low-protein diet or a very-low-protein diet with a keto acid-amino acid supplement, and a usual- or low-blood pressure groups. The mean follow-up was 2.2 years. In study 1, the mean decline in the GFR at 3 years did not differ significantly between the diet groups or between the blood pressure groups. There was no delay in the time to the occurrence of ESRD or death. In both studies, in post hoc analyses, patients who had more pronounced proteinuria at baseline had a significantly slower rate of decline in the GFR when they were randomized to the lower blood pressure group.

The AASK (Wright et al., 2002) used a 2 × 3 factorial design to compare the effects of two levels of blood pressure control and three antihypertensive drug classes on GFR decline in black patients with hypertension and CKD. African Americans (N = 1094) aged 18–70 years with GFR between 20 and 65 mL/min/1.73 m^2 from 21 clinical centres throughout the United States were randomly assigned to one of two mean arterial pressure goals, 102–107 mmHg (usual goal; N = 554) or 92 mmHg or less (lower goal; N = 540), and to initial treatment with either a beta blocker (metoprolol 50–200 mg/day; N = 441), an ACEI (ramipril 2.5–10 mg/day; N = 436) or a dihydropyridine calcium channel blocker (amlodipine 5–10 mg/day; N = 217). Open-label agents were added to achieve the assigned blood pressure goals. Participants were followed up for 3–6.4 years. The main outcome measures were the following: rate of change in GFR (GFR slope); clinical composite outcome of reduction from baseline in GFR by 50% or more (or 25 mL/min/1.73 m^2), ESRD, or death. Achieved blood pressure averaged (SD) 128/78 (12/8) mmHg in the lower-blood pressure group and 141/85 (12/7) mmHg in the usual-blood pressure group. The mean GFR slope from baseline through 4 years did not differ significantly between the lower-blood pressure group (−2.21 (0.17) mL/min per 1.73 m^2 per year) and the usual-blood pressure group (−1.95 (0.17) mL/min per 1.73 m^2 per year; P = 0.24), and the lower blood pressure goal did not significantly reduce the rate of the clinical composite outcome (risk reduction for lower blood pressure group = 2%; 95% CI −22% to 21%; P = 0.85). Thus, no additional benefit of slowing progression was observed with the lower blood pressure goal.

Blood pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2) (Ruggenenti et al., 2005) assessed the effect of intensified versus conventional blood pressure control on progression to ESRD. Participants with non-diabetic proteinuric nephropathies on ACEI ramipril (2.5–5 mg/day) were randomly assigned to either conventional (diastolic < 90 mmHg; N = 169) or intensified (systolic/diastolic < 130/80 mmHg; N = 169) blood pressure control. To achieve the intensified blood pressure level, patients received add-on therapy with the dihydropyridine calcium-channel blocker felodipine (5–10 mg/day). The primary outcome measure was time to ESRD over 36 month follow-up, and analysis was by intention to treat. Over a median follow-up of 19 months, 38/167 (23%) patients assigned to intensified blood pressure control and 34/168 (20%) allocated conventional control progressed to ESRD (hazard ratio (HR) 1.00; 95% CI 0.61–1.64; P = 0.99). The study was terminated early for futility. Among patients with non-diabetic proteinuric nephropathies receiving background ACEI therapy, no additional benefit from further blood pressure reduction by felodipine could be shown.

Taken together, no study testing two different levels of blood pressure control was able to demonstrate that lower blood pressure delayed the rate of progression of renal failure. Due to lack to robust data for lower blood pressure, the 2012 KDIGO guidelines on blood pressure control in CKD patients recommend changing blood pressure target to <140/90 mmHg in all CKD patients. However, in patients with proteinuria, weak evidence justifies blood pressure targeted to < 130/80 mmHg (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013).

Mild kidney disease as cause of hypertension

Early kidney disease as measured by albuminuria may antedate hypertension. We review the major studies to date that have associated albuminuria or proteinuria with the subsequent development of hypertension (Table 100.2).

The Prevention of REnal and Vascular ENd stage Disease (PREVEND) (Brantsma et al., 2006) cohort selected participants in 1997 from 40,856 individuals from the general population in the Netherlands. Selection was based on their albumin concentration in a spot morning urine sample to enrich the cohort for the presence of albuminuria. The number completing the first survey (1997–1998) was 8592. At follow-up (2001–2003), the number of individuals completing the second survey was 6894. For this analysis, 4635 individuals who did not have hypertension (N = 2247) or self-reported renal disease (N = 12) at baseline and participated in the first and second surveys were followed up for a mean of 4.3 years. Baseline urinary albumin excretion was measured on two consecutive 24-hour samples. A strong and independent association was found between urine albumin excretion with the risk of developing subsequent hypertension (OR 2.29; 95% CI 1.77–2.95). An interaction between urinary albumin excretion and estimated GFR was also found (P = 0.030), indicating that with elevated urinary albumin excretion and lowered estimated GFR, but still within the normal range, the risk for developing hypertension was the greatest.

The association between urinary albumin excretion and the risks of hypertension and blood pressure progression has been examined in the Framingham offspring study (Wang et al., 2005). Among 1499 non-hypertensive individuals (58% women) without diabetes, during a mean follow-up of 2.9 years, 230 participants (15%) developed hypertension and 499 (33%) progressed to a higher-blood pressure category; blood pressure categories were as defined by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. In multivariable logistic regression that adjusted for known risk factors, urine albumin/urine creatinine ratio (UACR) was a significant predictor of incident hypertension (adjusted OR 1.20; 95% CI 1.01–1.44, per 1-SD increment in log UACR). Compared with those in the lowest UACR quartile, participants in the highest quartile (men: > 6.66 mg/g; women: > 15.24 mg/g) had an approximately twofold risk of developing hypertension (adjusted OR 1.93; P = 0.006) and 1.5-fold risk of hypertension progression (adjusted OR 1.45; P = 0.03).

Among 1065 postmenopausal women from the first Nurses' Health Study and 1114 premenopausal women from the second Nurses' Health Study who had UACR < 25 mg/g and who did not have diabetes or hypertension, Forman et al. (2008) examined the association of UACR and incident hypertension. Among the older women, 271 incident cases of hypertension occurred during 4 years of follow-up, and among the younger women, 296 incident cases of hypertension occurred during 8 years of follow-up. Participants who had UACR in the highest quartile (4.34–24.17 mg/g for older women and 3.68–23.84 mg/g for younger women) were more likely to develop hypertension than those who had UACR in the lowest quartile (HR 1.76 (95% CI 1.21–2.56) and HR 1.35 (95% CI 0.97–1.91) for older and younger women, respectively). Higher UACRs, even within the normal range, are independently associated with increased risk for development of hypertension among women without diabetes. The effects of UACR on incident hypertension was independent of age, body mass index (BMI), estimated

Table 100.2 Details of studies relating albuminuria to hypertension

Study	Method	Results
PREVEND trial (Brantsma et al., 2006)	Community-based prospective cohort study Examined association of urinary albumin excretion (UAE) (measured by two 24-hour urine collections) and hypertension in 4635 patients with normal blood pressure followed for 4.3 years	Baseline UAE associated with risk of developing hypertension (OR 2.29; 95% CI 1.77–2.95 per tenfold increase in UAE)
Framingham offspring study (Wang et al., 2005)	Community-based prospective cohort study Followed 1499 patients for 2.9 years	15% developed hypertension and 33% progressed to higher blood pressure. Thus, UAE predicts hypertension (adjusted OR 1.2; 95% CI 1.01–1.44)
Forman et al. (2008)	Nurses' Health Study (NHS) cohort 1065 nurses from NHS I followed over 4 years 1114 nurses from NHS II followed over 8 years Participants did not have hypertension and diabetes and submitted a spot urine sample at enrolment	Compared to lowest quartile of UAE, highest quartile had HR 1.76 (P = 0.004) of incident hypertension in NHS I and HR 1.35 (P = 0.06 for trend) in NHS II
Jessani et al. (2012)	Cluster randomized controlled trial, nested cohort study Followed 1272 normotensive non-diabetic people in Pakistan for 2 years	Odds of developing hypertension higher in top quartile of UAE compared to lowest quartile
Palatini et al. (2005)	1033 patients screened for hypertension (ambulatory blood pressure monitoring) and never treated for disease. Required hypertension to be present for admission into the cohort. UAE assessed by 24-hour urine	UAE not helpful for predicting hypertension progression

GFR, baseline blood pressure, physical activity, smoking, and family history of hypertension.

Similar findings have emerged from an Indo Asian population (Jessani et al., 2012). In a nested cohort study with a cluster randomized controlled trial of 1272 normotensive, non-diabetic Pakistani adults aged ≥ 40 years with UACR < 30 mg/g, subjects were followed for up to 2 years for incident hypertension. Incident hypertension was defined as new onset of systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, or initiation of antihypertensive therapy. A total of 920 (72.3%) participants completed the 2-year final follow-up at which time 11.4% developed hypertension. The odds (95% CI) for incident hypertension were 2.45(1.21–4.98) for those in the fourth (top) quartile (≥ 6.1 mg/g) and 2.12 (1.04–4.35) in the third quartile (3.8–6.1 mg/g) compared to those in the lowest quartile (< 2.8 mg/g) of UACR. In addition, a significant interaction between UACR and baseline systolic blood pressure was observed suggesting that the odds (95% CI) of incident hypertension with UACR were greater at lower baseline systolic blood pressure (interaction P = 0.044).

Some studies have questioned the association of albuminuria with hypertension. The Hypertension and Ambulatory Recording Venetia STudy (HARVEST) (Palatini et al., 2005) study in 17 outpatient clinics in Italy evaluated 1041 young stage 1 hypertensive subjects. Thus, the HARVEST participants were required to have a baseline systolic blood pressure of 140–159 mm Hg or a diastolic blood pressure of 90–99 mm Hg. Such individuals would be classified as having prevalent hypertension. Urinary albumin excretion rate was measured from 24-hour collections and 24-hour ambulatory monitoring was performed to assess blood pressure. The end point the development of sustained hypertension as defined by supine office systolic blood pressure ≥ 150 mmHg or supine office diastolic blood pressure ≥ 95 mmHg on two consecutive visits. At baseline, when compared to subjects with normoalbuminuria and normal filtration, those with microalbuminuria with hyperfiltration (P < 0.001) and or normal filtration (P = 0.04) had higher 24-hour systolic blood pressure. During the 12 years of observation, 461 of 1033 available subjects developed sustained hypertension. In a Cox analysis, neither microalbuminuria nor hyperfiltration were significant predictors of development of sustained hypertension. Given the greater correlation of urinary albumin excretion with 24-hour ambulatory blood pressure, it is possible that when 24-hour ambulatory blood pressure monitoring is available urinary albumin excretion offers little to improve the prediction of incident hypertension. However, the results of the HARVEST study do not apply to a population that is truly normotensive at baseline.

Thus, hypertension is simply not a cause of kidney damage but taken together, the above studies suggest that early kidney damage may antedate hypertension in many people.

Nephron mass and hypertension

Loss of nephrons due to peripheral cysts supports the hypothesis proposed by Brenner et al. (1988) and others that reduced number of nephrons contributes to hypertension in the general hypertension. This is reviewed in Chapter 138. This nephron number hypothesis was tested in autopsy study in Germany (Keller et al., 2003). A three-dimensional stereologic technique was used to compare the number and volume of glomeruli in 10 middle-aged white patients (35–59 years of age) with a history of hypertension or left ventricular hypertrophy (or both) and renal arteriolar lesions with the number and volume in 10 normotensive subjects matched for sex, age, height, and weight. All 20 subjects had died in accidents. People with hypertension had significantly fewer glomeruli per kidney than matched normotensive controls (median 702,379 vs 1,429,200). Those with hypertension also had a significantly greater glomerular volume than the controls (median 6.50×10^{-3} mm^3 vs 2.79×10^{-3} mm^3; P < 0.001) but very few obsolescent glomeruli. These data provide evidence to support the concept that a low number of nephrons are associated with hypertension.

Genetic mutations as a cause of 'hypertensive' chronic kidney disease

In 2008, landmark papers reviewed in Chapter 341 showed a very strong association between the increased incidence of focal segmental glomerulosclerosis (FSGS) in African Americans and markers associated with the *MYH9* gene on chromosome 22. These analyses used the new technique of admixture analysis that depended on tracking segments on 'African' DNA in a mixed population. Further work showed that the same genetic variants could also account for much of the excess of renal disease in African Americans (Kao et al., 2008; Freedman et al., 2009). Renal disease in most of these individuals had been classified as hypertensive. African American patients have a high incidence rate of ESRD (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013) attributed to hypertension at 33% compared to < 25% in all other racial groups. Hypertensive ESRD is found to aggregate in select African American families and relatively few patients with mild to moderate essential hypertension ultimately develop CKD.

The *MYH9* gene is associated with autosomal dominant renal disease, but Genovese et al. (2010) showed that the strongest association signal came not from the *MYH9* gene but from the adjacent *APOL1* gene. *APOL1* (Freedman et al., 2010; Friedman and Pollak, 2011; Freedman and Langefeld, 2012) mutations are found exclusively among individuals of African descent and have traditionally been known to provide protection from sleeping sickness (trypanosomiasis). So far, little is known about how these variants might predispose to renal disease, but further evidence continues to emerge about their importance (see Chapter 341).

These studies have shown that *APOL1* mutations produce a distinct category of kidney disease that manifests in African ancestry population and support the notion that it is a genetic cause and not necessarily hypertension that predisposes to kidney disease.

This disease association has altered our understanding of the factors that initiate hypertensive ESRD. Several studies have previously shown that high blood pressure does not commonly lead to progressive nephropathy in African American patients. It is now apparent that many patients with African American ancestry and ESRD attributed to hypertension may have been misdiagnosed and actually have *APOL1*-associated FSGS. This could explain the failure of intensive blood pressure reduction, including with the use of ACE inhibition, to slow nephropathy progression in hypertensive African Americans with CKD.

Once translated from research to bedside genetic screening, these risk markers will have potential clinical uses especially in transplantation. Genetic screening could be used to identify those donors with better graft survival, as well as for high-risk, black, live donors, reducing risk of subsequent nephropathy.

Unusual renal causes of hypertension

Fatty kidney

Kidneys have the potential to accumulate ectopic fat in the renal sinus. Excessive accumulation of fat within the renal sinus (fatty kidney) displaces and compresses the low-pressure renal lymphatics and veins, as well as the ureters. It is thought that compression of these structures increases renal hydrostatic pressure and activates the renin–angiotensin–aldosterone system (RAAS) which leads to hypertension. Chughtai et al. (2010) tested this association among 205 patients aged 55–85 years who were recruited as part of the Pulmonary Edema and Stiffness of the Vascular System (PREDICT) trial, an ongoing prospective observational study the aim of which is to identify abnormalities of the cardiovascular system that predicts the first episode of congestive heart failure in middle-aged and elderly individuals. After accounting for age, sex, height, BMI, and intraperitoneal fat, multivariable linear regression revealed that renal sinus fat was associated with the number of prescribed antihypertensive medications ($P = 0.010$), stage II hypertension ($P = 0.02$), and renal size ($P \leq 0.001$). Foster et al. (2011) showed similar findings in the Framingham Heart Study cohort. In this cross-sectional study, 2923 patients (mean age: 54 years; 51% women and mainly white) underwent quantification of renal sinus fat area using computed tomography. They found that prevalence of fatty kidney was 30.1% (N = 879). Individuals with fatty kidney had a higher risk of hypertension (odds ratio (OR) 2.12; $P < 0.0001$), which persisted after adjustment for BMI (OR 1.49; $P < 0.0001$). In this study, fatty kidney was also associated with an increased risk for CKD (OR 2.30; $P = 0.005$), even after additionally adjusting for BMI (OR 1.86; $P = 0.04$).

However, further research is necessary to evaluate the longitudinal associations of renal sinus fat with markers of renal function.

Renal cysts

Hypertension has classically been associated with autosomal dominant polycystic kidney disease (ADPKD) (Chapman et al., 2010) and in fact predates the loss of renal function in these individuals (see Chapter 306). It has been postulated that in ADPKD, increased cyst growth and renal volume leads to compression of renal vasculature resulting in activation of the RAAS. RAAS activation leads to sodium retention, increased system vascular resistance, further cyst growth, and renal fibrosis, all of which lead to hypertension and renal disease.

Not only ADPKD but simple renal cysts have also been associated with hypertension (Luscher et al., 1986). A simple renal cyst is one of the most common types of acquired renal cysts whose prevalence increases with age and varies according to gender. In 1942, Farrell and Young first reported the association of a simple renal cyst in an 18-year-old student with hypertension following trauma to the right kidney at age 6 (Farrell and Young, 1942). Following nephrectomy, hypertension resolved. Since then several authors have reported cure or improvement of hypertension after decompression of large cysts while others have refuted this finding. To examine this association, investigators in Korea (Chin et al., 2006) retrospectively identified 436 persons with a simple renal cyst(s) and 436 matched controls from among 6603 patients having routine health check-ups and abdominal ultrasounds. They then analysed the medical record of study subjects with careful attention to the confounding effects of age, gender, proteinuria, GFR, and hypertension on the existence of a simple renal cyst, hypertension, and renal dysfunction. The presence of a cyst was related to hypertension but not to renal dysfunction. The number and the size of cysts were independent risk factors to the prevalence of hypertension. In this study, subjects with peripheral cysts had higher prevalence of hypertension compared to perihilar cysts refuting the role of RAAS activation by cysts as a cause of hypertension. The authors postulated that the loss of nephrons along with ageing was involved in both development of hypertension and formation of a simple renal cyst. Ageing process along with decreased cortical mass causes aberrant tubular growth to generate cyst formation, especially in peripheral region as well as hypertension subsequent to reduced number of nephrons. Additional loss of renal cortex by peripheral cysts may increase the probability of hypertension.

References

Brantsma, A. H., Bakker, S. J., de Zeeuw, D., *et al.* (2006). Urinary albumin excretion as a predictor of the development of hypertension in the general population. *J Am Soc Nephrol*, 17, 331–5.

Brenner, B. M., Garcia, D. L., and Anderson, S. (1988). Glomeruli and blood pressure. Less of one, more the other? *Am J Hypertens*, 1, 335–47.

Centers for Disease Prevention (2013). *High Blood Pressure*. [Online] <http://www.cdc.gov/bloodpressure/>

Chapman, A. B., Stepniakowski, K., and Rahbari-Oskoui, F. (2010). Hypertension in autosomal dominant polycystic kidney disease. *Adv Chronic Kidney Dis*, 17, 153–63.

Chin, H. J., Ro, H., Lee, H. J., *et al.* (2006). The clinical significances of simple renal cyst: Is it related to hypertension or renal dysfunction? *Kidney Int*, 70, 1468–73.

Chughtai, H. L., Morgan, T. M., Rocco, M., *et al.* (2010). Renal sinus fat and poor blood pressure control in middle-aged and elderly individuals at risk for cardiovascular events. *Hypertension*, 56, 901–6.

Farrell, J. I. and Young, R. H. (1942). Hypertension caused by unilateral renal compression. *JAMA*, 118, 711–12.

Forman, J. P., Fisher, N. D., Schopick, E. L., *et al.* (2008). Higher levels of albuminuria within the normal range predict incident hypertension. *J Am Soc Nephrol*, 19, 1983–8.

Foster, M. C., Hwang, S. J., Porter, S. A., *et al.* (2011). Fatty kidney, hypertension, and chronic kidney disease: the Framingham Heart Study. *Hypertension*, 58, 784–90.

Freedman, B. I., Hicks, P. J., Bostrom, M. A., *et al.* (2009). Polymorphisms in the non-muscle myosin heavy chain 9 gene (MYH9) are strongly associated with end-stage renal disease historically attributed to hypertension in African Americans. *Kidney Int*, 75, 736–45.

Freedman, B. I., Kopp, J. B., Langefeld, C. D., *et al.* (2010). The apolipoprotein L1 (APOL1) gene and nondiabetic nephropathy in African Americans. *J Am Soc Nephrol*, 21, 1422–6.

Freedman, B. I. and Langefeld, C. D. (2012). The new era of APOL1-associated glomerulosclerosis. *Nephrol Dial Transplant*, 27, 1288–91.

Freedman, B. I., Soucie, J. M., McClellan, W. M. (1997). Family history of end-stage renal disease among incident dialysis patients. *J Am Soc Nephrol*, 8, 1942–5.

Friedman, D. J. and Pollak, M. R. (2011). Genetics of kidney failure and the evolving story of APOL1. *J Clin Invest*, 121, 3367–74.

Genovese, G., Tonna, S. J., Knob, A. U., *et al.* (2010). A risk allele for focal segmental glomerulosclerosis in African Americans is located within a region containing APOL1 and MYH9. *Kidney Int*, 78, 698–704.

Jafar, T. H., Schmid, C. H., Landa, M., *et al*. (2001). Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med*, 135, 73–87.

Jafar, T. H., Stark, P. C., Schmid, C. H, *et al*. (2003). Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med*, 139, 244–52.

Jessani, S., Levey, A. S., Chaturvedi, N., *et al*. (2012). High normal levels of albuminuria and risk of hypertension in Indo-Asian population. *Nephrol Dial Transplant*, 27 Suppl 3, iii58–64.

Kao, W. H., Klag, M. J., Meoni, L. A., *et al*. (2008). MYH9 is associated with nondiabetic end-stage renal disease in African Americans. *Nat Genet*, 40, 1185–92.

Keller, G., Zimmer, G., Mall, G., *et al*. (2003). Nephron number in patients with primary hypertension. *N Engl J Med*, 348, 101–8.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*, 3, 1–150.

Klag, M. J., Whelton, P. K., Randall, B. L., *et al*. (1996). Blood pressure and end-stage renal disease in men. *N Engl J Med*, 334, 13–8.

Klahr, S., Levey, A. S., Beck, G. J., *et al*. (1994). The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med*, 330, 877–84.

Luscher, T. F., Wanner, C., Siegenthaler, W., *et al*. (1986). Simple renal cyst and hypertension: cause or coincidence? *Clin Nephrol*, 26, 91–5.

Palatini, P., Mormino, P., Mos, L., *et al*. (2005). Microalbuminuria, renal function and development of sustained hypertension: a longitudinal study in the early stage of hypertension. *J Hypertens*, 23, 175–82.

Ruggenenti, P., Perna, A., Loriga, G., *et al*. (2005). Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet*, 365, 939–46.

Svenningsen, P., Bistrup, C., Friis, U. G., *et al*. (2009). Plasmin in nephrotic urine activates the epithelial sodium channel. *J Am Soc Nephrol*, 20, 299–10.

Tozawa, M., Iseki, K., Iseki, C., *et al*. (2003). Blood pressure predicts risk of developing end-stage renal disease in men and women. *Hypertension*, 41, 1341–5.

United States Renal Data System (2013). *USRDS 2012 Annual Data Report: Atlas of CKD and ESRD in United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Wang, T. J., Evans, J. C., Meigs, J. B., *et al*. (2005). Low-grade albuminuria and the risks of hypertension and blood pressure progression. *Circulation*, 111, 1370–6.

Wright, J. T., Jr., Bakris, G., Greene, T., *et al*. (2002). Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*, 288, 2421–31.

CHAPTER 101

Diet and the progression of chronic kidney disease

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Introduction

The dietary management of non-dialysed CKD patients has focused on limiting the intake of substances which lead to accumulation of urea, potassium, phosphorus, and sodium.

The hypothesis that a high dietary protein intake leads to progressive CKD through a mechanism of glomerular hyperfiltration has been taught for decades. However, the evidence that low-protein diets (LPDs) halt CKD progression is weak. Recent advances in nutritional epidemiology have given us the opportunity to examine the relationships between diet and CKD. This chapter is an overview of dietary factors and interventions that can affect progression. We restrict this review to patients in the earlier stages of CKD; conservative management of Stage 5 CKD is considered in Chapter 145.

Nutritional epidemiology is complex. The estimation of individuals' nutritional intake depends mostly on semi-quantitative food frequency questionnaires and food diaries, which are dependent on the accuracy of the reporters, and the precision by which these records are translated into estimation of actual intakes by use of food composition tables. The study of diet and disease progression or incidence also assumes that dietary habits remain more or less constant over time. Given the mixture of nutrients (we eat meals, not single nutrients), the effect attributed to a single item may be influenced by other components in the foods. Finally, diet is inevitably linked to lifestyle-related factors such as obesity, smoking, and physical activity which also influence patient outcomes.

Macronutrients and progression of chronic kidney disease

Protein intake: not high, but weak evidence for restriction

From early studies it was postulated that a high-protein diet results in glomerular hyperfiltration, leading to kidney injury. Thus, it is plausible that the high protein intake would affect the kidneys of healthy adults or those with CKD. In the Nurse's Health Study, a high intake of non-dairy animal protein in women with mild kidney insufficiency was associated with albuminuria and a significantly greater loss in glomerular filtration rate (GFR) (Lin et al., 2011). This agreed with observational data linking higher intake of protein-rich foods with albuminuria in the community and in individuals with hypertension and diabetes.

High-protein diets are therefore not recommended in patients with clear-cut CKD. Apart from its effect on renal blood flow, dietary protein is a source of nitrogen, phosphorus, potassium, and metabolic acids that need to be excreted by the kidneys. Conversely, dietary protein restriction may protect against the progression of CKD by haemodynamic-mediated reductions in intraglomerular pressure as well as by changes in cytokine expression and matrix synthesis.

Various randomized controlled trials (RCTs) have evaluated both the efficacy and safety of a LPD in patients with progressive CKD, but the evidence remains inconclusive. Protein restriction to approximately 0.6–0.8 g/kg/day improved a number of uraemic symptoms and was associated with a modest and not significant benefit on CKD progression (Aparicio et al., 2000; Bernhard et al., 2001). Other RCTs including those in type 1 diabetic nephropathy patients showed that LPDs resulted in slower decline of GFR (Walker et al., 1989; Zeller et al., 1991). However, in the Modification of Diet in Renal Diseases (MDRD) Study, 600 individuals with moderate CKD, a low- versus usual-protein diet (0.58 vs 1.3 g/kg/day) did not result in a slower decline of kidney function (Klahr et al., 1994). A longer-term follow-up using national registries of these patients suggested that there might be an early benefit with low protein intake on the need for renal replacement therapy initiation or the composite of ESRD or all-cause mortality (Levey et al., 2006). Several meta-analyses have examined the relationship between a LPD and the initiation of renal replacement therapy by pooling data from previous interventions. The largest of these, based on 10 RCTs, concluded that CKD patients taking a LPD had a reduced risk for end-stage renal disease (ESRD) than those consuming higher amounts of protein (Fouque and Laville, 2009). To date, given the lack of conclusive data, dietary protein restriction cannot be recommended as a *routine* kidney protective strategy for patients with CKD. However, the safety of LPD and its beneficial effects on uraemic symptoms are obvious so its prescription may be justified in selected cases.

Apart from the quantity of protein intake, the source of protein may also be important. Whereas animal protein and amino acid mixtures may increase GFR, vegetable protein and egg whites produce little or no effect. However, it should be noted that

animal protein intake can increase serum creatinine directly as well as indirectly by increasing muscle mass, which could have influenced the interpretation of those trials. Interventional studies with non-serum creatinine-based measures of GFR as the outcome are needed before strong recommendations can be made about animal versus vegetable sources of protein in early CKD. In more advanced CKD, however, vegetable sources of protein might have additional benefits, such as lower absorption rate of bound-phosphate. Indeed, a cross-over trial in CKD stage 4 patients showed that 7 days of vegetarian diet with equivalent nutrients to a meat diet led to lower serum phosphate and decreased fibroblast growth factor 23 (FGF23) levels (Moe et al., 2011). Vegetarian diets are also associated with a decreased production of uraemic toxins such as *p*-cresyl sulphate and indoxyl sulphate, which have been implicated in CKD progression. Finally, a diet high in vegetable sources of protein might lead to lower endogenous production of acid.

The 2012 KDIGO guidelines suggest the use of a lower, high-quality protein diet of 0.8 g/kg/day among select pre-dialysis patients who are highly motivated to follow such a diet (Stevens et al., 2013). Other recommendations, such as those from the US National Kidney Foundation or International Society of Renal Nutrition and Metabolism suggest a lower range of protein restriction in CKD stages 3–5 to 0.6–0.8 g/kg/day, provided there are no signs of malnutrition.

A concern of LPDs in non-dialysed CKD is that they might eventually compromise nutritional status. RCTs have not shown that a LPD results in malnutrition (Klahr et al., 1994; Aparicio et al., 2000; Bernhard et al., 2001), possibly because these studied patients are subjected to more stringent dietary counselling and control. This supports the advantages of appropriate dietary counselling and monitoring in CKD. Adequate caloric intake must be ensured and at least 60% of the ingested protein must be of high biologic value or contain a high percentage of essential amino acids to ensure net nitrogen balance. Because dietary protein is a source of metabolic acids that stimulate skeletal muscle protein breakdown, LPDs may be associated with less metabolic acidosis. If the patients appear to be at risk of malnutrition, the LPD can be supplemented with essential amino acids and/or keto acids. The use of hypercaloric renal-specific supplements in the context of a LPD was associated with protein intake closer to the target values, better nutritional measures, and better adherence to therapy than a LPD alone (Montes-Delgado et al., 1998). Likewise, keto-acids of essential amino acids can also be used because of their capacity to neutralize the excessive nitrogen residues through transamination and limit the production of urea, while, at the same time, allowing the preservation of nutritional status (Mircescu et al., 2007).

Adherence to a LPD is often difficult for an individual. The question of the effectiveness of LPD in slowing the progression of CKD is irrelevant if patients are not able to follow it. Nutritional education programmes and dietitians' advice are effective in increasing patient adherence (Paes-Barreto et al., 2013), but the support of family members and whoever prepares the food is also critical. Ideally, the LPD prescribed has to be pleasant, varied, and not too restrictive. A recent study proposed a simplified approach to a LPD prescription (Piccoli et al., 2013), using a vegetarian LPD supplemented with ketoanalogues. The simplified diet was based on the idea of forbidden and allowed foods (forbidden: fish, meat, milk, eggs and derivatives (except in the context of the free-choice meals); everything else is allowed). The diet was essentially vegan, with an average of 0.6 g/kg/day protein intake and of 30–35 kcal/kg/day, and was supplemented with ketoanalogues. To improve compliance, one to three free-choice meals per week were allowed and the foods were not weighed. Adherence and feasibility were good, suggesting this as an easier way to put this theory into practice.

Compliance with dietary protein restriction can be estimated from measurement of urea in a 24-hour urine collection, assuming that daily intake is relatively constant and the patient is in a steady state (shown by a stable blood urea nitrogen and/or body weight). In this setting, nitrogen (N) excretion roughly equals nitrogen intake. The former can be estimated from:

$$\text{N excretion} = \text{urinary urea N excretion} + \text{non-urea N excretion}$$

Non-urea nitrogen excretion (sum of non-urea urine nitrogen plus faecal nitrogen) is relatively constant, averaging 31 mg/kg per day.

Moderate urinary protein loss can be ignored, but each gram excreted above 5 g/day should be added to the above formula. Each gram of nitrogen is derived from 6.25 g of protein. Thus:

$$\text{Estimated dietary protein intake} = 6.25\left(\text{urine urea N} + 31\ \text{mg/kg}\right)$$

If, for example, 24-hour urine urea nitrogen excretion is 8.2 g in a 60 kg woman excreting 3.5 g of protein per day, then:

$$\text{Estimated dietary protein intake} = 6.25\left(8.2 + 1.86\right) = 62.9\ \text{g}$$

Thus, protein intake in this example is approximately 1 g/kg per day.

Fat intake

Although there is limited evidence that reduction in total dietary fat intake per se decreases CVD, replacement of dietary saturated fat and trans-fat with unsaturated fat is recommended for prevention of CVD in the general population. The potential of dietary fat interventions for CKD progression has so far been mainly limited to the study of *n*-3 polyunsaturated fatty acids (PUFAs) derived from fish oil. Less is known of the health risks of a diet with an unhealthy fat profile.

There are three main types of fatty acids in humans: saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), and PUFAs. The latter two are further classified into *n*-3, *n*-6, and *n*-9 (or omega-3, -6, and -9) subfamilies (IUPAC-IUB Commission on Biochemical Nomenclatur, 1978). Major dietary sources of fatty acids are summarized in Table 101.1. Fatty acids have many biological functions, for example, a source of energy, basic building blocks of lipids and membranes, second messengers regulating gene expression, precursors of eicosanoids, and as antioxidants, anti-inflammatory agents, and anticoagulants.

Epidemiological studies investigating associations between SFAs and kidney function suggest a negative effect of SFAs on kidney function. In the Nurses' Health Study, women within the highest quartile of SFA intake had increased odds of GFR decline ≥ 30% during 12 years (Lin et al., 2010). In contrast, most, but not all epidemiological studies investigating associations between *n*-3 PUFA and kidney function suggest a protective effect against the decline in GFR. Owing to the purported salutary effects of *n*-3 PUFAs,

Table 101.1 Major dietary sources of fatty acids

Common name	Dietary sources
Saturated fatty acids	
Palmitic acid	Meats, cheeses, butter, palm oil
Stearic acid	Animal fat, cocoa butter and shea butter
Monounsaturated fatty acids	
Palmitoleic acid	Macadamia oil, sea buckthorn oil
Oleic acid	Sunflower oil, safflower oil
Polyunsaturated fatty acids	
n-6 subfamily:	
Linoleic acid	Sunflower seed, corn, soya, sesame, canola, safflower and their oils
Arachidonic acid	Meat, eggs
n-3 subfamily:	
Alpha-linolenic acid	Rapeseed, soybeans, walnuts, flaxseed, perilla, chia, hemp and their oils
Eicosapentaenoic acid	Oily fish, seafood, seaweed, krill oil, seal oil
Docosahexaenoic acid	Oily fish, seafood, seaweed, krill oil, seal oil

several RTCs have tested benefits of *n*-3 PUFA supplementation on proteinuria/albuminuria and renal function in patients mostly with diabetic nephropathy, immunoglobulin A (IgA) nephropathy, or lupus nephritis. These studies are characterized by their small sample size and short duration. Only a few found significant effects of reducing proteinuria/albuminuria or retarding the reduction of GFR. Though not reaching statistical significance, the other RCTs generally showed benefits on markers of kidney damage. A meta-analysis pooling all these studies concluded that there was a greater reduction in urine protein excretion in the intervention group compared to the control group (Miller et al., 2009). Moreover, this pooled analysis showed that the decline in GFR is slower in those with *n*-3 PUFA supplementation than in the controls, but this effect did not reach statistical significance (Miller et al., 2009). Currently, there are no specific recommendations regarding dietary fat intake in patients with CKD. Along with the recommendations made at the general population level, a reduction in SFA intake and an increase in *n*-3 PUFA intake should be advocated for cardioprotection. When recommending fish intake in CKD patients, prescribers should advice on the phosphate to protein ratio of different fish species.

Carbohydrate intake

Sugar and sweeteners

There is no macronutrient whose consumption has increased as much in humans as sugars and sweeteners, especially after the introduction of soda drinks in the 1940s. Much research is devoted to the association between these nutrients and the development of obesity. What are the potential roles in the development of CKD? A number of epidemiological studies have suggested an association between consumption of sugary drinks/sodas and the presence of CKD in the community. The consumption of these items has also been associated with the development of albuminuria or CKD and with a faster GFR decline (Bomback et al., 2009; Lin et al., 2011). There is currently no evidence of an effect of interventional studies restricting sugar/sweetener intake in CKD patients. A RCT in patients with CKD stages 2–3 demonstrated, however, that a low fructose diet significantly reduced a number of inflammatory biomarkers and blood pressure (Brymora et al., 2012). There are some plausible explanations to explain these links. First, dietary sugar (and particularly fructose) may increase uric acid levels, which in turn may promote hypertension and kidney damage. Second, excessive sugar intake may promote obesity, which in turn may promote kidney damage. Third, excessive sugar intake increases the risk of diabetes mellitus, which is the most common cause of CKD (Karalius and Shoham, 2013).

Fibre intake

Because potassium concentrations are high in fruits and vegetables, CKD and dialysis patients are counselled against taking these. This might result in a decreased intake of fibre. A recent study found that CKD patients with lower fibre intake have elevated serum C-reactive protein levels and increased mortality (Krishnamurthy et al., 2012). In a series of RCTs, a higher intake of fruits and vegetables in patients with CKD stages 1–4 was compared to the efficacy of oral bicarbonate. The rationale was that high-alkali fruit intake would reduce the dietary acidic load and be able to control acidic status and subsequent kidney injury; In CKD stage 2, both treatments attenuated kidney injury to a similar extent (Goraya et al., 2012). In CKD stages 3–4, metabolic acidosis was significantly reduced by both treatments (although as expected more in the bicarbonate group) (Goraya et al., 2013). With increased but controlled fruit/vegetable intake, hyperkalaemia was not induced (Goraya et al., 2013). There is no evidence that fibre or fruit/vegetable intake can delay CKD progression.

Micronutrients and progression of chronic kidney disease

Dietary salt: usually restrict intake

Hypertension is a well-established cause and complication of CKD and a mediator of CKD progression. Epidemiological evidence suggests that salt consumption at a community level may impair kidney function. For instance, dietary sodium was associated with an increased odds ratio for albuminuria in obese, but not in normal-weight, adults (Aaron et al., 2011). In a 14-years follow-up study, higher dietary sodium intake was independently associated with an estimated GFR decline ≥ 30% from baseline (Lin et al., 2010). Dietary programmes restricting salt intake in the community are effective in controlling hypertension, for example, the Dietary Approaches to Stop Hypertension (DASH)-Sodium study, in which lowering sodium intake to 1 or 0.6–1.0 g/day reduced systolic blood pressure by 7.1 and 11.5 mmHg, respectively (Sacks et al., 2001). There is, however, no evidence from interventional trials to support the belief that a reduction of dietary sodium will prevent the development of CKD.

The kidney is the major organ of salt excretion and so plays a key role in the maintenance of sodium balance. Most patients with moderate-advanced CKD have decreased ability to excrete a high sodium load and develop salt sensitive hypertension. Indeed, the prevalence of salt sensitive hypertension increases with age especially when kidney function is declining. In contrast, CKD subjects

with tubulointerstitial disease may maintain normal blood pressure because they excrete salt more readily. An interventional study (Yu et al., 2012) assigned 176 patients with non-dialysed hypertensive CKD to a low-sodium diet (2300 mg/day) over 7 days. Compared with a control group, the sodium restriction group had greater reduction in systolic and diastolic blood as well as a reduction in urine protein excretion.

The ideal sodium intake for non-dialysed CKD patients is a matter of debate. Most guidelines specific to the nutritional management of CKD patients recommend an upper limit of 2.3 g/day (Fouque et al., 2007; Levin et al., 2008). The United States dietary guidelines recommend a stricter target of 1.5 g/day for people with CKD. The nature of the Western diet and the excess of salt in processed foods, mean that a careful dietary plan may not be sufficient to achieve these goals. In fact, mean 24-hour urinary sodium excretion in large studies suggests that CKD patients commonly have sodium intakes far above those recommendations. Identified barriers to adherence to a salt restrictive diet are (a) perceived taste/palatability of low-sodium foods, (b) convenience/difficulty (e.g. time, availability of low-sodium foods, interference with socialization, and cost) or, (c) lack of knowledge or understanding (e.g. lack of perceived benefit and inability to identify low-sodium foods). Bread, baked products, pre-cooked foods, and sausages are the most common sources of sodium in a Western diet besides the salt added to meals. Sodium content is often reported on food labels, and as a rule of thumb, foods containing < 0.5 g of sodium/100 g can be considered low in sodium. Spices and aromatic herbs may replace sodium to enhance taste and appetite. A skilled nutritionist is needed to assist patients in restricting dietary salt.

Various RCTs suggest that dietary sodium restriction enhances the renal and cardiovascular protective effects of first-choice antihypertensive therapies in patients with diabetic and non-diabetic kidney disease. For instance, treatment with angiotensin receptor blockers (ARBs) compared with non-renin–angiotensin–aldosterone system (RAAS) intervention produced the greatest long-term effects on renal and cardiovascular events in the lowest tertile of sodium intake (Fig. 101.1) (Lambers Heerspink et al., 2012). Conversely, drug-resistant hypertension, including therapy with angiotensin-converting enzyme inhibitors (ACEIs) or ARBs, is often caused by a high level of salt intake.

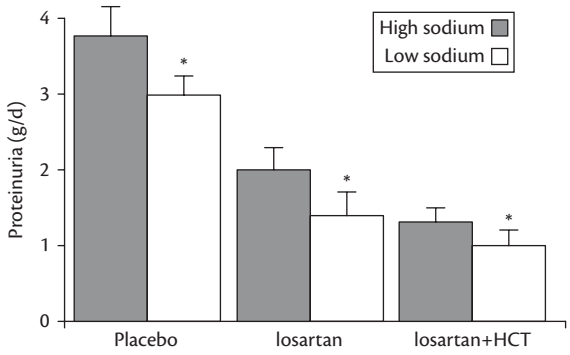

Fig. 101.1 Effect of dietary salt reduction, hydrochlorothiazide, and their combination on proteinuria in proteinuric patients treated with losartan. Reproduced from Lambers Heerspink et al. (2012).

Dietary potassium: restrict only when indicated

The kidney excretes 90% of dietary potassium and in the presence of kidney dysfunction, the intestinal excretion of potassium is increased as a compensatory mechanism. With advanced renal insufficiency, acidosis, or other chronic conditions, the patient's ability to excrete potassium can be impaired. Impaired potassium excretion is the consequence not only of the loss of kidney function, but also an impairment in the action of protective hormones (e.g. aldosterone) or use of medication than can influence potassium levels, such ACEIs, ARBs, or non-steroidal anti-inflammatory drugs. Fortunately, there are adaptative mechanisms that increase the excretion of potassium through both the kidney and gut, making it possible to comply with potassium restriction approaches.

There have been few investigations of the influence of dietary potassium modifications on CKD progression, but the clinical consequences of hyperkalaemia justify the need to reduce potassium intake. On the other hand, there is substantial evidence that diets rich in potassium (e.g. fruits and vegetables) reduce the likelihood of developing chronic diseases, such as coronary heart disease and diabetes. The National Kidney Foundation's expert panel recommended potassium restriction for individuals with advanced CKD stages 4–5 (Kidney Disease Outcomes Quality Initiative (K/DOQI), 2004). However, in pre-dialysis patients, the need for potassium restriction is variable and limits the validity of general recommendations. For instance, potassium supplementation is seldom justified in those on diuretics. In contrast, potassium restriction is needed in those with hyperkalaemia receiving RAAS blockers. Steroids, ACEIs, and potassium-sparing diuretics may induce hyperkalaemia. Loss of intracellular potassium is promoted by acidosis and hyperglycaemia. Hence, serum potassium levels should guide the potassium intake in these patients, and before restricting dietary potassium, a careful exploration for other causes of hyperkalaemia is necessary.

As a practical recommendation to patients, leaching or boiling vegetables in water reduces their mineral content and may be a useful adjunct to a diet low in potassium. However, such techniques may induce loss of nutrients other than potassium, so the patient's nutritional status must be continuously monitored. An excessive consumption of fruits and vegetables may lead to hyperkalaemia, but fruits and vegetables also provide other nutrients of interest for CKD management. Finally, it should also be remembered that food additives may contain significant quantities of 'hidden' potassium.

Dietary phosphorus: restrict when indicated

Organic phosphorus is bound to protein, so the amount of protein eaten will predict phosphorus intake. The intestinal absorption of dietary phosphorus is lower if it comes from animal sources (40–60% absorbed) than that from vegetable sources (10–30% absorbed). In addition, inorganic phosphorus, which is added to processed foods for conservation and enhancement of taste, is almost entirely absorbed in the intestine and represents an important 'hidden' source of phosphorus in the diet. As the amount of inorganic phosphorus is often not reported in food labels, accurate estimation of the real phosphorus intake of CKD patients is difficult. Besides the amount of protein in the diet and its absorption, serum phosphorus concentration depends on additional processes that regulate phosphorus metabolism, including renal excretion of phosphorus, and changes in bone turnover.

Because there are physiologic adaptations in the stages of earlier CKD that prevent excessive phosphorus retention, the inability to promote phosphorus excretion to avoid phosphorus accumulation and hyperphosphataemia occurs when GFR level decreases below 40 mL/min (Moranne et al., 2009). The major adaptation is the stimulation of parathyroid hormone (PTH) release, which increases phosphorus excretion by the proximal tubule. In addition, FGF23 activation will reduce serum phosphorus concentration because phosphorus excretion is stimulated, and the production of calcitriol is reduced, suppressing intestinal phosphorus absorption. The metabolism of these molecules is described in more detail in Chapter 119.

In patients with moderate/advanced CKD, higher serum phosphorus levels have been associated with increased mortality risk (Eddington et al., 2010). There is no clinical evidence that high phosphorus intake accelerates CKD progression. In CKD individuals with moderate/advanced CKD in whom the phosphorus is high, it is reasonable to restrict phosphorus intake and to prescribe phosphorus binders. A low-phosphorus diet decreases serum phosphorus and FGF23 levels (Di Iorio et al., 2012), but the combined prescription of this diet and phosphate binders was more effective than either of those approaches alone (Isakova et al., 2013). The rationale for limiting phosphorus intake in non-dialysed CKD should not be CKD slowing CKD progression but preventing secondary hyperparathyroidism and renal bone disease. It will also reduce the need for calcium-containing phosphate binders which carry a risk of promoting soft tissue calcification. Current recommendations for phosphorus intake in CKD stages 3 and 4 are similar to dialysis patients, that is, to reduce intake to 800–1000 mg/day, in conjunction with use of phosphate binders if appropriate (Ikizler et al., 2013).

Dietary calcium

Calcium supplementation of 2–4 g/day reduces PTH levels in advanced CKD (Barsotti et al., 1998). Given that administration of calcium-containing phosphate binders in haemodialysis patients results in increased vascular calcification, concern has been raised regarding the safety of the excess calcium intake in non-dialysed individuals with CKD. There are no RCTs establishing the safe level of calcium intake in pre-dialysis CKD or its role in disease progression. In a calcium balance study, normal individuals and patients with CKD stages 3 and 4 were in slightly negative to neutral calcium balance on an 800-mg calcium diet (Spiegel and Brady, 2012). Normal individuals were in modest positive calcium balance on a 2000-mg diet, whereas CKD patients on the same diet were in marked positive calcium balance. Furthermore, increased calcium intake significantly decreased 1,25-dihydroxy-vitamin D and PTH levels, but it did not alter the serum calcium concentration. On the basis of this study, a diet of 2000 mg/day of calcium in CKD patients might result in a positive calcium balance with the extra calcium deposited in tissues leading to metastatic calcification. Therefore, it is reasonable to restrict total calcium intake to the currently recommended dose of 1500 mg/day (National Kidney Foundation, 2000).

Vitamins

Vitamins are essential co-factors in normal metabolism. Besides an insufficient intake, vitamin deficiency can occur because of proteinuria with losses of protein-bound elements or decreased intestinal absorption of micronutrients, impaired cellular metabolism, circulating inhibitors, or increased losses during dialysis. There is very little information about the minimum requirements or recommended dietary vitamin allowances in patients with CKD. With the exception of vitamin D, no single study has provided evidence of a possible role of vitamin supplementation in retarding CKD progression.

Because one of the premises of the science of nutrition is to restore levels of defined nutrients, vitamin supplementation probably does little harm and may provide benefits. Because peripheral neuropathy and hyperoxalaemia can occur with high doses of vitamin B_6 (pyridoxine) and vitamin C (ascorbic acid), respectively, megavitamin therapy should be avoided. Plasma vitamin A (retinol) levels are usually increased in CKD patients and, as excess can cause anaemia, dry skin, pruritus, and even hepatic dysfunction in uraemic patients, vitamin A supplementation is not recommended. Vitamin E has the potential to suppress oxidative injury of cells and therefore protect against progressive renal insufficiency in CKD. In experimental models of CKD, vitamin E supplementation reduced renal injury in rats with IgA nephropathy or glomerulosclerosis following subtotal nephrectomy or diabetes. Plasma vitamin E concentrations are usually normal in non-dialysed CKD patients.

Serum vitamin D concentrations in individuals with CKD not on dialysis decrease progressively with the reduction in GFR. Low vitamin D levels have been associated with inflammation and insulin resistance and predict mortality in non-dialysed CKD patients. A recent study demonstrated an association between vitamin D metabolites and ESRD initiation in patients with moderate/advanced CKD (Kendrick et al., 2012). Recommendations on vitamin D at these disease stages are complex. Opinion-based guidelines (<http://www.kidney.org/professionals/kdoqi/guidelines_bone/Guide7.htm>) indicate vitamin D supplementation in CKD patients with serum vitamin D levels < 30 ng/mL. There are still no RCTs demonstrating a benefit of vitamin D supplementation in this patient population.

Diet as a whole

Excessive calorie intake

Caloric restriction is the only intervention that consistently reduces the primary ageing process across multiple species. In addition, and regardless of protein intake, caloric restriction seems to slow kidney injury in various animal models of glomerular adaptation. It has been speculated that in conjunction with the epidemic of obesity as a risk factor for CKD progression, excessive calorie intake rather than specific micro- or macronutrients may influence this risk (Kramer, 2013). Interestingly, a RCT allocated overweight and obese adults with proteinuria from diabetic and non-diabetic kidney diseases to either a usual diet or a diet that reduced their caloric intake by 500 kcal/day (Morales et al., 2003). The study maintained the same protein intake in both groups during 5 months of treatment. Results showed that the group with caloric restriction lost only approximately 4% of their initial body weight, yet proteinuria decreased by > 30%. In comparison, the group that continued to follow the usual diet showed increased proteinuria (Morales et al., 2003). When considering the risk of CKD progression, total caloric intake along with the caloric source should at least be considered as risk factors.

Dietary patterns and CKD progression

Because of the correlation of micro- and macronutrients within dietary patterns and the consistent dietary behaviour over time for most individuals, it is likely that the overall dietary pattern and cumulative exposure to a particular dietary pattern may be more influential on CKD than excess or deficiency of one specific macro- or micronutrient (Kramer, 2013). Much has been said about the problems of the 'Western diet', which is characterized by high intake of red meat; animal fat; sweets and desserts; low intake of fresh fruits and vegetables and low-fat dairy products; and contains a high amount of highly processed foods containing refined sugars and saturated fats and trans-fats. In the Nurses' Health Study, increased urine albumin excretion and higher odds of rapid decline in estimated GFR have been reported among individuals with consistent Western dietary patterns (Lin et al., 2011).

In contrast, more healthy dietary patterns are associated with decreased risk for chronic diseases. This is true of the Mediterranean diet, characterized by a high intake of vegetables, legumes, fruits, nuts, cereals, and olive oil; a moderately high intake of fish; a low-to-moderate intake of dairy products; a low intake of saturated fats, meat, and poultry; and a regular but moderate intake of wine during meals. In a population-based study, a greater adherence to a Mediterranean diet associated with lower odds on presenting with CKD (Fig. 101.2) and was a predictor of mortality in those with manifest CKD (Huang et al., 2013). A recent RCT showed as an ancillary outcome, an improvement of renal function after 1-year following a Mediterranean-like dietary pattern in elderly individuals at high risk of coronary heart disease (Diaz-Lopez et al., 2012). Because blood pressure reduction may be one of the most important means of mitigating progression of established CKD, the DASH diet, especially when combined with salt restriction, could theoretically delay kidney disease progression as long as serum phosphorous levels could be controlled despite the high intake of dairy products in this diet. Adherence to a DASH-type dietary pattern was associated with incident microalbuminuria (Chang et al., 2013) and more rapid kidney function decline (Lin et al., 2011).

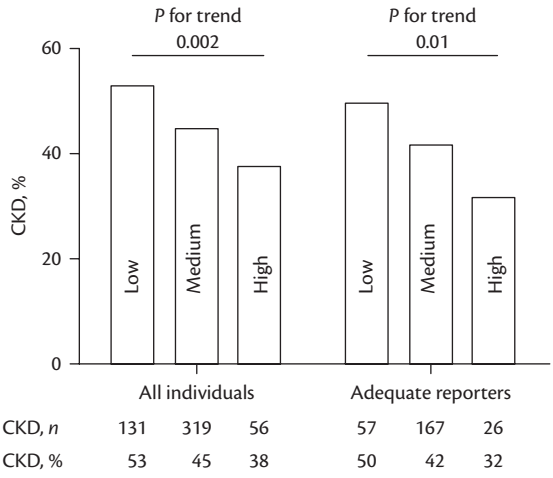

Fig. 101.2 Proportions of men with manifest CKD (GFR < 60 mL/min/1.73 m^2) across different degrees of adherence to a Mediterranean diet in a population-based study of Swedish men. On the left all participants are shown. On the right only those identified as adequate dietary reporters.
Reproduced from Huang et al. (2013).

A secondary analysis of the original DASH study also showed that a diet high in fruits and vegetables decreases urinary albumin excretion in those with urinary albumin excretion > 7 mg/24 hours (Jacobs et al., 2009).

It is possible that physical activity and smoking or occupational exposures that affect kidney disease risk correlate with dietary patterns. Thus, a recent study from the National Health and Nutrition Examination Survey (NHANES) III cohort of about 3000 participants with GFR < 60 mL/min/1.73 m^2 showed that adherence to a healthy lifestyle (assessed on the basis of smoking habits, body mass index, physical activity, and dietary quality) was associated with lower all-cause mortality risk (Ricardo et al., 2013).

Summary

There is anecdotal and experimental evidence that high protein intake may be harmful in moderate CKD, and cause symptoms in advanced CKD. Evidence for low-protein diets slowing the rate of progression of CKD comes from animal experiments, but in studies in CKD in humans in which blood pressure is well controlled, its effects are weak or absent. Furthermore the diets are different to comply with and carry some risk of malnutrition.

Salt intake should be restricted in most patients with reduced GFR or proteinuria, except where there is a salt-wasting tubular problem.

Diet otherwise should be generally healthy and mixed, without substantial restriction unless or until blood levels (in particular potassium, phosphate) dictate otherwise.

References

Aaron, K. J., Campbell, R. C., Judd, S. E., *et al.* (2011). Association of dietary sodium and potassium intakes with albuminuria in normal-weight, overweight, and obese participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Am J Clin Nutr*, 94, 1071–8.

Aparicio, M., Chauveau, P., De Precigout, V., *et al.* (2000). Nutrition and outcome on renal replacement therapy of patients with chronic renal failure treated by a supplemented very low protein diet. *J Am Soc Nephrol*, 11, 708–16.

Barsotti, G., Cupisti, A., Morelli, E., *et al.* (1998). Secondary hyperparathyroidism in severe chronic renal failure is corrected by very-low dietary phosphate intake and calcium carbonate supplementation. *Nephron*, 79, 137–41.

Bernhard, J., Beaufrere, B., Laville, M., *et al.* (2001). Adaptive response to a low-protein diet in predialysis chronic renal failure patients. *J Am Soc Nephrol*, 12, 1249–54.

Bomback, A. S., Katz, R., He, K., *et al.* (2009). Sugar-sweetened beverage consumption and the progression of chronic kidney disease in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Clin Nutr*, 90, 1172–8.

Brymora, A., Flisinski, M., Johnson, R. J., *et al.* (2012). Low-fructose diet lowers blood pressure and inflammation in patients with chronic kidney disease. *Nephrol Dial Transplant*, 27, 608–12.

Chang, A., Van Horn, L., Jacobs, D. R., Jr., *et al.* (2013). Lifestyle-related factors, obesity, and incident microalbuminuria: the CARDIA (Coronary Artery Risk Development in Young Adults) Study. *Am J Kidney Dis*, 62(2), 267–75.

Di Iorio, B., Di Micco, L., Torraca, S., *et al.* (2012). Acute effects of very-low-protein diet on FGF23 levels: a randomized study. *Clin J Am Soc Nephrol*, 7, 581–7.

Diaz-Lopez, A., Bullo, M., Martinez-Gonzalez, M. A., *et al.* (2012). Effects of Mediterranean diets on kidney function: a report from the PREDIMED Trial. *Am J Kidney Dis*, 60, 380–9.

Eddington, H., Hoefield, R., Sinha, S., *et al*. (2010). Serum phosphate and mortality in patients with chronic kidney disease. *Clin J Am Soc Nephrol*, 5, 2251–7.

Fouque, D. and Laville, M. (2009). Low protein diets for chronic kidney disease in non diabetic adults. *Cochrane Database Syst Rev*, 3, CD001892.

Fouque, D., Vennegoor, M., ter Wee, P., *et al*. (2007). EBPG guideline on nutrition. *Nephrol Dial Transplant*, 22 Suppl 2, ii45–87.

Goraya, N., Simoni, J., Jo, C., *et al.* (2012). Dietary acid reduction with fruits and vegetables or bicarbonate attenuates kidney injury in patients with a moderately reduced glomerular filtration rate due to hypertensive nephropathy. *Kidney Int*, 81, 86–93.

Goraya, N., Simoni, J., Jo, C. H., *et al.* (2013). A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate. *Clin J Am Soc Nephrol*, 8, 371–81.

Huang X, Jimenez-Moleon JJ, Lindholm B, *et al*. (2013). Mediterranean diet, kidney function, and mortality in men with CKD. *Clin J Am Soc Nephrol*, 8(9), 1548–55.

Ikizler, T. A., Cano, N. J., Franch, H., *et al*. (2013). Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. *Kidney Int*, 84(6), 1096–107.

Isakova, T., Barchi-Chung, A., Enfield, G., *et al.* (2013). Effects of dietary phosphate restriction and phosphate binders on FGF23 levels in CKD. *Clin J Am Soc Nephrol*, 8, 1009–18.

IUPAC-IUB Commission on Biochemical Nomenclature (1978). The nomenclature of lipids (recommendations 1976). IUPAC-IUB Commission on Biochemical Nomenclature. *J Lipid Res*, 19, 114–28.

Jacobs, D. R., Jr., Gross, M. D., Steffen, L., *et al.* (2009). The effects of dietary patterns on urinary albumin excretion: results of the Dietary Approaches to Stop Hypertension (DASH) Trial. *Am J Kidney Dis*, 53, 638–46.

Karalius, V. P. and Shoham, D. A. (2013). Dietary sugar and artificial sweetener intake and chronic kidney disease: a review. *Adv Chronic Kidney Dis*, 20, 157–64.

Kendrick J, Cheung AK, Kaufman JS, *et al*. (2012). Associations of plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations with death and progression to maintenance dialysis in patients with advanced kidney disease. *Am J Kidney Dis*, 60, 567–75.

Kidney Disease Outcomes Quality Initiative (K/DOQI) (2004). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*, 43, S1–290.

Klahr, S., Levey, A. S., Beck, G. J., *et al*. (1994). The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med*, 330, 877–84.

Kramer, H. (2013). Dietary patterns, calories, and kidney disease. *Adv Chronic Kidney Dis*, 20, 135–40.

Krishnamurthy, V. M., Wei, G., Baird, B. C., *et al.* (2012). High dietary fibre intake is associated with decreased inflammation and all-cause mortality in patients with chronic kidney disease. *Kidney Int*, 81, 300–6.

Lambers Heerspink, H. J., Holtkamp, F. A., Parving, H. H., *et al.* (2012). Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. *Kidney Int*, 82, 330–7.

Levey, A. S., Greene, T., Sarnak, M. J., *et al.* (2006). Effect of dietary protein restriction on the progression of kidney disease: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. *Am J Kidney Dis*, 48, 879–88.

Levin, A., Hemmelgarn, B., Culleton, B., *et al.* (2008). Guidelines for the management of chronic kidney disease. *CMAJ*, 179, 1154–62.

Lin, J. and Curhan, G. C. (2011). Associations of sugar and artificially sweetened soda with albuminuria and kidney function decline in women. *Clin J Am Soc Nephrol*, 6, 160–6.

Lin, J., Fung, T. T., Hu, F. B., *et al.* (2011). Association of dietary patterns with albuminuria and kidney function decline in older white women: a subgroup analysis from the Nurses' Health Study. *Am J Kidney Dis*, 57, 245–54.

Lin, J., Hu, F. B., and Curhan, G. C. (2010). Associations of diet with albuminuria and kidney function decline. *Clin J Am Soc Nephrol*, 5, 836–43.

Miller, E. R., 3rd, Juraschek, S. P., Appel, L. J., *et al.* (2009). The effect of n-3 long-chain polyunsaturated fatty acid supplementation on urine protein excretion and kidney function: meta-analysis of clinical trials. *Am J Clin Nutr*, 89, 1937–45.

Mircescu, G., Garneata, L., Stancu, S. H., *et al.* ((2007). Effects of a supplemented hypoproteic diet in chronic kidney disease. *J Ren Nutr*, 17, 179–88.

Moe, S. M., Zidehsarai, M. P., Chambers, M. A., *et al.* (2011). Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. *Clin J Am Soc Nephrol*, 6, 257–64.

Montes-Delgado, R., Guerrero Riscos, M. A., Garcia-Luna, P. P., *et al.* (1998). [Treatment with low-protein diet and caloric supplements in patients with chronic kidney failure in predialysis. Comparative study]. *Rev Clin Esp*, 198, 580–6.

Morales E, Valero MA, Leon M, *et al.* ((2003). Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. *Am J Kidney Dis*, 41, 319–27.

Moranne, O., Froissart, M., Rossert, J., *et al.* (2009). Timing of onset of CKD-related metabolic complications. *J Am Soc Nephrol*, 20, 164–71.

National Kidney Foundation (2000). Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. *Am J Kidney Dis*, 35, S1–140.

Paes-Barreto, J. G., Silva, M. I., Qureshi, A. R., *et al.* (2013). Can renal nutrition education improve adherence to a low-protein diet in patients with stages 3 to 5 chronic kidney disease? *J Ren Nutr*, 23, 164–71.

Piccoli, G. B., Ferraresi, M., Deagostini, M. C., *et al.* (2013). Vegetarian low-protein diets supplemented with keto analogues: a niche for the few or an option for many? *Nephrol Dial Transplant*, 28(9), 2295–305.

Ricardo, A. C., Madero, M., Yang, W., *et al.* (2013). Adherence to a healthy lifestyle and all-cause mortality in CKD. *Clin J Am Soc Nephrol*, 8, 602–9.

Sacks, F. M., Svetkey, L. P., Vollmer, W. M., *et al.* (2001). Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med*, 344, 3–10.

Spiegel, D. M. and Brady, K. (2012). Calcium balance in normal individuals and in patients with chronic kidney disease on low- and high-calcium diets. *Kidney Int*, 81, 1116–22.

Stevens, P. E., Levin, A., Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group M (2013). Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*, 158, 825–30.

Walker, J. D., Bending, J. J., Dodds, R. A., *et al.* (1989). Restriction of dietary protein and progression of renal failure in diabetic nephropathy. *Lancet*, 2, 1411–15.

Yu, W., Luying, S., and Haiyan, W. (2012). Importance and benefits of dietary sodium restriction in the management of chronic kidney disease patients: experience from a single Chinese center. *Int Urol Nephrol*, 44, 549–56.

Zeller, K., Whittaker, E., Sullivan, L., *et al.* (1991). Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. *N Engl J Med*, 324, 78–84.

CHAPTER 102

Lipid disorders of patients with chronic kidney disease

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Introduction

Chronic kidney disease (CKD) is associated with dyslipidaemia and a high prevalence of cardiovascular disease (CVD) (Kidney Disease Outcomes Quality Initiative (K/DOQI) Group, 2003; Prichard, 2003; Sarnak et al., 2003; Jardine et al., 2008). The pattern of dyslipidaemia is variable, and depends on the stage of CKD, dialysis and transplantation, proteinuria, drug therapy, and primary disease (e.g. diabetes). It is simplest, therefore, to refer to dyslipidaemia, rather than hyperlipidaemia, as cholesterol concentrations may not be raised.

The pattern of CVD in patients with CKD is unusual. Atheromatous coronary disease is common in early CKD but, in advanced and end-stage CKD, where absolute cardiovascular (CV) event rates are greatly increased, sudden death and heart failure predominate (coronary artery disease (CAD)) (Sarnak et al., 2003). Moreover, there are confounding factors, such as the presence of malnutrition and inflammation (Liu et al., 2004), and co-morbid disease, specifically diabetes. In spite of this, most clinical guidelines, now recommend that CKD be treated as a CV risk factor and recommend the use of statin-based, lipid lowering therapy (Kidney Disease Outcomes Quality Initiative (K/DOQI) Group, 2003).

Understanding the relationship of CV risk factors with glomerular filtration rate (GFR) is central to understanding the impact and treatment of dyslipidaemia in this population. It relies on interpreting data from the range of patient groups—from those with minimal reduction in GFR to those with end-stage renal disease (ESRD), treated by dialysis, where the pattern of dyslipidaemia and CV disease is closer to that seen in pre-dialysis patients with CKD 4 and 5 (Jardine et al., 2008).

Lipid metabolism in chronic kidney disease

The characteristic features of dyslipidaemia associated with CKD are elevated triglycerides (TGs), reduced high-density lipoprotein cholesterol (HDL-C), increased intermediate-density lipoprotein cholesterol (IDL-C), but no consistent effect on low-density lipoprotein cholesterol (LDL-C) and total cholesterol (Kidney Disease Outcomes Quality Initiative (K/DOQI) Group, 2003; Prichard, 2003; Jardine et al., 2008). These are associated with qualitative changes in lipoproteins, including an excess of TG-rich, immature, atherogenic lipoproteins (Vaziri, 2006). The determinants of these abnormalities include reduced GFR, proteinuria, drug therapy, primary disease (notably diabetes), and the associated effects of advanced CKD, which are mediated by altered enzyme and receptor function (Vaziri, 2006; Jardine et al., 2008). The major effects are due to reduced lipoprotein lipase (*LPL*) gene expression and function (Roullet et al., 1986; Pandak et al., 1994; Klin et al., 1996; Attman et al., 1997; Vaziri et al., 2001a). In CKD, circulating factors also impair LPL function, including low APOE, which reduces substrate binding to endothelial LPL (Attman et al., 1993; Vaziri et al., 2001b). LPL is also inhibited by other factors in CKD including drugs, elevated parathyroid hormone (PTH), and insulin resistance (Guarnieri et al., 1978; Attman et al., 1993). Impaired LPL-mediated lipolysis of very low-density lipoproteins (VLDLs) and chylomicrons (CMs), contributes to increased circulating CMs and VLDLs. Hepatic lipase (HL) activity (Kimura) is also impaired (Deighan et al., 2001; Kimura et al., 2003; Vaziri et al., 2004; Jardine et al., 2008) causing impaired clearance of IDL and increased TG content in IDL, LDL, HDL, and CM.

The rate-limiting enzyme for cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, is not affected by GFR (Vaziri et al., 1999). In patients with nephrotic-range proteinuria, HMG-CoA reductase expression is increased (Acton et al., 1996; Liang and Vaziri, 2002) and may contribute to increased cholesterol concentration. A low GFR is also associated with reduced hepatic lecithin:cholesterol acyl transferase (*LCAT*) gene expression (Vaziri et al., 2004) and consequently, in cholesterol esterification. LCAT deficiency in models of CKD (Guarnieri et al., 1978; Roullet et al., 1986) and patients with ESRD also causes failure of HDL maturation, and reduced plasma HDL cholesterol. Cholesterol ester transfer protein (CETP) promotes exchange of cholesterol ester for TG, between HDL and IDL. CETP is increased in patients receiving haemodialysis and in the presence of proteinuria, causing elevated HDL-TGs (Guarnieri et al., 1978).

CKD-associated changes in lipoproteins also contribute to reduced synthesis and maturation of HDL. HDL contains APOA-I and -II, which activate LCAT and hepatic lipase, and which are reduced in CKD (Vaziri et al., 1999). APOA-II is also a ligand for SRB-1, an HDL binding protein which mediates the disposal of HDL cholesterol ester and TG (Acton et al., 1996). Acyl-coenzyme A cholesterol acyl transferase (ACAT) prevents de-esterification of cholesterol esters (Vaziri, 2006), the increase in ACAT activity in CKD thus further impairs HDL-mediated cholesterol uptake and maturation (Liang and Vaziri, 2002).

Hypertriglyceridaemia is one of the characteristic features of uraemic dyslipidaemia (Keane, 1996; Prichard, 2003; Cases and Coll, 2005; Vaziri, 2006). Hepatic acyl-coenzyme A diglyceryl transferase (DGAT) activity, the final step in TG biosynthesis (Vaziri, 2003), is increased in proteinuric states.

These enzymatic changes in CKD combine with alterations in receptor proteins to produce the characteristic dyslipidaemia. In the liver, LDL receptor-related protein (LRP) clears plasma IDL and CM remnants (targeted by APOE and APOB) (Vaziri, 2006). Its reduction in CKD, leads to elevated levels of CMs and IDL. Similarly, reduced expression of the VLDL receptor impairs APOE-dependent VLDL clearance and results in increased plasma VLDL (Vaziri and Liang, 1996b; Liang et al., 1998). Low levels of the LDL receptor in the liver, in the presence of proteinuria, but not low GFR (Liang and Vaziri, 1999; Fielding and Fielding, 2001; Vaziri, 2006), contribute to increased LDL and dyslipidaemia. APOA-I and -II are key constituents of HDL, which are reduced in ESRD (Vaziri et al., 1991; Vaziri, 2006) and contribute to low HDL levels. APOA-I is the ligand for the ATP binding cassette transporter (ABCA1) and SRB-1 that mediate incorporation of cholesterol by HDL in cells, and cholesterol transfer to the liver (Vaziri and Liang, 1996a). Reduced SRB-1 in proteinuric states (Vaziri et al., 2001a; Vaziri, 2003) also contributes to failure of reverse cholesterol transport.

All these defects contribute to the overall pattern of dyslipidaemia—the pattern reflecting the effects of low GFR and proteinuria. The key features are an increase in TG-rich, immature particles; with elevated TGs, reduced HDL-C and increased IDL-C rather than the increase in LDL-C that is associated with increased risk of CVD in other populations (Vaziri, 2006; Jardine et al., 2008).

Dyslipidaemia and cardiovascular disease in chronic kidney disease

Cardiovascular outcomes

Many studies have examined the relationship between GFR and CV outcomes. These include post hoc analyses of CV intervention trials. These must be interpreted with caution, as patients were recruited on the basis of pre-existing coronary heart disease or CV risk, and a high risk of coronary disease. Patients with primary progressive renal disease do not necessarily share the same pattern of CVD; whilst coronary heart disease may predominate in early CKD, the excess risk in advanced and RSRD is for heart failure and sudden cardiac death. This has important implications for interpretation of the relationship between lipids and CV events. Analysis of data from a large US healthcare network demonstrated that estimated GFR (eGFR) < 60 mL/min was associated with increased risk of CV events (Go et al., 2004) in > 1 million patients with a mixture of underlying diseases. Post hoc analyses of interventional trials of lipid-lowering therapy (Prichard, 2003; Anavekar et al., 2004; Tonelli et al., 2006) have shown a similar inverse relationship between eGFR and outcome. However, in end-stage renal failure (and most likely pre-dialysis CKD 4 and 5), the relationship between total cholesterol or LDL-C and CV mortality is 'J' or 'U' shaped, in contrast to the linear relationship seen in other high-risk populations (Liu et al., 2004). This is an example of reverse epidemiology (K. Kalantar-Zadeh et al., 2003; C. P. Kalantar-Zadeh, 2007). When inflammatory markers, such as interleukin 6 and C-reactive protein, are corrected for, the underlying relationship between lipids and CV events is similar to the general population (Liu et al., 2004). These observations highlight two issues with the application of established relationships between dyslipidaemia and their management in CKD. The first is that the dyslipidaemia is different from that in the general population, and that there are confounding risk factors in advanced and end-stage CKD, such as inflammation, that mask the relationship between dyslipidaemia and CV events (K. Kalantar-Zadeh et al., 2003). The second is that hyperlipidaemia is an established risk factor for atheromatous CAD and this relationship holds with pooled CV events only when CAD is the major component. In advanced and end-stage CKD, coronary events are a minor component of total CV disease and relationship between lipids and individual events are obscured. These observations are relevant because we rely on the established relationship between lipids and CV disease in the general population, and the proven benefit of lipid lowering with statins, for primary and secondary prevention. If these relationships do not hold in the renal population then it is difficult to plan preventative strategies without specific trial data (Jardine et al., 2008).

Renal outcomes

Glomerulosclerosis shares histological and pathophysiological features with atherosclerosis (Border and Ruoslahti, 1992; Attman et al., 1993). The glomeruli are replaced by extracellular matrix, produced by mesangial cells. LDL-C and oxidized LDL increase matrix production by mesangial cells *in vitro*, and are found in biopsies (Takemura et al., 1993; Abrass, 2004). Experimental hypercholesterolaemia causes glomerulosclerosis and tubular injury that is limited by lipid-lowering therapy (Takemura et al., 1993; Marsh, 1996; Yoshimura et al., 1999; Abrass, 2004; Verhulst et al., 2004). A similar association in patients with CKD (Attman et al., 1993, 1997) has been interpreted as suggesting that statin therapy may limit renal damage.

Lipid-lowering therapy in chronic kidney disease

HMG-CoA reductase inhibitors (statins)

Short-term studies have shown the efficacy and safety of statin therapy in patients with CKD (Baigent et al., 2005, 2011; Landray et al., 2006). Many have been post hoc analyses (based on eGFR) of statin intervention trials, and there are relatively few trials in patients with primary renal disease, or who were selected on the basis of GFR. Of these, the UK-HARP study (Baigent et al., 2005), a prelude to the SHARP study, was a 2 × 2 placebo controlled study of aspirin and simvastatin 20 mg per day in 448 patients with CKD (serum creatinine >150 μmol/L; including 206 patients receiving renal replacement therapy, two-thirds of whom were transplant recipients). Simvastatin reduced total cholesterol by 18%, LDL-C by 30%, non-HDL-C by 28%, and TG by 15%; there was a 5% increase in HDL-C. Similar effects were seen in dialysis and non-dialysis patients. In the subsequent UK-HARP-II study (Landray et al., 2006), 203 non-transplant patients with CKD (152 pre-dialysis) received simvastatin with, or without, ezetimibe 10 mg per day; the combination offering a further substantial reduction in lipids benefit compared to simvastatin alone, without increasing adverse events. Ezetimibe addition resulted in a 25% greater reduction

in total cholesterol, 21% in LDL-C, and 27% greater reduction in non-HDL-C (Baigent et al., 2005). In the main outcome study that followed—the Study of Heart and Renal Protection (SHARP)—patients with CKD (two-thirds of whom were dialysis independent) received simvastatin 20 mg plus ezetimibe 10 mg daily or placebo with an associated mean reduction in LDL-C (68%) compared to 14% in the control arm, and similar relative changes in other subfractions (Baigent et al., 2011). However, the absolute effect of the combination of ezetimibe and simvastatin was no greater than statin alone in other studies, and in the HARP-I and -II studies. In ESRD, which is most likely to reflect the response in patients with pre-dialysis CKD, the Die Deutsche Diabetes Dialyse Studie (4D study) of atorvastatin 10 mg per day in type 2 diabetic haemodialysis patients, active therapy reduced LDL-C from 121 to 72 mg/day (Wanner et al., 2005). The AURORA Study (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: An Assessment of Survival and Cardiovascular Events) (Fellstrom et al., 2009), of 10 mg rosuvastatin daily produced a 43% reduction in LDL-C, 27% reduction in total cholesterol, and 16% reduction in TG, with a 2.9% rise in HDL-C after 3 months. In renal transplant recipients, with varying degrees of renal impairment, in the Assessment of LEscol in Renal Transplantation (ALERT) study, fluvastatin 40–80 mg per day was associated with a 32% reduction in LDL-C compared with placebo (Holdaas et al., 2003, 2005).

Non-statin agents

Fibrates are used in the treatment of hypertriglyceridaemia, which might suggest a role in CKD. However, their use has been associated with myositis, rhabdomyolysis and acute kidney injury (Broeders et al., 2000; Deighan et al., 2001) particularly when used in combination with statins. An older study which compared cerivastatin and fenofibrate in the nephrotic syndrome showed comparable reductions in total cholesterol, but cerivastatin had greater impact on LDL-C (23 vs 8% reduction) atherogenic LDL, whereas fenofibrate produced a greater reduction in TG (41 vs 14%), TG-rich remnants, and an increase in HDL. Niacin, and nicotinic acid derivatives, have a spectrum of actions that suggest possible benefits in uraemic dyslipidaemia—to increase HDL-C and reduce TG. However, efficacy data are limited and these agents are not universally available (Owada et al., 2003). The use of phosphate binders, specifically sevelamer and related compounds, which bind lipids in the gut reducing cholesterol absorption, may also contribute to lipid lowering, although this is not their primary indication (Chertow et al., 2002).

Adverse effects and guidelines

Statins commonly cause gastrointestinal symptoms including bloating, diarrhoea, nausea, and constipation, but these do not appear more common in CKD. There may be an increased risk of muscular symptoms and rhabdomyolysis (particularly when combined with fibrates) although the absolute risk is very small. Fibrates have been associated with acute kidney injury (Broeders et al., 2000). Thus, although fibrates have their benefits, statins have been favoured in clinical use but the combination of statins and fibrate is discouraged in published guidelines. Statins are the most commonly used first-line agents. They differ in their metabolism and, specifically, metabolism by the microsomal enzymes—CYP3A4 and CYP2C9. Recommendations about dosage reduction for individual agents according to the degree of renal impairment vary, but in general it is not necessary to reduce dosage by > 50%, unless agents are used in combination with ciclosporin (Broeders et al., 2000; Chertow et al., 2002; Prichard, 2003; Vaziri, 2006; Campese and Park, 2007).

Intervention—clinical trials

Several studies have investigated lipid-lowering therapies in patients at different stages of CKD, with varying degrees of renal impairment and proteinuria. In general, the pattern and proportional effects on lipid subtypes are similar to those seen in other patient populations, but cardiovascular protection and survival benefits have been more difficult to demonstrate in patients with advanced and ESRD.

Analysis of the Pravastatin Pooling Project (PPP) of 19,700 patients from the LIPID, WOSCOPS, and CARE studies (Shepherd et al., 1995; Sacks et al., 1996; The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998; Tonelli et al., 2004), identified 63% of patients with 'mild' CKD (eGFR 60–90 mL/min) and 23% with eGFR < 60 mL/min; lower eGFR being associated with older age, coronary disease, and hypertension. Patients randomized to statin therapy had a lower risk of CV endpoints regardless of the level of CKD (Heart Protection Study Collaborative Group, 2002; Sever et al., 2003; Tonelli et al., 2005). Mortality was also reduced in the subgroup recruited from secondary prevention studies, where CV mortality is the main contributor to all-cause mortality (Sever et al., 2003). A further analysis showed comparable benefits on CV events of pravastatin in patients with CKD (eGFR < 60 mL/min or < 90 mL/min plus proteinuria) and diabetes, who are more likely to have a defined renal disease.

Similar proportionate benefits of statin therapy have been reported in post hoc analyses of large-scale CV outcome studies including the Heart Protection Study (HPS) (Holdaas et al., 2001) which included 20,500 patients with serum creatinine 1.5–2.3 mg/dL) treated with simvastatin 40 mg per day; the 4S study (Holdaas et al., 2011), patients recruited to the JUPITER study of rosuvastatin 10 mg daily (identified on the basis of a modest increase in CRP as the primary CV risk factor), and a pooled analysis of all studies involving fluvastatin (Upadhyay et al., 2012), 20–80mg. The detail of these studies has been extensively reviewed, along with many other similar analyses, in three contemporary meta-analyses (Tonelli et al., 2004; Holdaas et al., 2001; Kassimatis and Goldsmith, 2010). Further detail is provided below but the overall message can be summarized. All statins provide comparable short-term lipid-lowering effects in patients with CKD, with placebo-like adverse event profiles. In patients with mild to moderate CKD, the reduction in CV risk is comparable to non-renal populations and, in populations with the very highest risk of coronary disease and coronary mortality (e.g. 4S), the reduction in CVD is accompanied by a reduction in mortality. However, the precise benefits of lipid lowering are less clear in patients with advanced CKD.

The Prevention of Renal and Vascular End stage Disease Intervention Trial (PREVEND-IT) is the only prospective, interventional trial of lipid lowering confined to patients with pre-dialysis CKD. With hindsight, it was underpowered, including just 864 patients with microalbuminuria, randomized to fosinopril 20 mg and pravastatin 40 mg daily, or placebo, in a 2 × 2 design. Although the main study failed to show a significant benefit other than reduction of microalbuminuria by angiotensin blockade (Asselbergs et al., 2004), a subsequent analysis

showed a significant reduction in CV events in a subgroup of patients with microalbuminuria as part of the metabolic syndrome (Geluk et al., 2005). Renal transplant recipients (RTRs) commonly have a degree of renal impairment. In the Assessment of LEscol in Renal Transplantation (ALERT) study (Holdaas et al., 2001, 2003, 2005), RTRs with a mean serum creatinine of around 150 μmol/L were treated with fluvastatin, 40–80 mg/day, or placebo. All lipid parameters were associated strongly with the development of coronary events, and although the primary study failed to show a significant benefit of statin therapy on pooled CV events, a 2-year extension to the main study did reveal a benefit of statin therapy.

Since it is likely that patients with advanced CKD have CVD that is most like that of patients with ESRD, it is worth considering the available trials in ESRD. The 4D trial (Wanner et al., 2005), failed to show a significant reduction in CV events in 1255 type 2 diabetic haemodialysis recipients, despite the potent effects of atorvastatin 20 mg/day on lipid levels. Post hoc analyses did, however, how a significant reduction in the risk of cardiac events and all-cause mortality in patients with high baseline LDL-C (> 145 mg/dL) (Palmer et al., 2012). In the AURORA trial of rosuvastatin 10 mg/day in 2776 haemodialysis patients (Fellstrom et al., 2009), LDL-C was reduced by 43% but there was no reduction in the composite CV endpoint. There was, however, a reduction in CV events in a post hoc analysis of patients with diabetes (Holdaas et al., 2011). Thus, whilst neither 4D nor AURORA showed overall benefit, post hoc analyses suggest benefits in patients at high risk of atheromatous coronary disease, although dyslipidaemia is a relatively minor CV risk factor in this group while other factors such as inflammation or vascular calcification may play a larger part. The intervention may have been too late in the natural history of such a complex disease.

The most informative study for the management of dyslipidaemia across the spectrum of CKD is the SHARP study (Baigent et al., 2011). SHARP included 9270 CKD patients, allocated to simvastatin 20 mg plus ezetimibe 10 mg daily (SIM/EZE, see HARP-II above) (Landray et al., 2006). One-third of the population were dialysis dependent at the outset, another third developed ESRD during the study. In the two-thirds who were not dialysis dependent at the outset, the eGFR spanned the range. The primary endpoint was refined in the light of the studies above to focus on atheromatous CV disease, more likely to be responsive to lipid-lowering therapy. In patients treated with SIM/EZE, LDL-C fell by 0.85 mmol/L and major adverse CV events by 17% (hazard ratio 0.83, 95% confidence interval 0.74–0.94, P = 0.0021). Reduction in coronary revascularization was a major determinant of benefit. However, there was no survival benefit. The benefit was seen despite a high discontinuation rate, typical of this population, and in spite of a placebo-like side effect profile. SHARP is a study that is unlikely to be replicated and thus provides the best trial evidence we have for statin therapy. The 'take-home message' is clear: lipid lowering has significant benefits across the spectrum of CKD, specifically the prevention of atherosclerotic CV events.

Three recent systematic reviews and meta-analyses provide further support for the benefit of statins in CKD patients. They provide a list of the primary CV intervention trials which have been subjected to post hoc analysis on the basis of eGFR (see above). Upadhyay et al. included five randomized trials in CKD (including dialysis) and 13 post hoc analyses from CV intervention trials. Lipid lowering using statin-based therapy was associated with a 22% reduction in CV events and 26% reduction in myocardial infarction (Upadhyay et al., 2012). Palmer et al. included 80 studies with 51,099 subjects, confirming the benefit of statins on all-cause and CV mortality and CV events in non-dialysis CKD patients (Palmer et al., 2012). The most recent meta-analysis, by Hou and colleagues, of 48,000 patients included 31 clinical trials, and is probably the most complete and informative (Hou et al., 2013). In these studies statin therapy—regardless of the agent used—was associated with a 23% reduction in relative risk for major CV events, an 18% reduction in coronary events, and a 9% relative risk reduction in cardiac death. However, there was no significant effect on stroke, renal function, progression to ESRD, or side effects. Although the take-home message from this meta-analysis is broadly similar to the other two, the authors clearly showed that the relative benefits of statin therapy are less in more advanced CKD. This may reflect the impact of confounding risk factors as CKD progresses, or the relative reduction in the proportion of CV events that are lipid dependent and therefore receptive to statin therapy.

There are few trials that have assessed non-statin therapy in CKD. However, a post hoc analysis of the VA-HIT study (Tonelli et al., 2004) in which patients with coronary disease and low HDL received gemfibrozil identified 40% of the patients with a creatinine clearance < 75 mL/min. This subgroup had a similar 25% reduction in CV events to the overall study population. Gemfibrozil use was associated with a 35% reduction in TG, a 5% increase in HDL-C, but no significant reduction in LDL-C, with the implication that fibrates may have similar benefits to statins in patients with pre-existing CHD, who have low HDL-C. However, there are no large-scale trials of fibrates in CKD and the side effect profile is less good than statins which is one of the reasons that statins have been almost exclusively adopted in the CKD population and in other patient groups.

Renal endpoints

The parallels between atherosclerosis, and the evidence linking hyperlipidaemia and progression of renal disease, have led to the expectation that statins may protect against progression of CKD. Small-scale studies using simvastatin, pravastatin, and fluvastatin have provided evidence to support this notion. A study by Bianchi and colleagues in 56 patients with proteinuric, progressive renal disease, demonstrated that atorvastatin (in combination with blockade of the renin–angiotensin system) reduced proteinuria, and the rate of loss of GFR by approximately 50% (Bianchi et al., 2003). A pooled analysis of nearly 4000 patients included in clinical trials of rosuvastatin noted a progressive increase (1–3 mL/min) in patients receiving rosuvastatin therapy (Vidt et al., 2006). The rosuvastatin development programme identified a small increase in proteinuria in patients receiving statin therapy. However, meta-analyses of the available data do not support a major effect of statins on renal function or proteinuria (Upadhyay et al., 2012). A small Australian study—the Lipid lowering and Onset of Renal Disease (Fassett et al., 2010) (LORD) study of 123 patients reported a 29% reduction in the rate of decline of GFR over 3 years in CKD stage 2–4 patients receiving atorvastatin 10 mg/day, associated with a reduction in NGAL, a marker of renal injury. Overall, the available data do not suggest a particularly strong effect of statins on renal function, but provide reassurance for the absence of significant adverse effects.

Treatment: guidelines and targets

The majority of national and international guidelines for patients with renal disease support the use of statins in patients with CKD. Similar guidelines from other national and international bodies aimed at other primary disease groups in cardiology, diabetes transplantation, and hypertension, recommend the use of statins for patients with coexistent CKD.

The National Kidney Foundation KDOQI guidelines (KDOQI, 2007; Slinin et al., 2012) chose to endorse the use of statins and targets from other populations. They recommend annual measurements of lipids for all patients, statin therapy, and target LDL-C levels ≥ 2.6 mmol/L (100 mg/dL). They also recommended that CKD 1–4 be treated as a CV risk factor equivalent. In practice, most patients with CKD stages 1–4 have other risk factors (diabetes, hypertension, and dyslipidaemia) that would make them eligible for CV risk management.

A similar approach has been adopted in the guidelines for treatment in other countries including the United Kingdom although most guidelines acknowledge the absence of specific outcome trial data. The most recent KDOQI guidelines (<http://www.kdigo.org>) have endorsed CKD as a CV risk, and the use of statins for all patients with CKD. However, rather than adopt targets from other populations these guidelines recommend only a single lipid measurement and no target lipid levels 'fire and forget'.

The UK National Institute for Health and Care Excellence (NICE) guideline on lipid lowering recommends use of atorvastatin 20 mg for primary or secondary prevention, increasing the dose if the achieved reduction in non-HDL cholesterol is < 40% (rather than a target level) (NICE, 2014).

Conclusions

The risk of developing CVD is increased in patients with CKD. There is no doubt that dyslipidaemia is a major contributory factor to the development of premature CVD but the relationship is complex. The pattern of dyslipidaemia is related to GFR, the presence and severity of proteinuria, diabetes, and other confounding factors. The spectrum of CVD changes from lipid-dependent, atheromatous coronary disease in early CKD, to lipid-independent, non-coronary disease—which manifests itself as heart failure, and sudden cardiac death—in advanced and ESRD.

The value of statin-based, lipid-lowering therapy is proven to reduce coronary events across the spectrum of CKD; the relative reduction in overall CV events, however, diminishes as CKD progresses and the proportion of lipid-dependent coronary events declines. Nonetheless, there is a strong argument, enshrined in clinical guidelines, for the use of statin-based therapy across the spectrum of CKD. The argument is particularly strong for those patients with progressive loss of GFR who will eventually require transplantation, where preventive therapy should commence as early as possible in the course of the disease process. The SHARP study establishes the benefits and endorses the use of lipid-lowering therapy in CKD stages 1–4 (Baigent et al., 2011) and, although there is uncertainty about the initiation of statin therapy in CKD stage 5, there is no rationale for stopping agents started earlier in the natural history of progressive disease for compelling indications, or in those who will ultimately be transplanted.

The place of HDL-raising and TG-lowering therapy will need to be assessed in future trials. The most important result of the trials of lipid lowering in CKD is that lipid-dependent atheromatous cardiovascular disease is only one component of the greatly increased burden of CVD that affects patients, proportionately less in advanced CKD, and that lipid-lowering therapy is only one element of management.

References

Abrass, C. K. (2004). Cellular lipid metabolism and the role of lipids in progressive renal disease. *Am J Nephrol*, 24(1), 46–53.

Acton, S., Rigotti, A., Landschulz, K. T., *et al.* (1996). Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. *Science*, 271(5248), 518–20.

Anavekar, N. S., McMurray, J. J., Velazquez, E. J., *et al.* (2004). Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*, 351(13), 1285–95.

Asselbergs, F. W., Diercks, G. F., Hillege, H. L., *et al.* (2004). Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation*, 110(18), 2809–16.

Attman, P. O., Samuelsson, O., and Alaupovic, P. (1993). Lipoprotein metabolism and renal failure. *Am J Kidney Dis*, 21(6), 573–92.

Attman, P. O., Samuelsson, O., and Alaupovic, P. (1997). Progression of renal failure: role of apolipoprotein B-containing lipoproteins. *Kidney Int Suppl*, 63, S98–101.

Baigent, C., Landray, M., Leaper, C., *et al.* (2005). First United Kingdom Heart and Renal Protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. *Am J Kidney Dis*, 45(3), 473–84.

Baigent, C., Landray, M. J., Reith, C., *et al.* (2011). The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*, 377(9784), 2181–92.

Bianchi, S., Bigazzi, R., Caiazza, A., *et al.* (2003). A controlled, prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. *Am J Kidney Dis*, 41(3), 565–70.

Border, W. A. and Ruoslahti, E. (1992). Transforming growth factor-beta in disease: the dark side of tissue repair. *J Clin Invest*, 90(1), 1–7.

Broeders, N., Knoop, C., Antoine, M., *et al.* (2000). Fibrate-induced increase in blood urea and creatinine: is gemfibrozil the only innocuous agent? *Nephrol Dial Transplant*, 15(12), 1993–9.

Campese, V. M. and Park, J. (2007). HMG-CoA reductase inhibitors and renal function. *Clin J Am Soc Nephrol*, 2(6), 1100–3.

Cases, A. and Coll, E. (2005). Dyslipidemia and the progression of renal disease in chronic renal failure patients. *Kidney Int Suppl*, 99, S87–93.

Chertow, G. M., Burke, S. K., and Raggi, P. (2002). Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int*, 62(1), 245–52.

Deighan, C. J., Caslake, M. J., McConnell, M., *et al.* (2001). Comparative effects of cerivastatin and fenofibrate on the atherogenic lipoprotein phenotype in proteinuric renal disease. *J Am Soc Nephrol*, 12(2), 341–8.

Deighan, C. J., Caslake, M. J., McConnell, M., *et al.* (2001). The atherogenic lipoprotein phenotype: small dense LDL and lipoprotein remnants in nephrotic range proteinuria. *Atherosclerosis*, 157(1), 211–20.

Fassett, R. G., Robertson, I. K., Ball, M. J., *et al.* (2010). Effect of atorvastatin on kidney function in chronic kidney disease: a randomised double-blind placebo-controlled trial. *Atherosclerosis*, 213(1), 218–24.

Fellstrom, B. C., Jardine, A. G., Schmieder, R. E., *et al.* (2009). Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*, 360(14), 1395–407.

Fielding, C. J. and Fielding, P. E. (2001). Cellular cholesterol efflux. *Biochim Biophys Acta*, 1533(3), 175–89.

Geluk, C. A., Asselbergs, F. W., Hillege, H. L., *et al.* (2005). Impact of statins in microalbuminuric subjects with the metabolic syndrome: a substudy of the PREVEND Intervention Trial. *Eur Heart J*, 26(13), 1314–20.

Go, A. S., Chertow, G. M., Fan, D., *et al.* (2004). Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*, 351(13), 1296–305.

Guarnieri, G. F., Moracchiello, M., Campanacci, L., *et al.* (1978). Lecithin-cholesterol acyltransferase (LCAT) activity in chronic uremia. *Kidney Int Suppl*, 8, S26–30.

Heart Protection Study Collaborative Group (2002). MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*, 360(9326), 7–22.

Holdaas, H., Fellstrom, B., Cole, E., *et al.* (2005). Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. *Am J Transplant*, 5(12), 2929–36.

Holdaas, H., Fellstrom, B., Holme, I., *et al.* (2001). Effects of fluvastatin on cardiac events in renal transplant patients: ALERT (Assessment of Lescol in Renal Transplantation) study design and baseline data. *J Cardiovasc Risk*, 8(2), 63–71.

Holdaas, H., Fellstrom, B., Jardine, A. G., *et al.* (2003). Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet*, 361(9374), 2024–31.

Holdaas, H., Holme, I., Schmieder, R. E., *et al.* (2011). Rosuvastatin in diabetic hemodialysis patients. *J Am Soc Nephrol*, 22(7), 1335–41.

Holdaas, H., Wanner, C., Abletshauser, C., *et al.* (2007). The effect of fluvastatin on cardiac outcomes in patients with moderate to severe renal insufficiency: a pooled analysis of double-blind, randomized trials. *Int J Cardiol*, 117(1), 64–74.

Hou, W., Lv, J., Perkovic, V., *et al.* (2013). Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. *Eur Heart J*, 34(24), 1807–17.

Jardine, A. G., Mark, P. M., Holdaas, H., *et al.* (2008). Special patient populations: chronic renal disease. In C. M. Ballantyne (ed.) *Ballantyne: Clinical Lipidology*, pp. 500–508. Philadelphia, PA: Saunders.

Kalantar-Zadeh, C. P., Anderson, J. E., and Kalantar-Zadeh, K. (2007). Inverse association between lipid levels and mortality in men with chronic kidney disease who are not yet on dialysis: effects of case mix and the malnutrition-inflammation-cachexia syndrome. *J Am Soc Nephrol*, 18(1), 304–11.

Kalantar-Zadeh, K., Block, G., Humphreys, M. H., *et al.* (2003). Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int*, 63(3), 793–808.

Kassimatis, T. I. and Goldsmith, D. J. (2010). New hope for chronic kidney disease patients after the JUPITER trial: myth or reality? *J Am Coll Cardiol*, 56(6), 529.

KDOQI (2007). KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis*, 49(2 Suppl 2), S12–154.

Keane, W. F. (1996). Lipids and progressive renal failure. *Wien Klin Wochenschr*, 108(14), 420–4.

Kidney Disease Outcomes Quality Initiative (K/DOQI) Group (2003). K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. *Am J Kidney Dis*, 41(4 Suppl 3), 1–91.

Kilpatrick, R. D., McAllister, C. J., Kovesdy, C. P., *et al.* (2007). Association between serum lipids and survival in hemodialysis patients and impact of race. *J Am Soc Nephrol*, 18(1), 293–303.

Kimura, H., Miyazaki, R., Imura, T., *et al.* (2003). Hepatic lipase mutation may reduce vascular disease prevalence in hemodialysis patients with high CETP levels. *Kidney Int*, 64(5), 1829–37.

Klin, M., Smogorzewski, M., Ni, Z., *et al.* (1996). Abnormalities in hepatic lipase in chronic renal failure: role of excess parathyroid hormone. *J Clin Invest*, 97(10), 2167–73.

Landray, M., Baigent, C., Leaper, C., *et al.* (2006). The second United Kingdom Heart and Renal Protection (UK-HARP-II) Study: a randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD. *Am J Kidney Dis*, 47(3), 385–95.

Liang, K. and Vaziri, N. D. (1999). Down-regulation of hepatic high-density lipoprotein receptor, SR-B1, in nephrotic syndrome. *Kidney Int*, 56(2), 621–6.

Liang, K. and Vaziri, N. D. (2002). Upregulation of acyl-CoA: cholesterol acyltransferase in chronic renal failure. *Am J Physiol Endocrinol Metab*, 283(4), E676–81.

Liang, K., Oveisi, F., and Vaziri, N. D. (1998). Role of secondary hyperparathyroidism in the genesis of hypertriglyceridemia and VLDL receptor deficiency in chronic renal failure. *Kidney Int*, 53(3), 626–30.

Liu, Y., Coresh, J., Eustace, J. A., *et al.* (2004). Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA*, 291(4), 451–9.

Marsh, J. B. (1996). Lipoprotein metabolism in experimental nephrosis. *Proc Soc Exp Biol Med*, 213(2), 178–86.

National Institute for Health and Care Excellence (2014). *Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease*. [Online] <http://www.nice.org.uk/guidance/cg181/chapter/1-recommendations>

Owada, A., Suda, S., and Hata, T. (2003). Antiproteinuric effect of niceritrol, a nicotinic acid derivative, in chronic renal disease with hyperlipidemia: a randomized trial. *Am J Med*, 114(5), 347–53.

Palmer, S. C., Craig, J. C., Navaneethan, S. D., *et al.* (2012). Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*, 157(4), 263–75.

Pandak, W. M., Vlahcevic, Z. R., Heuman, D. M., *et al.* (1994). Post-transcriptional regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase and cholesterol 7 alpha-hydroxylase in rats with subtotal nephrectomy. *Kidney Int*, 46(2), 358–64.

Prichard, S. S. (2003). Impact of dyslipidemia in end-stage renal disease. *J Am Soc Nephrol*, 14(9 Suppl 4), S315–20.

Roullet, J. B., Lacour, B., Yvert, J. P., *et al.* (1986). Correction by insulin of disturbed TG-rich LP metabolism in rats with chronic renal failure. *Am J Physiol*, 250(4 Pt 1), E373–6.

Sacks, F. M., Pfeffer, M. A., Moye, L. A., *et al.* (1996). The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*, 335(14), 1001–9.

Sarnak, M. J., Levey, A. S., Schoolwerth, A. C., *et al.* (2003). Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*, 108(17), 2154–69.

Sever, P. S., Dahlof, B., Poulter, N. R., *et al.* (2003). Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*, 361(9364), 1149–58.

Shepherd, J., Cobbe, S. M., Ford, I., *et al.* (1995). Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*, 333(20), 1301–7.

Slinin, Y., Ishani, A., Rector, T., *et al.* (2012). Management of hyperglycemia, dyslipidemia, and albuminuria in patients with diabetes and CKD: a systematic review for a KDOQI clinical practice guideline. *Am J Kidney Dis*, 60(5), 747–69.

Takemura, T., Yoshioka, K., Aya, N., *et al.* (1993). Apolipoproteins and lipoprotein receptors in glomeruli in human kidney diseases. *Kidney Int*, 43(4), 918–27.

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group (1998). Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*, 339(19), 1349–57.

Tonelli, M., Collins, D., Robins, S., *et al.* (2004). Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney Int*, 66(3), 1123–30.

Tonelli, M., Isles, C., Curhan, G. C., *et al.* (2004). Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation*, 110(12), 1557–63.

Tonelli, M., Jose, P., Curhan, G., *et al*. (2006). Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial. *BMJ*, 332(7555), 1426.

Tonelli, M., Keech, A., Shepherd, J., *et al.* (2005). Effect of pravastatin in people with diabetes and chronic kidney disease. *J Am Soc Nephrol*, 16(12), 3748–54.

Upadhyay, A., Earley, A., Lamont, J. L., *et al.* (2012). Lipid-lowering therapy in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*, 157(4), 251–62.

Vaziri, N. D. (2003). Molecular mechanisms of lipid disorders in nephrotic syndrome. *Kidney Int*, 63(5), 1964–76.

Vaziri, N. D. (2006). Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences. *Am J Physiol Renal Physiol*, 290(2), F262–72.

Vaziri, N. D., Deng, G., and Liang, K. (1999). Hepatic HDL receptor, SR-B1 and Apo A-I expression in chronic renal failure. *Nephrol Dial Transplant*, 14(6), 1462–6.

Vaziri, N. D., Kim, C. H., Dang, B., *et al*. (2004). Downregulation of hepatic acyl-CoA:diglycerol acyltransferase in chronic renal failure. *Am J Physiol Renal Physiol*, 287(1), F90–4.

Vaziri, N. D. and Liang, K. H. (1996a). Down-regulation of hepatic LDL receptor expression in experimental nephrosis. *Kidney Int*, 50(3), 887–93.

Vaziri, N. D. and Liang, K. (1996b). Down-regulation of tissue lipoprotein lipase expression in experimental chronic renal failure. *Kidney Int*, 50(6), 1928–35.

Vaziri, N. D., Liang, K., and Parks, J. S. (2001a). Acquired lecithin-cholesterol acyltransferase deficiency in nephrotic syndrome. *Am J Physiol Renal Physiol*, 280(5), F823–8.

Vaziri, N. D., Liang, K., and Parks, J. S. (2001b). Down-regulation of hepatic lecithin:cholesterol acyltransferase gene expression in chronic renal failure. *Kidney Int*, 59(6), 2192–6.

Verhulst, A., D'Haese, P. C., and De Broe, M. E. (2004). Inhibitors of HMG-CoA reductase reduce receptor-mediated endocytosis in human kidney proximal tubular cells. *J Am Soc Nephrol*, 15(9), 2249–57.

Vidt, D. G., Harris, S., McTaggart, F., *et al*. (2006). Effect of short-term rosuvastatin treatment on estimated glomerular filtration rate. *Am J Cardiol*, 97(11), 1602–6.

Wanner, C., Krane, V., Marz, W., *et al*. (2005). Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*, 353(3), 238–48.

Yoshimura, A., Nemoto, T., Sugenoya, Y., *et al*. (1999). Effect of simvastatin on proliferative nephritis and cell-cycle protein expression. *Kidney Int Suppl*, 71, S84–7.

CHAPTER 103

Smoking in chronic kidney disease

Stephan R. Orth

Introduction

Chronic kidney disease (CKD) is a growing worldwide problem. The prevalence of CKD in Western populations is high (Hallan et al., 2006), and the number of CKD stage 5 patients has increased dramatically during the last decades. This rise is expected to continue, particularly in developing countries where—in contrast to developed countries—smoking and other cardiovascular risk factors are increasing substantially.

Diabetes and hypertension are major risk factors for CKD, and data increasingly indicate that smoking also has a negative effect on the kidney. The consequences of cigarette smoking for CKD patients are severe, affecting both the progression of CKD and cardiovascular disease. This is not fully acknowledged by physicians and CKD patients. The lack of any change in smoking behaviours of patients entering renal replacement therapy between 2000 and 2005 (Orth and Hallan, 2008) emphasizes the need to improve smoking cessation rates in CKD patients.

Smoking-associated chronic kidney disease risk in the general population

The Multiple Risk Factor Intervention Trail (MRFIT) investigated 332,544 men and documented that smoking was significantly associated with an increased risk of end-stage renal disease (ESRD) (Klag et al., 1996), but the magnitude of the effect was not reported. A study by Pinto-Sietsma et al. (2000) involved 7476 participants of the Prevention of REnal and Vascular ENd stage Disease (PREVEND) trial. They found a correlation of urine albumin excretion rate with the number of cigarettes smoked. After adjustment for potential confounders, current smokers smoking < 20 cigarettes/day or > 20 cigarettes/day had an elevated risk of high normal urine albumin concentration (relative risk (RR) 1.33 and 1.98, respectively). Halimi et al. (2000) studied 28,409 volunteers from the general population. They found that current and former smokers had a marked risk of macroalbuminuria (adjusted RR 3.26 and 2.69, respectively), indicating irreversible kidney damage related to smoking. Smokers had a slight, but significantly higher creatinine clearance than non-smokers, at least in men, leading to the hypothesis that smoking induces hyperfiltration in the early phase of smoking-related renal functional alteration (Orth, 2002a, 2002b); this notion has recently been supported by a Japanese study investigating 10,118 middle-aged men with no signs of renal dysfunction at study entry (Maeda et al., 2011). After 6 years of observation, current smokers had a 1.32 higher risk for the development of glomerular hyperfiltration and a 1.51 times higher risk for proteinuria than non-smokers. This effect was dose dependent and adjusted for several renal risk factors. A study by Briganti et al. (2002) involving 11,247 randomly selected, population-based Australians, showed that lifetime smoking exposure was significantly associated with CKD stage ≥ 3 in men, but not women. This finding led to the hypothesis that men may be more susceptible to the adverse renal effects of smoking (Orth and Ritz, 2002).

One of the first cohort studies focusing on change in kidney function related to smoking analysed data obtained from 4142 non-diabetic subjects (Bleyer et al., 2000). After adjustment for potential confounding factors, the number of cigarettes smoked/day was highly correlated with progression of CKD. For every five cigarettes smoked/day the RR for an increase in serum creatinine ≥ 27 μmol/L over a minimum of 3 years increased by 31%. The corresponding increase per 10 mmHg rise in blood pressure was 16%.

Since 2003, smoking as a renal risk factor in the general population has been addressed in several studies. Two studies found no effect of smoking on renal function: the study by Vupputuri and Sandler (2003) was a case–control study (N = 1070) limited by its retrospective nature investigating incident CKD only. The other study used baseline data of the PREVEND trial (Verhave et al., 2005). In a cross-sectional analysis, no contribution of smoking, cholesterol:high-density lipoprotein ratio, and antidiabetic medication was found. However, a large number of studies have documented a negative effect of smoking on renal function, the most important being that of Haroun et al. (2003). The endpoint of this large, community-based prospective cohort study of 20 years' duration was ESRD or kidney disease listed on the death certificate. Current cigarette smoking was associated with ESRD or CKD death in both men (hazard ratio (HR) 2.4) and women (HR 2.9). The risk attributed to smoking was 31%. Similarly, current smoking had an adjusted HR of 1.84 for ESRD after 25 years in a recent analysis of 12,866 randomly assigned men of the Multiple Risk Factor Intervention Trial (MRFIT) (Ishani et al., 2006).

A recent community-based, 10-year follow-up study from Japan investigating 123,764 subjects aged > 40 years (Yamagata et al., 2007) found that smoking was a predictor of CKD in men and women (RR for CKD stages 3 and 4 1.13 and 1.16, respectively). The equal risk in men and women was also found in a

population-based, cross-sectional study from Norway involving 65,193 subjects (Hallan et al., 2006). A significant, dose-dependent increase in risk of CKD (glomerular filtration rate (GFR) < 45 mL/min/1.73 m^2) in men and women was seen above a cumulative lifetime cigarette exposure of 25 pack-years (adjusted RR 1.42 for 25–49 pack-years and 2.05 for > 50 pack-years, respectively). Of note, the CKD risk was very high in subjects who, in addition to smoking > 25 pack-years, were obese and physically inactive, pointing to the possibility of a biological interaction of these lifestyle-related variables. In 2981 Italian subjects aged 65–84 years, current smoking (> 20 cigarettes/day) was the strongest independent predictor of a pathological loss of renal function (odds ratio (OR) 2.3) (Baggio et al., 2005). This was independent of baseline serum creatinine and argues for smoking being a very important risk factor for CKD in elderly subjects, which was also confirmed by a South-East Asian population-based study (Joshi et al., 2006). Using a hard clinical endpoint, that is, CKD stage 5, an analysis of a population-based cohort of 65,589 Norwegians who had been followed up for a median time-period of 10.3 years (Hallan and Orth, 2011) revealed that former and current smokers < 70 years of age at inclusion had significant multi-adjusted HRs of 3.32 and 4.01 for CKD stage 5 compared to those who never smoked. In men, the risk increased with a significantly higher trend for strong smoking; however, the risk significantly decreased with increased elapsed years since smoking cessation. Despite the fact that, as often observed, females had smoked less than males (10.2 vs 15.8 pack-years) and the number of females reaching CKD stage 5 was lower (46 vs 78), the effect of smoking on the risk of CKD stage 5 was similar (HRs of 2.94 and 4.3 in current-smoking women and men, respectively), but probably due to these reasons the statistical power was insufficient to reach statistical significance in females.

Taken together, these recent studies clearly demonstrate that smoking, particularly heavy smoking and high cumulative smoking exposure, is an independent risk factor for CKD in both male and female subjects of the general population.

Smoking-associated histological renal findings in the general population

Only a little information is available about the type of CKD associated with smoking. In a population-based case–control study, Ejerblad et al. (2004) documented that the strongest association was found with nephrosclerosis, but significant positive associations were also reported for glomerulonephritis.

Smoking-associated renal risk in patients with diabetes mellitus

From 1978 to 2002, numerous studies (for review, see Orth, 2002a, 2002b) have accumulated evidence that smoking promotes the progression of all stages of diabetic nephropathy in both type 1 and type 2 diabetes: it

1. increases the risk to develop microalbuminuria
2. accelerates progression from the stage of microalbuminuria to macroalbuminuria
3. accelerates progression from early stages of diabetic nephropathy to ESRD.

Recent prospective studies have supported these earlier findings: de Boer et al. (2007) reported the data from an observational extension of the randomized, prospective Diabetes Control and Complications Trial (DCCT). Among 1105 patients with type 1 diabetes and normal urine albumin excretion at baseline, a 4.3-fold greater rate of GFR decline (measured by [^{125}]-iothalamate clearance) was observed in active versus non-active smokers, tht is, −0.77 versus −0.18 mL/min/1.73 m^2 per year. Additional data were provided by a prospective observational study involving 227 Caucasian patients with type 2 diabetes and nephropathy (Rossing et al., 2004). The subjects were followed for 6.5 years, and a mean of 7 measurements of GFR (using ^{51}Cr-EDTA plasma clearance) was performed per patient over time. A faster rate of GFR decline was independently associated with heavy smoking.

A cross-sectional study evaluating 32,208 type 2 diabetes patients not known to have albuminuria adds further information regarding the early stage of diabetic renal involvement (Parving et al., 2006). Smoking was an independent risk factor for increased urine albumin excretion. A follow-up study of 185 patients with type 1 and type 2 diabetes with and without nephropathy found that smoking was independently associated with a decrease of estimated GFR (Orth et al., 2005).

In summary, several recent studies provide evidence that smoking is a risk factor for all stages of diabetic renal damage. The impact on the rate of progression seems to be substantial, resulting in a shortening of the dialysis-free interval by a factor of 2–4.

Smoking-associated renal risk in patients with primary (essential) hypertension

Smoking is a strong predictor of increased urine albumin in patients with primary hypertension (for review, see Orth, 2002a, 2002b). Furthermore, a prospective 7-year study investigating 225 patients (Warmoth et al., 2005) found that estimated GFR declined faster in patients with 'severe' as compared to those with 'mild' hypertension, and GFR declined faster in smokers versus non-smokers, independent of urine albumin:creatinine ratio. An approximately fourfold faster decline of GFR was seen in smokers with severe primary hypertension, despite optimal blood pressure control (Regalado et al., 2000). In this latter study smoking was by far the most powerful predictor of renal functional decline.

Smoking-associated renal risk in patients with primary renal disease

The diseased kidney appears to be particularly sensitive to the adverse effects of smoking. The data available are, however, limited. A retrospective case–control study in patients with immunoglobulin (IgA)-nephropathy and autosomal dominant polycystic kidney disease (ADPKD) was the first to document an increased risk of ESRD in the 144 male patients investigated (Orth et al., 1998). The risk increased with the number of cigarettes smoked over time. After adjustment for possible confounders, multivariate analysis revealed that the risk of ESRD was excessively high in patients who had not been treated with an angiotensin-converting enzyme inhibitor. On the other hand, a study of 554 patients with ADPKD did not find that cigarette smoking influenced the disease course (Paterson et al., 2005). This conflicts with a recent study of

323 patients where smoking was correlated with rapid progression of ADPKD (Ozkok et al., 2013).

Smoking-associated renal risk in renal transplant recipients

There is evidence that smoking is a risk factor for progressive loss of renal graft function. A cohort study of 645 adult renal allograft recipients (Sung et al., 2001) found that smokers had a significantly worse kidney graft survival as compared to non-smokers (84%, 65%, and 48% at 1, 5, and 10 years, respectively, vs 88%, 78%, and 62%). Pre-transplant smoking adversely affected death-censored graft survival in recipients of cadaveric ($P = 0.02$) and of living donor kidneys ($P = 0.02$), independent of acute rejection episodes. In a multivariate analysis, pre-transplant smoking was associated with a RR of 2.3 for graft loss. Among patients with a smoking history, death-censored graft survival was significantly improved by quitting smoking before transplantation. This finding is of major importance for the management of patients with CKD who are being considered for renal transplantation.

Other studies have also found an adverse effect of smoking (Matas et al., 2001; Lin et al., 2005; Zitt et al., 2007). Of the 279 patients investigated in an Austrian study (Zitt et al., 2007), smokers had higher serum creatinine concentrations (2.3 ± 2.7 mg/dL vs 1.8 ± 1.4 mg/dL, $P = 0.21$) and were more likely to develop transplant failure (33.3 vs 21.2%, $P = 0.25$). Statistical significance was not achieved perhaps because of the small number of smokers included in the study. Others have found only a negative impact of smoking on graft survival which was not censored for recipient death (Fellstrom et al., 2005). It is worth noting that three studies have shown that the donors' history of smoking is an independent risk factor for shortened graft survival (Sung et al., 2001; Lin et al., 2005; Heldt et al., 2011). This deserves further investigation and, if confirmed, should be considered in the validation of organ quality.

Undergoing renal transplantation showed a strong incentive for patients to stop smoking (Banas et al., 2008).

Potential mechanisms of smoking-associated renal damage

Investigations of the mechanisms underlying the adverse effects of smoking on the kidney are hampered by several factors. First, renal susceptibility genes or polymorphisms may play a role influencing the magnitude of the nephrotoxic effect of smoking in different individuals. Second, it has become clear that a number of complex and heterogenous mechanisms play a role. This may be complicated by several yet unidentified confounding factors associated with smoking or interacting with smoking. Third, > 4000 chemicals in the form of particles and gases found in cigarette smoke could be responsible for its nephrotoxic effect. Both non-haemodynamic and haemodynamic mechanisms potentially play a role.

Non-haemodynamic mechanisms

Endothelial cell dysfunction, activation of growth factors (angiotensin II (ANG II), endothelin 1 (ET-1), transforming growth factor beta 1 (TGF-β1)), tubulotoxic effects, oxidative stress, platelet activation, impaired lipoprotein and glycosaminoglycan metabolism, modulation of immune mechanisms, vasopressin-mediated antidiuresis, and insulin resistance are all affected by exposure to cigarette smoke (for review, see Orth, 2002a, 2002b).

In an *in vitro* study using human mesangial cells, Jaimes et al. (2007) reported that nicotine induced cell proliferation and increased fibronectin production by 50%. Both mesangial cell proliferation and increased production of fibronectin are mediators of progression of CKD. This study documented that nicotinic acetylcholine receptors (nAChRs), which mediates cell proliferation (Dasgupta and Chellappan, 2006), are expressed on human mesangial cells. In a study using rat mesangial cells it was shown that exposure of these cells to cigarette smoke concentrate (CSC) induced an increase of TGF-β1, a major mediator in the genesis of renal fibrosis, and 8-epi-prostaglandin F2 alpha (8-epi-PGF2α), a marker of lipid peroxidation (Mur et al., 2004). Similar results have been found both in other experimental models and in humans (Cucina et al., 1999; Esmatjes et al., 1999; Chuahirun et al., 2004). In non-macroalbuminuric patients with type 2 diabetes, cessation of smoking led to a significant reduction of urine TGF-β1 excretion. This supports the view that there is likely to be a beneficial effect of smoking cessation on progression of early diabetic renal damage.

Other environmental and occupational exposures may influence the magnitude of renal damage caused by smoking. Cigarette smokers are exposed to significant amounts of cadmium (Cd) and lead (Pb) which accumulate in kidney tissue more than in any other organ and are toxic at very low doses. In studies from Egypt, smoking was shown to have toxic effects on tubular cells and these were synergistic to occupational Pb, mercury, and silica exposure. Dietary Cd and Pb appear to confer mild tubular dysfunction, whereas dietary exposure plus cigarette smoking is associated with tubular and glomerular dysfunction (for review, see Orth and Hallan, 2008). The dietary risk for renal Cd toxicity in the general population of the United States (Diamond et al., 2003) and Japan (Ikeda et al., 2006) seem to be negligible, provided that there are no additional exposures. Smoking 20 cigarettes/day over longer periods of time leads to 45–70% higher accumulation doses of Cd in the renal cortex (Diamond et al., 2003). In patients at high risk for CKD the burden of cumulative exposure to the nephrotoxins conferred by smoking may increase its impact on the kidney: in subjects with diabetes, low-level Cd exposure is associated with early-onset diabetic nephropathy (Satarug and Moore, 2004).

The magnitude of the effect of the different non-haemodynamic mechanisms contributing to smoking-associated renal damage remains unclear.

Haemodynamic mechanisms

Blood pressure and heart rate are increased by smoking, largely from the action of nicotine (for review, see Orth, 2004). Since increased blood pressure is the most important factor promoting progression of CKD, it is likely to play an important role in mediating smoking-induced renal damage. The rise in blood pressure is due to an increase in cardiac output and total peripheral vascular resistance. The blood pressure rise appears immediately and occurs before any increase in circulating catecholamines (for review, see Omvik, 1996). Some data implicate an alteration of the diurnal rhythm of blood pressure in smokers, for example, a lower night:day ratio of systolic and diastolic blood pressure in healthy smokers as compared to non-smokers (Hansen et al., 1994). Alterations of the night:day blood pressure profile are associated

with a change in renal and cardiovascular risk. It is of note that smoking interacts with the effects of some antihypertensive drugs. At least in non-renal patients, smoking blunts the antihypertensive effect of β-blockers (Trap-Jensen, 1988). Furthermore, in the short term, cigarette smoking blunts the beneficial effect of amlodipine on arterial stiffness (Matsui et al., 2005).

Besides changes in systemic haemodynamics, smoking also alters intrarenal haemodynamics (Orth, 2004). In brief, the data support the hypothesis that smoking induces an increase in glomerular pressure through impaired renal autoregulation, especially in patients with renal disease. In healthy subjects, an increase in renal vascular resistance (RVR) is observed. This is thought to be 'physiologic' and to protect the glomeruli from the increase in systemic blood pressure resulting in unchanged intraglomerular pressure. The 'physiologic' increase in RVR is inhibited by pretreatment with a β-blocker (Benck et al., 1999), which led to the hypothesis of smoking-induced β_1-receptor mediated renin and ANG II production (Orth, 2002a, 2002b).

Histopathological features of smoking-induced renal damage

Bangstad et al. (2002) prospectively investigated 18 patients with type 1 diabetes and microalbuminuria over 8 years. A renal biopsy was performed at baseline and at the end of the study. The progression of glomerular structural damage was more pronounced in smokers than in non-smokers. Baggio et al. (2002) performed a renal biopsy study in 96 patients with type 2 diabetes and found that heavy smoking was associated with increased glomerular basement membrane thickness.

Lhotta et al. (2002) investigated 107 patients with CKD. Most of them had glomerular disease with marked proteinuria and uncontrolled blood pressure. The only histopathological alteration associated with smoking in male patients was more severe myointimal hyperplasia of intrarenal arterioles. In patients with a renal transplant, the same group reported that fibrous intimal thickening of small arteries was the only significant lesion associated with smoking (Zitt et al., 2007). Only one more study in patients with primary renal disease is available: Myllymaki et al. (2005) investigated 202 patients with IgA nephropathy. No correlation of smoking habits with histopathological changes was observed.

In the general population without apparent renal disease, only little information on the effect of smoking is available. Arteriolar wall thickening, mainly as a result of fibroelastic intimal proliferation and hyaline thickening in the intima have been reported (for review, see Orth, 2002a, 2002b, 2004). These findings support the notion that the CKD of smokers in the general population is related to nephrosclerosis (Ejerblad et al., 2004). The fact that smoking is a risk factor for ischaemic nephropathy, which is an increasing cause of ESRD in elderly subjects, is undisputed (for review, see Orth, 2002a, 2002b).

Idiopathic nodular glomerulosclerosis (INGS) is a rare entity linked to heavy smoking (Nasr and D'Agati, 2007), with < 50 cases documented. Median time from biopsy to ESRD was < 3 years (Nasr and D'Agati, 2007). In cases of rapid CKD progression in heavy smokers, even in those who gave up several years previously, or without other risk factors that might result in vascular injury, INGS should be considered. Nasr and D'Agati (2007) proposed the term 'smoking-associated nodular glomerulosclerosis' for this entity.

In summary, the histopathological changes conferred by smoking are mainly in the renal artery and the intrarenal arterioles. A specific, but rare smoking-related renal manifestation is INGS.

Smoking cessation improves the prognosis of chronic kidney disease

The studies of this issue all find a positive effect of smoking cessation. Chase et al. (1991) observed that in patients with type 1 diabetes and nephropathy in whom blood pressure was adequately controlled, cessation of smoking significantly reduced urine albumin excretion, although glycaemia was not perfectly controlled. Sawicki et al. (1994) performed a prospective follow-up study over 1 year in a sequential sample of 34 smokers, 35 non-smokers, and 24 ex-smokers with type 1 diabetes, hypertension, and diabetic nephropathy. They reported progression of diabetic nephropathy in 53% of current smokers, but only 33% of ex-smokers (and 11% of non-smokers). These data were confirmed in patients with type 2 diabetes (Gambaro et al., 2001) with progression in 22% of ex-smokers vs 42% in smokers (and 23% in non-smokers). They also found a reduction of urine TGF-β1 excretion as a marker of renal injury after smoking cessation (Chuahirun et al., 2004). Smoking cessation before renal transplantation leads to better graft survival. The most convincing evidence is the observation that in male subjects in the general population the risk of CKD stage 5 significantly decreased with increased elapsed years since smoking cessation (Hallan and Orth, 2011).

Conclusion

Smoking emerges as an important modifiable renal risk factor for the following reasons:

1. Multiple studies document an association of smoking with renal damage in subjects of the general population, patients with diabetes mellitus, and hypertension.
2. There is evidence of a beneficial effect of smoking cessation on renal outcome.
3. Some smoking-related phenomena are proven to be harmful for the kidney, for example, an increase in blood pressure.
4. Experimental evidence shows that cigarette smoke affects systems which are known to be mediators in the genesis of progressive renal damage, both *in vivo* and *in vitro*.

Motivation of patients to quit smoking should be immediately implemented, because it is certainly a cost-effective and beneficial strategy in the management of CKD, ESRD, and cardiovascular disease morbidity and mortality in renal patients. Advice to stop smoking is an integral part of the management of patients with renal disease.

References

Baggio, B., Budakovic, A., Dalla, V. M., *et al.* (2002). Effects of cigarette smoking on glomerular structure and function in type 2 diabetic patients. *J Am Soc Nephrol*, 13, 2730–6.

Baggio, B., Budakovic, A., Perissinotto, E., *et al.* (2005). Atherosclerotic risk factors and renal function in the elderly: the role of hyperfibrinogenaemia and smoking. Results from the Italian Longitudinal Study on Ageing (ILSA). *Nephrol Dial Transplant*, 20, 114–23.

Banas, M. C., Banas, B., Wolf, J., *et al.* (2008). Smoking behaviour before and after renal transplantation. *Nephrol Dial Transplant*, 23, 1442–6.

Bangstad, H. J., Osterby, R., Rudberg, S., *et al.* (2002). Kidney function and glomerulopathy over 8 years in young patients with type I (insulin-dependent) diabetes mellitus and microalbuminuria. *Diabetologia*, 45, 253–61.

Benck, U., Clorius, J. H., Zuna, I., *et al.* (1999). Renal hemodynamic changes during smoking: effects of adrenoreceptor blockade. *Eur J Clin Invest*, 29, 1010–18.

Bleyer, A. J., Shemanski, L. R., Burke, G. L., *et al.* (2000). Tobacco, hypertension, and vascular disease: risk factors for renal functional decline in an older population. *Kidney Int*, 57, 2072–9.

Briganti, E. M., Branley, P., Chadban, S. J., *et al.* (2002). Smoking is associated with renal impairment and proteinuria in the normal population: the AusDiab kidney study. Australian Diabetes, Obesity and Lifestyle Study. *Am J Kidney Dis*, 40, 704–12.

Chase, H. P., Garg, S. K., Marshall, G., *et al.* (1991). Cigarette smoking increases the risk of albuminuria among subjects with type I diabetes. *JAMA*, 265, 614–17.

Chuahirun, T., Simoni, J., Hudson, C., *et al.* (2004). Cigarette smoking exacerbates and its cessation ameliorates renal injury in type 2 diabetes. *Am J Med Sci*, 327, 57–67.

Cucina, A., Corvino, V., Sapienza, P., *et al.* (1999). Nicotine regulates basic fibroblastic growth factor and transforming growth factor beta1 production in endothelial cells. *Biochem Biophys Res Commun*, 257, 306–12.

Dasgupta, P. and Chellappan, S. P. (2006). Nicotine-mediated cell proliferation and angiogenesis: new twists to an old story. *Cell Cycle*, 5, 2324–8.

De Boer, I. H., Sibley, S. D., Kestenbaum, B., *et al.* (2007). Central obesity, incident microalbuminuria, and change in creatinine clearance in the epidemiology of diabetes interventions and complications study. *J Am Soc Nephrol*, 18, 235–43.

Diamond, G. L., Thayer, W. C., Choudhury, H. (2003). Pharmacokinetics/pharmacodynamics (PK/PD) modeling of risks of kidney toxicity from exposure to cadmium: estimates of dietary risks in the U.S. population. *J Toxicol Environ Health A*, 66, 2141–64.

Ejerblad, E., Fored, C. M., Lindblad, P., *et al.* (2004). Association between smoking and chronic renal failure in a nationwide population-based case-control study. *J Am Soc Nephrol*, 15, 2178–85.

Esmatjes, E., Flores, L., Lario, S., *et al.* (1999). Smoking increases serum levels of transforming growth factor-beta in diabetic patients. *Diabetes Care*, 22, 1915–16.

Fellstrom, B., Holdaas, H., Jardine, A. G., *et al.* (2005). Risk factors for reaching renal endpoints in the assessment of Lescol in renal transplantation (ALERT) trial. *Transplantation*, 79, 205–12.

Gambaro, G., Bax, G., Fusaro, M., *et al.* (2001). Cigarette smoking is a risk factor for nephropathy and its progression in type 2 diabetes mellitus. *Diabetes Nutr Metab*, 14, 337–42.

Halimi, J. M., Giraudeau, B., Vol, S., *et al.* (2000). Effects of current smoking and smoking discontinuation on renal function and proteinuria in the general population. *Kidney Int*, 58, 1285–92.

Hallan, S. I., Coresh, J., Astor, B. C., *et al.* (2006). International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol*, 17, 2275–84.

Hallan, S., de Mutsert, R., Carlsen S *et al.* (2006). Obesity, smoking, and physical inactivity as risk factors for CKD: are men more vulnerable? *Am J Kidney Dis*, 47, 396–405.

Hallan, S. I. and Orth, S. R. (2011). Smoking is a risk factor in the progression to kidney failure. *Kidney Int*, 80, 516–23.

Hansen, K. W., Pedersen, M. M., Christiansen, J. S., *et al.* (1994). Night blood pressure and cigarette smoking: disparate association in healthy subjects and diabetic patients. *Blood Press*, 3, 381–8.

Haroun, M. K., Jaar, B. G., Hoffman, S. C., *et al.* (2003). Risk factors for chronic kidney disease: a prospective study of 23,534 men and women in Washington County, Maryland. *J Am Soc Nephrol*, 14, 2934–41.

Heldt, J., Torrey, R., Han, D., *et al.* (2011). Donor smoking negatively affects donor and recipient renal function following living donor nephrectomy. *Adv Urol*, 2011, 929263.

Ikeda, M., Ezaki, T., Moriguchi, J., *et al.* (2006). No meaningful increase in urinary tubular dysfunction markers in a population with 3 microg cadmium/g creatinine in urine. *Biol Trace Elem Res*, 113, 35–44.

Ishani, A., Grandits, G. A., Grimm, R. H., *et al.* (2006). Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the multiple risk factor intervention trial. *J Am Soc Nephrol* 17, 1444–52.

Jaimes, E. A., Tian, R. X., and Raij, L. (2007). Nicotine: the link between cigarette smoking and the progression of renal injury? *Am J Physiol Heart Circ Physiol*, 292, H76–82.

Joshi, V. D., Mooppil, N., and Lim, J. (2006). Prevalence and risk factors of undetected proteinuria in an elderly South-East Asian population. *Nephrology (Carlton)*, 11, 347–54.

Klag, M. J., Whelton, P. K., Randall, B. L., *et al.* (1996). Blood pressure and end-stage renal disease in men. *N Engl J Med*, 334, 13–18.

Lhotta, K., Rumpelt, H. J., Konig, P., *et al.* (2002). Cigarette smoking and vascular pathology in renal biopsies. *Kidney Int*, 61, 648–54.

Lin, S. J., Koford, J. K., Baird, B. C., *et al.* (2005). Effect of donors' intravenous drug use, cigarette smoking, and alcohol dependence on kidney transplant outcome. *Transplantation*, 80, 482–6.

Maeda I, Hayashi T, Sato KK, *et al.* (2011). Cigarette smoking and the association with glomerular hyperfiltration and proteinuria in healthy middle-aged men. *Clin J Am Soc Nephrol*, 6, 2462–9.

Matas, A. J., Payne, W. D., Sutherland, D. E., *et al.* (2001). 2,500 living donor kidney transplants: a single-center experience. *Ann Surg*, 234, 149–64.

Matsui, Y., Kario, K., Ishikawa, J., *et al.* (2005). Smoking and antihypertensive medication: interaction between blood pressure reduction and arterial stiffness. *Hypertens Res*, 28, 631–8.

Mur, C., Claria, J., Rodela, S., *et al.* (2004). Cigarette smoke concentrate increases 8-epi-PGF2alpha and TGFbeta1 secretion in rat mesangial cells. *Life Sci*, 75, 611–21.

Myllymaki, J., Honkanen, T., Syrjanen, J., *et al.* (2005). Uric acid correlates with the severity of histopathological parameters in IgA nephropathy. *Nephrol Dial Transplant*, 20, 89–95.

Nasr, S. H. and D'Agati, V. D. (2007). Nodular glomerulosclerosis in the nondiabetic smoker. *J Am Soc Nephrol*, 18: 2032–6.

Omvik, P. (1996). How smoking affects blood pressure. *Blood Press*, 5, 71–7.

Orth, S. R. (2002a). Cigarette smoking: an important risk factor—far beyond carcinogenesis. *Tob Induced Dis*, 1, 137–55.

Orth, S. R. (2002b). Smoking and the kidney. *J Am Soc Nephrol*, 13, 1663–72.

Orth, S. R. (2004). Effects of smoking on systemic and intrarenal hemodynamics: influence on renal function. *J Am Soc Nephrol*, 15 Suppl 1, S58–63.

Orth, S. R. and Hallan, S. I. (2008). Smoking: a risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients—absence of evidence or evidence of absence? *Clin J Am Soc Nephrol*, 3, 226–36.

Orth, S. R. and Ritz, E. (2002). Adverse effect of smoking on renal function in the general population: are men at higher risk? *Am J Kidney Dis*, 40, 864–6.

Orth, S. R., Schroeder, T., Ritz, E., *et al.* (2005). Effects of smoking on renal function in patients with type 1 and type 2 diabetes mellitus. *Nephrol Dial Transplant*, 20, 2414–9.

Orth, S. R., Stockmann, A., Conradt, C., *et al.* (1998). Smoking as a risk factor for end-stage renal failure in men with primary renal disease. *Kidney Int*, 54, 926–31.

Ozkok, A., Akpinar, T. S., Tufan, F., *et al.* (2013). Clinical characteristics and predictors of progression of chronic kidney disease in autosomal dominant polycystic kidney disease: a single center experience. *Clin Exp Nephrol*, 17(3), 345–51.

Parving, H. H., Lewis, J. B., Ravid, M., *et al.* (2006). Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. *Kidney Int*, 69, 2057–63.

Paterson, A. D., Magistroni, R., He, N., *et al.* (2005). Progressive loss of renal function is an age-dependent heritable trait in type 1 autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*, 16, 755–62.

Pinto-Sietsma, S. J., Mulder, J., Janssen, W. M., *et al.* (2000). Smoking is related to albuminuria and abnormal renal function in nondiabetic persons. *Ann Intern Med*, 133, 585–591.

Regalado, M., Yang, S., and Wesson, D. E. (2000). Cigarette smoking is associated with augmented progression of renal insufficiency in severe essential hypertension. *Am J Kidney Dis*, 35, 687–94.

Rossing, K., Christensen, P. K., Hovind, P., *et al.* (2004). Progression of nephropathy in type 2 diabetic patients. *Kidney Int*, 66, 1596–605.

Satarug, S. and Moore, M. R. (2004). Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. *Environ Health Perspect*, 112, 1099–103.

Sawicki, P. T., Didjurgeit, U., Muhlhauser, I., *et al.* (1994). Smoking is associated with progression of diabetic nephropathy. *Diabetes Care*, 17, 126–31.

Sung, R. S., Althoen, M., Howell, T. A., *et al.* (2001). Excess risk of renal allograft loss associated with cigarette smoking. *Transplantation*, 71, 1752–7.

Trap-Jensen, J. (1988). Effects of smoking on the heart and peripheral circulation. *Am Heart J*, 115, 263–7.

Verhave, J. C., Hillege, H. L., Burgerhof, J. G., *et al.* (2005). The association between atherosclerotic risk factors and renal function in the general population. *Kidney Int*, 67, 1967–73.

Vupputuri, S. and Sandler, D. P. (2003). Lifestyle risk factors and chronic kidney disease. *Ann Epidemiol*, 13, 712–20.

Warmoth, L., Regalado, M. M., Simoni, J., *et al.* (2005). Cigarette smoking enhances increased urine albumin excretion as a risk factor for glomerular filtration rate decline in primary hypertension. *Am J Med Sci*, 330, 111–19.

Yamagata, K., Ishida, K., Sairenchi, T., *et al.* (2007). Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int*, 71, 159–66.

Zitt, N., Kollerits, B., Neyer, U., *et al.* (2007). Cigarette smoking and chronic allograft nephropathy. *Nephrol Dial Transplant*, 22(10), 3034–9.

CHAPTER 104

Analytical aspects of measurements and laboratory values in kidney disease

Edmund J. Lamb and Finlay MacKenzie

Introduction

Nephrology has always been closely linked to the laboratory. In the early nineteenth century, Dr Richard Bright at Guy's Hospital, London, demonstrated the presence of heat 'coagulable' urine amongst some patients with dropsy, effectively linking laboratory investigation with a clinical syndrome (albuminous nephritis, later Bright disease). Bright and others subsequently effectively established the forerunner of a laboratory service to support the management of patients with kidney disease, including the demonstration of raised concentrations of blood urea in such patients (Peitzman, 2007; Cameron and Turner 2015). Even in the late twentieth century, many renal wards had a laboratory side-room where basic tests were undertaken. Many of the present senior generation of nephrologists would have trained with a basic knowledge of urinalysis by microscopy.

Today's high-throughput, highly automated laboratories are a different environment altogether, run by laboratory professionals with their own specialized knowledge of analytical technology and serving many masters. But the strong link with nephrology remains. Kidney function tests are the commonest request made to most clinical biochemistry laboratories (e.g. ~ 50 million serum creatinine requests per year in the United Kingdom) and the laboratory support required by an average renal centre is extensive (Table 104.1). As with many areas of medicine, guidelines and targets have become central to the practice of nephrology. Given their quantitative nature, laboratory values provide attractive targets for guideline makers and national registries now routinely amass data from patients with kidney failure throughout the Western world. But for guidelines to be useful, the results they rely upon must be standardized: the same result should be produced on a clinical sample, within clinically meaningful limits, in all laboratories in which it is measured.

Clinicians generally believe the numbers with which laboratories provide them, but this faith is not always well placed. It is important that the factors that contribute to a laboratory result and its variability are understood and taken into account.

Sources of variation in laboratory results

Laboratory analytes are subject to three main sources of variation: pre-analytical, analytical, and biological. Pre-analytical influences include patient preparation (e.g. fasting/non-fasting, posture, diurnal variation), sample collection (e.g. preservative, tourniquet application) and handling (e.g. transport time, storage, centrifugation procedure). Pre-analytical variation can be significantly minimized by adopting standard practice (e.g. phlebotomy practices, time of day). Analytical variation is of two types, random and systematic, and these are usually termed precision and bias respectively. Random analytical variation is inherent to an analytical system and the methodology used which arises from sources such as fluctuations in temperature, variability in volume of sample and/or reagent and inconsistent handling of materials. The analytical precision of a method is typically expressed as its coefficient of variation (CV_A, standard deviation/mean × 100%): nowadays, for most automated methods for most analytes CV_As of < 5% are achieved by laboratories.

Systematic error or bias is, in practice, the difference between obtained results and the estimate of the true value obtained using an accepted reference method, that is, accuracy. Quantitative laboratory results rely on the principle of comparing the reaction of the unknown solution (e.g. serum or urine) with that of a standard solution containing a known quantity of the analyte of interest. The nature of that standard, and the matrix in which it is dissolved, can be crucial to the way in which it reacts in a chemical assay. Clearly both a standard's nature and matrix should behave as per the sample and analyte of interest; this is known as commutability. Non-laboratorians are often surprised to realize that this is not the case; furthermore that such standards are often not internationally or even nationally agreed, resulting in variation between laboratories (and hospitals/healthcare systems). The design of an assay can also have a profound influence on the result that is produced: for example, the time at which the rate reaction is initiated in a Jaffe assay for creatinine, or the antibodies used in an immunoassay (see below). Ideally these problems are attenuated by the use of high-order reference measurement materials and/or reference procedures, often based on isotope dilution-mass spectrometry (ID-MS), as promoted by the Joint Committee of Traceability in Laboratory Medicine (JCTLM) (<http://www.bipm.org/en/committees/jc/jctlm>). Once an exact concentration has been assigned to an internationally agreed reference preparation of the compound of interest, routine clinical methods can then be aligned to this

Table 104.1 Basic laboratory support for renal replacement therapy programmes

Clinical condition	Laboratory tests
Acute dialysis	
Dialysis disequilibrium	Creatinine, urea and electrolytes, bicarbonate, calcium
Pyrexia	C-reactive protein, white cell count, blood cultures
Bleeding	Clotting screen, platelets
Chronic dialysis programmes	
Anaemia	Ferritin, transferrin saturation, vitamin B_{12}, folate, blood film, PTH, C-reactive protein
Sepsis	C-reactive protein, blood, urine specimens for microscopy, culture and sensitivity
Nutrition	Albumin, phosphate
Cardiovascular disease risk	Lipid profile
Dialysis-related amyloid	β_2-microglobulin (not routinely measured)
CKD-MBD	Pre-dialysis plasma calcium, phosphate (monthly in haemodialysis patients; 3-monthly in peritoneal dialysis patients) Alkaline phosphatase PTH (at least every 3 months) Aluminium in patients receiving aluminium-based phosphate binders (3-monthly)
Adequacy of haemodialysis as assessed by urea clearance	Pre-dialysis and post-dialysis urea
Sepsis, abdominal pain in peritoneal dialysis	Microscopy and culture of peritoneal dialysate
Adequacy of peritoneal dialysis as assessed by weekly small solute clearance	Dialysate creatinine, urea
Peritoneal membrane characteristics assessed by peritoneal equilibration test	Plasma and dialysate glucose and creatinine
Transplant monitoring	
Immunosuppression	Trough (or 2-hour) whole blood ciclosporin, tacrolimus, and sirolimus
Graft function	Serum creatinine, serum and urine electrolytes

CKD = chronic kidney disease; MBD = mineral and bone disorder; PTH = parathyroid hormone.

procedure. This process represents an enormous undertaking, initiated and supported by professional bodies (e.g. the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)). It is commonly many years before a suitable reference material can be produced, characterized, value-assigned by a reference measurement procedure, and transferred to routine practice. Even then, the process is not infallible. Furthermore, for some analytes with complex molecular forms it is likely that higher-order reference measurement procedures can never be developed: in these instances the best solution is to obtained harmonized, as distinct from standardized, laboratory methods (Miller et al., 2011).

Biological variation has two components: (1) within-subject/intraindividual (CV_I) variation, the random fluctuation around a homeostatic set-point, and (2) between subject/interindividual variation, the difference between different individuals' set points. The components of variation can be derived from carefully controlled studies (Fraser and Harris, 1989). The data can be used in several ways by clinicians to aid interpretation of laboratory data, in particular when monitoring a patient's condition. From knowledge of the CV_I and CV_A it is possible to calculate the reference change value (RCV), the critical difference between two sets of results that must be exceeded before it can be inferred, with 95% confidence, that a true change has occurred. Data can also be used to calculate the number of samples required to estimate the homeostatic set point (true value) of an individual, and assess the utility of reference values: for example, when an analyte shows low intraindividual but high interindividual variation (e.g. serum creatinine), then population-derived reference intervals will be of limited value. The significance of biological variation and, in particular, the RCV is often underestimated. From the laboratory perspective, biological variation data can be used as one means of setting analytical performance targets. For example, it is generally considered that minimum, desirable, and optimal performance in terms of analytical precision should be defined by $CV_A < 75\%$, 50%, and 25% respectively of the corresponding CV_I for an analyte. These specifications correspond to increases in result variability (over and above biological variation) of 25%, 12%, and 3% respectively.

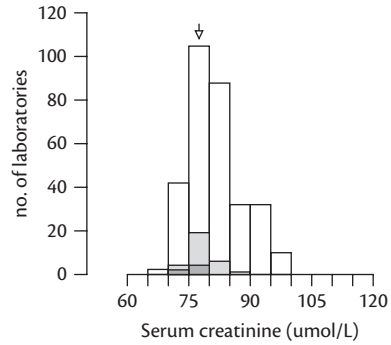
Creatinine measurement

Creatinine (Mr 113 Da) is a nitrogenous waste product derived from breakdown of phosphocreatine in muscle. The use of creatinine as a marker of glomerular filtration rate (GFR) was first developed in 1926 by Rehberg and it is now the most widely used endogenous marker of GFR, expressed either as its serum concentration or its renal clearance (Rehberg, 1926) (NB creatinine measurements are equivalent in serum and plasma. The term 'serum' is used throughout this chapter). Consequently, it is the most common means by which chronic kidney disease (CKD) is staged and progression assessed, and by which acute kidney injury is identified.

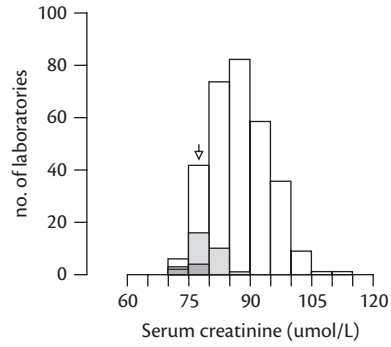
A method for the assay of serum creatinine was first described by Jaffe in 1886, involving reaction with alkaline sodium picrate to form an orange-red coloured complex. Although there are now a variety of approaches to creatinine measurement, including enzymatic, high-performance liquid chromatography and ID-MS methods, the Jaffe assay remains the commonest method. However, 125 years later, the precise reaction mechanism remains unclear. Measurement of creatinine using the Jaffe reaction suffers from two main problems: non-specificity and spectral interferences.

Many compounds have been reported to produce a Jaffe-like chromogen, including ketone bodies, protein, glucose (Fig. 104.1), ascorbic acid, pyruvate, guanidine, levulose, aminohippurate, uric acid, blood-substitute products, and cephalosporins (Spencer, 1986; Weber and van Zanten, 1991). Jaffe assays are also highly susceptible to spectral interference from bilirubin, haemoglobin, and lipaemia. Enzymatic assays are also not immune to these effects.

Specimen : 60A	n	Mean	SD	CV(%)
All methods	311	81.6	6.4	7.8
Dry slide	23	80.0	2.2	2.7
OCD (J&J) Gen 80+ [1JJ2]	15	80.5	2.1	2.6
Compensated Kinetic Jaffe	190	79.5	4.8	6.0
Abbott reagents [10AB]	45	74.8	2.3	3.1
Beckman reagents [10BK]	32	79.6	4.0	5.0
Roche Modular reagents [10BO]	82	82.6	3.2	3.9
Traditional Kinetic Jaffe	56	90.8	5.9	6.5
Olympus reagents [11OL]	34	93.1	2.8	3.0
Enzymatic	30	78.9	2.7	3.5
Abbott reagents [9AB]	6	77.3	3.5	4.6
Roche Modular reagents [9BO]	15	79.2	2.5	3.2



Specimen : 60B	n	Mean	SD	CV(%)
All methods	311	87.6	7.2	8.2
Dry slide	23	80.3	2.3	2.8
OCD (J&J) Gen 80+ [1JJ2]	15	80.8	2.2	2.7
Compensated Kinetic Jaffe	190	87.1	4.5	5.1
Abbott reagents [10AB]	45	90.1	2.5	2.7
Beckman reagents [10BK]	32	85.7	3.8	4.4
Roche Modular reagents [10BO]	82	86.5	3.6	4.2
Traditional Kinetic Jaffe	56	96.5	5.0	5.2
Olympus reagents [11OL]	34	97.8	2.8	2.8
Enzymatic	30	79.3	2.4	3.1
Abbott reagents [9AB]	6	77.8	3.1	3.9
Roche Modular reagents [9BO]	15	79.3	2.0	2.5



Specimen : 60C	n	Mean	SD	CV(%)
All methods	311	93.9	11.0	11.7
Dry slide	23	80.6	2.9	3.6
OCD (J&J) Gen 80+ [1JJ2]	15	81.3	2.9	3.5
Compensated Kinetic Jaffe	190	94.7	8.4	8.8
Abbott reagents [10AB]	45	105.4	2.4	2.3
Beckman reagents [10BK]	32	91.8	3.9	4.2
Roche Modular reagents [10BO]	82	90.9	3.3	3.6
Traditional Kinetic Jaffe	56	102.3	5.1	5.0
Olympus reagents [11OL]	34	101.9	3.2	3.2
Enzymatic	30	78.8	2.3	3.0
Abbott reagents [9AB]	6	77.3	3.5	4.6
Roche Modular reagents [9BO]	15	79.1	2.1	2.7

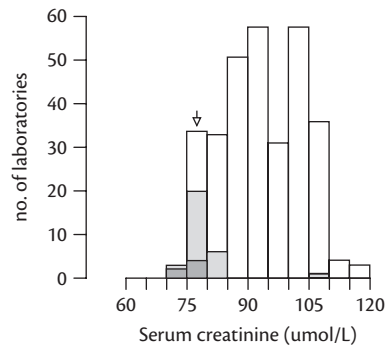


Fig. 104.1 Variability of serum creatinine measurement as demonstrated by quality assessment data with particular emphasis on the effects of glucose. The top panel (specimen 60A) consists of an unadulterated serum sample with an approximate serum creatinine concentration of 82 umol/L. It can be seen that the overall coefficient of variation across all 311 laboratories participating in the scheme is 7.8%, with reported concentrations varying from approximately 70 to 100 umol/L. Specimens 60B and 60C consist of the same base serum with 16 and 32 mmol/L glucose added respectively. Note the right shift of the data, with means of the largest Jaffe method group (compensated kinetic Jaffe), for example, shifting from 80 to 87 to 95 umol/L. For a 72-year-old Caucasian female this would equate to GFRs estimated using the MDRD equation of 64, 58, and 52 mL/min/1.73 m^2. By contrast, the mean of the enzymatic method group (shaded, arrow) is unaffected by the addition of glucose. (Exercise dated January 2011.)

The degree and direction of interference depends on the precise reaction conditions chosen and the concentration of the interferent present in the patient's sample. As a result of reaction with non-creatinine chromogens, Jaffe methods typically overestimated true serum creatinine concentration by approximately 20% at physiological concentrations (Myers et al., 2006). Many manufacturers have addressed this problem by taking into account these non-specific reactions, aligning the calibration of their assays so that results more closely mimic those of the reference method (ID-MS). These so-called compensated assays generally produce more accurate results but may over-compensate at low concentrations. They make an assumption that the non-creatinine chromogen interference is a constant between samples, which is clearly an over-simplification (Fig. 104.1).

There are also physiological reasons why creatinine is an imperfect marker of kidney function. Its serum concentration is affected by age, gender, exercise, certain drugs (e.g. cimetidine, trimethoprim), muscle mass, and nutritional status. Creatine in muscle is converted to creatinine when meat is cooked with resultant increases in serum creatinine after cooked meat ingestion (Preiss et al., 2007). The impact may be large, for example, producing 25% decreases in estimated GFR. Delayed separation (beyond 14 hours) of serum from erythrocytes leads to a significant increase in apparent serum creatinine concentration using some Jaffe (but not enzymatic) assays, possibly due to release of non-creatinine chromogens from the red cells (Shepherd et al., 2007). Perhaps most importantly, serum creatinine concentration remains within the reference interval until significant renal function has been

lost. The reference interval encompasses the range of muscle mass observed in the population. This contributes to the insensitivity of creatinine as a marker of diminished GFR. Additionally, in patients with CKD, extrarenal clearance of creatinine becomes significant due to degradation as a result of bacterial overgrowth in the small intestine, further blunting the anticipated increase in serum creatinine in response to falling GFR. Thus, whilst an increased serum creatinine concentration does generally equate to impaired kidney function, a normal serum creatinine does not necessarily equate to normal kidney function.

Mean CV_I for serum creatinine has been reported as 4.3% (Gowans and Fraser, 1988), indicating a desirable analytical performance goal of < 2.2%. Intralaboratory imprecision at a concentration of 88 umol/L varies between approximately 2.0% and 8.4% (Myers et al., 2006). Clearly, many laboratories are therefore outside desirable and even minimum performance standards. Allowing for a CV_I of 4.3% and a CV_A of 3.0% generates an RCV for serum creatinine of approximately 14%. Proficiency studies demonstrate that whilst between-laboratory CVs of approximately 3% are achievable within method groups, overall between-laboratory agreement across methods is much poorer, for example, approximately 8% at a concentration of 80 umol/L (Fig. 104.1).

The publication of the Modification of Diet in Renal Disease (MDRD) Study equation in 1999 (Levey et al., 1999) and its subsequent use in the classification of CKD (National Kidney Foundation, 2002) refocused efforts on the problems of standardization of serum creatinine assays. The realization that international creatinine standardization didn't exist, and that bias between methods affected GFR estimates (Coresh et al., 2002; Lamb et al., 2005; Murthy et al., 2005) surprised the nephrology community. The more a method overestimates 'true' creatinine, the greater will be the underestimation of GFR, and vice versa. Miller et al. calculated that allowing for a total error in estimated GFR of 15%, the maximal allowable bias of a creatinine assay at a concentration of 88 umol/L would be 3 umol/L, a target achieved by very few laboratories or methods (Miller et al., 2005).

Recently, the National Institute of Standards and Technology (NIST) in collaboration with the National Kidney Disease Education Program (NKDEP) have developed standard reference material (SRM) 967, with target creatinine concentrations of 88 umol/L (1.0 mg/dL) and 354 umol/L (4.0 mg/dL) in a frozen serum matrix. The material was value-assigned using mass spectrometry and issued in 2007 (Dodder et al., 2007). This material, in combination with gas chromatography-ID-MS reference methodology, was used by reagent manufacturers to restandardize their methods (Panteghini et al., 2006) and by the end of 2009 most clinical laboratory methods had calibration traceable to the reference measurement procedure and standard (Miller, 2009).

International standardization is clearly desirable but will not eliminate problems due to imprecision and the variable non-specificity of Jaffe reactions. The latter can only be overcome by the use of more specific methods; that is, effectively enzymatic assays for routine clinical purposes. Problems of both bias and imprecision with creatinine measurement remain and, in both cases, have their greatest impact in the near-normal range. The last decade witnessed an impressive realignment of nephrology, pathology, and industry efforts to improve the measurement of serum creatinine for the benefits of patients. It is disappointing that only approximately 25% of UK laboratories currently use enzymatic methods and, as we have seen, old problems of non-specificity have not gone away. Nevertheless creatinine measurement (and GFR estimation) is performed better than hitherto. But continued efforts at quality improvement are still required.

Urinary protein and albumin

As observed by Bright nearly 200 years ago, the appearance of notable amounts of protein in the urine suggests renal disease. Its presence defines a patient as having kidney disease, irrespective of their GFR. Although not all patients with CKD will have proteinuria, proteinuria is a common finding in patients with kidney disease and its presence is a strong indicator of a poorer prognosis (Chapter 50; Turner 2013). Here we consider the analytical approach and rationale used in the measurement of urinary total protein compared to that of albumin.

There is no consistent definition of proteinuria (Lamb et al., 2009). 'Clinical' proteinuria has commonly been defined as equivalent to a colour change of '+' or greater on the relevant pad on a reagent strip. This equates to approximately 300 mg/L of total protein or a protein:creatinine ratio (PCR) of 50 mg/mmol, or protein loss of approximately 500 mg/day (assuming an average urine volume of 1.5 L/day). The normal urinary total protein loss is < 150 mg/day. The proteins lost are made up of albumin (typically < 30 mg/day) and some smaller proteins, together with proteins secreted by the tubules, of which Tamm–Horsfall glycoprotein predominates. In almost all pathological situations, as urinary total protein increases so does the relative contribution of albumin: when proteinuria exceeds 1 g/day, it is usual for 70–90% of this to be attributable to albumin.

For more than 50 years, proteinuria has commonly been detected using reagent strip ('dipstick') devices. In these, the reagent pad is impregnated with tetrabromphenol blue and a citrate pH 3 buffer. The reaction is based on the 'protein error of indicators' phenomenon in which certain chemical indicators demonstrate one colour in the presence of protein and another in its absence. Thus tetrabromphenol blue is green in the presence of protein at pH 3 but yellow in its absence. A variety of laboratory methods exist for the measurement of protein in urine. They include (1) the original Lowry method (Lowry et al., 1951), (2) turbidimetry after mixing with trichloroacetic or sulphosalicylic acid (Nishi and Elin, 1985), (3) turbidimetry with benzethonium chloride (McDowell, 1985), and dye binding with (4) Coomassie Brilliant Blue (Wimsatt and Lott, 1987), (5) pyrogallol red molybdate (Watanabe et al., 1986), and (6) pyrocatecholviolet-molybdate, which is used in dry-slide applications. The benzethonium chloride and dye-binding methods are the most popular in current clinical use.

These methods do not give equal analytical specificity and sensitivity for all proteins, tending to react more strongly with albumin than with globulin and other non-albumin proteins (e.g. Bence Jones protein) (Sedmak and Grossberg, 1977; McElderry et al., 1982; Nishi and Elin, 1985): the same is true of reagent strips (Bowie et al., 1977; Gyure, 1977; James et al., 1978). Indeed, somewhat confusingly, one commercial application of this principle has been manufactured as Albustix™, although the chemical principle underlying this test is identical to those devices that claim to measure 'protein' (Gyure, 1977).

Total protein measurement is more difficult in urine than in serum. The concentration of urinary protein is normally low

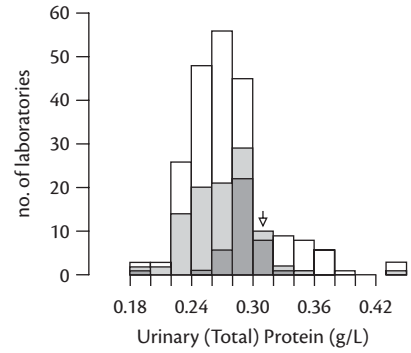
(100–200 mg/L); large sample-to-sample variation in the amount and composition of proteins is common; the concentration of non-protein potentially interfering substances is high relative to the protein concentration and very variable; and the inorganic ion content is high. Significant positive interferences include aminoglycosides (Marshall and Williams, 2004), non-visible haematuria (Yilmaz and Yucel, 2006), and certain plasma expanders (de Keijzer et al., 1999). Reagent strips are also subject to false positive interferences, including alkalinized urine (e.g. due to urinary tract infection or the presence of quaternary ammonium compounds). Their performance is also affected by the presence of coloured compounds such as bilirubin and certain drugs (e.g. ciprofloxacin, quinine, and chloroquine) (Scotti da Silva-Colombeli and Falkenberg, 2007). Further, results appear to be operator dependent (Rumley, 2000). An evaluation of two commercial reagent strips concluded that these devices could only reliably distinguish between urinary protein concentrations of < 200 and > 3000 mg/L (James et al., 1978). Performance of reagent strips in quality assessment schemes is generally poor (Fig. 104.2).

There is no JCTLM reference measurement procedure and no SRM for urinary total protein. Since a variable mixture of proteins is measured this is unlikely to ever be achieved. Calibration differences are one of the major determinants of intermethod variability (Heick et al., 1980; Chambers et al., 1991; Marshall and Williams, 2000).

Following the advent of radioimmunoassay, work by Keen, Viberti, and others in the 1960s and 1970s demonstrated that patients with diabetes mellitus often had increased loss of urinary albumin compared to the non-diabetic population (Keen and Chlouverakis, 1963, 1964). Loss of > 20 micrograms/min (approximately > 30 mg/24 hours) came to be termed 'microalbuminuria' and it was soon realized that this was a risk factor for progression of diabetic nephropathy (Viberti et al., 1982). With the availability of sensitive assays for urinary albumin and effective treatments, validated in large multinational trials, measurement of urinary albumin became standard practice in diabetes during the 1980s and 1990s and enshrined in clinical practice guidelines (National Institute for Health and Clinical Excellence, 2004, 2008b). Amongst patients with diabetes, the classification of diabetic nephropathy has been based upon urinary albumin loss (commonly expressed as an albumin:creatinine ratio (ACR)).

There is also strong evidence linking albuminuria to cardiovascular and non-cardiovascular morbidity and mortality in non-diabetic individuals (Matsushita et al., 2010). Albuminuria also predicts future decline in GFR (Kronborg et al., 2008; Obermayr et al., 2008) and requirement for renal replacement therapy

Specimen : 18A	n	Mean	SD	CV(%)
All methods	218	0.28	0.03	12.4
Dry slide	17	0.35	0.02	4.7
OCD (J&J) slides [1JJ]	17	0.35	0.02	4.7
Turbidimetry	62	0.27	0.02	7.6
Abbott reagents [5AB]	31	0.28	0.02	6.4
Roche Modular reagents [5BO]	28	0.27	0.03	10.4
Colorimetric	100	0.27	0.03	10.6
Beckman reagents [6BK]	25	0.25	0.01	6.0
Olympus reagents [6OL]	39	0.29	0.01	4.6
Randox reagents [6RX]	11	0.29	0.04	14.1
Not stated please specify	37	0.27	0.03	10.1



Specimen : 18A	n	Mean	SD	CV(%)
All methods	166	145.3	8.4	5.8
Nephelometry	13	157.1	12.1	7.7
Turbidimetry	121	144.7	7.7	5.3
Abbott reagents [5AB]	23	151.0	4.9	3.3
Bayer reagents [5TE]	9	141.4	3.6	2.6
Beckman reagents [5BK]	10	149.5	15.0	10.0
Olympus reagents [5OL]	23	145.4	2.8	2.0
Randox reagents [5RX]	12	137.6	7.7	5.6
Roche Integra reagents [5RO]	10	139.8	8.0	5.7
Roche Modular reagents [5BO]	30	142.0	5.9	4.1
Not stated please specify	27	146.0	4.6	3.1

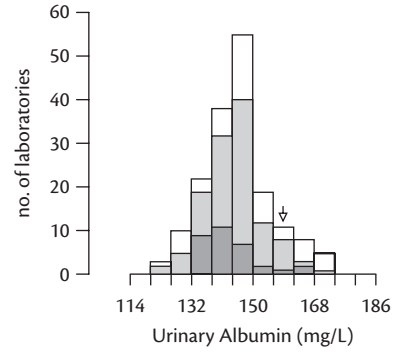


Fig. 104.2 Between-laboratory variability of urinary albumin and total protein measurement. Data from the United Kingdom National External Quality Assessment Scheme (UKNEQAS) illustrating typical between-laboratory agreement of urinary total protein and albumin assays in a urine sample. Note the relatively wide range of responses overall with the total protein data (upper panel), and the high within-method CVs for the total protein method groups. This situation can be compared with that for urinary albumin (lower panel). It can be seen that nearly all laboratories are using specific antibody-based turbidimetric methods. The mean result is 145 mg/L (0.145 g/L) and between-laboratory agreement is better than that for total protein, with an overall CV of 5.8%. At higher concentrations the between-laboratory variation of total protein methods improves and equals that of urinary albumin measurement, presumably in part as albumin becomes the predominant protein. The UKNEQAS also surveys the quality of reagent strip devices. Although several types of device are in use, the predominant method group (87 of 135 participants) is that manufactured by Siemens (Siemens plc, Camberley, Surrey, UK). In this distribution 8% of Siemens users classified the sample as negative, 30% as 'trace', 56% as + and 6% as ++ or greater. (Exercise dated May 2007.)

(van der Velde et al., 2009). Most commonly, proteinuria reflects albuminuria and there are calls (Lamb et al., 2009), including amongst guideline groups (National Kidney Foundation, 2002; Levey et al., 2005; National Institute for Health and Clinical Excellence, 2008a) suggesting that urinary total protein measurement should be replaced by albumin in most situations. Certainly the Kidney Disease: Improving Global Outcomes (KDIGO) classification of CKD is clear in that it requires urinary albumin measurement as a marker of kidney damage to facilitate diagnosis of stage 1 and 2 CKD and for risk stratification (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013), with a diagnostic threshold value of 3.0 mg/mmol.

There are physiological and analytical reasons why albumin should be preferred to total protein as a marker of glomerular damage. In health, relatively small amounts of albumin (< 30 mg/day) are lost in the urine. Because of this, and additionally because total protein assays are imprecise at low concentrations, relatively large (e.g. several-fold) increases in urine albumin loss can occur without causing a significant measurable increase in urinary total protein (Newman et al., 1995).

Urinary albumin is predominantly measured using quantitative immunoturbidimetric or nephelometric approaches capable of detecting albumin at low (e.g. 5–10 mg/L) concentrations. As for total protein, there is currently no JCTLM listed reference measurement procedure or SRM available, although ongoing work by NKDEP, the IFCC, and the Japanese Society of Clinical Chemistry is addressing this issue (Miller, 2008; Miller et al., 2009). Most commonly, urinary albumin assays are standardized against a serum-based calibrant (ERM_DA-470k/IFCC) distributed by the Institute for Reference Materials and Measurements of the European Commission, as has been recommended by KDIGO (Levey et al., 2005). Consequently both within-method agreement and between-laboratory agreement tends to be superior for urinary albumin compared to total protein (Fig. 104.2).

However, there are some grounds for caution. Changes in albumin loss may also reflect overall changes in vascular permeability and therefore may not indicate an explicit deterioration in renal function (Gosling, 1995). Concerns have been expressed that replacing urinary total protein measurement with albumin may cause tubular proteinuria to be missed (National Kidney Foundation, 2002) although there seems to be no foundation for this (Lamb et al., 2009). Although, intuitively, standardization issues should be more easily addressed than those for total protein measurement, albumin is a complex protein with varying forms identified (Blaabjerg and Hyltoft Petersen, 1979; Miller, 2008). The most significant concern is the risk of the antigen excess ('prozone' phenomenon), in which samples with very high albumin concentrations may be falsely reported as low or normal using some immunoassay approaches (Fig. 104.3).

Protein excretion displays considerable biological variability, and may be increased by upright posture, exercise, fever, symptomatic urinary tract infection (Carter et al., 2006), heart failure, and kidney disease (Chapter 50). Biological variation studies have reported CV_I of 40% for urinary total protein (36% for urinary albumin) from an early morning urine sample in healthy individuals. Thus a desirable performance goal of 20% for urine protein assays can be set. Whilst most laboratories should be able to achieve this, between-method and between-laboratory variation remains poor (Fig. 104.2). A significant reduction in intraindividual variation can be obtained by expressing results as a PCR (or ACR in the case of albumin), effectively correcting for urinary concentration/dilution (Newman et al., 2000). Standard urine reagent strips cannot make this adjustment; hence these tests can only give a rough indication of the presence or absence of pathological proteinuria (Ralston et al. 1988; Waugh et al. 2004). Recently, automated devices capable of reading the colour changes of reagent strips using reflectance spectrometry have become available. These reduce interoperator variability and improve diagnostic accuracy (Rumley, 2000; Waugh et al., 2005). A creatinine test pad has been added to some reagent strip systems to enable a PCR to be reported and so reduce the intraindividual variation seen with random urine collections (Guy et al., 2009). Similarly, reagent strip devices are now available that can measure urinary albumin at low concentrations and report the result as an ACR (Graziani et al., 2009).

Although Bright was detecting a mixture of proteins in heated urine, it was recognized that the major protein coagulating was albumin. For many years, methods of specifically measuring low concentrations of albumin were unavailable, and the clinical science and underpinning evidence of nephrology evolved based upon measurement of total protein in urine using chemical or

Specimen : 47A	n	Mean	SD	CV(%)
All methods	144	3406	1009	29.6
Nephelometry	11	3992	422	10.6
Dade Behring reagents [4BE]	6	4248	442	10.4
Turbidimetry	121	3296	1177	35.7
Abbott reagents [5AB]	23	3950	216	5.5
Bayer reagents [5TE]	12	3945	862	21.8
Beckman reagents [5BK]	8	3850	289	7.5
Olympus reagents [5OL]	15	3565	944	26.5
Randox reagents [5RX]	3	3443		
Roche Integra reagents [5RO]	15	3688	283	7.7
Roche Modular reagents [5BO]	43	2290	2147	93.7

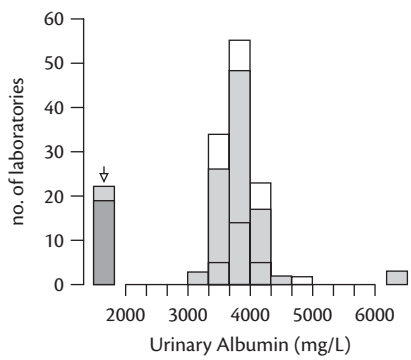


Fig. 104.3 Risk of falsely low urinary albumin results due to antigen excess. Data from the United Kingdom National External Quality Assessment Scheme (UKNEQAS) illustrating typical laboratory responses to distribution of a urine sample containing approximately 4 g/L (4000 mg/L) albumin. Whilst most laboratories obtained a result close to the expected value, a significant number of laboratories, more than 10%, returned a value of < 500 mg/L. Antigen excess is a problem that can affect any immunoassay, but is especially likely to occur in situations where the pathological range of concentrations encountered can be many fold higher than the typical values that the assay is designed to measure. (Exercise dated November 2009.)

physical methods. The technical merits of using albumin measurement rather than total protein have been discussed above. Routine, sensitive and cheap methods for urinary albumin measurement have been available for many years. It is time for nephrology to fully embrace the advantages of specifically measuring the single most important protein in kidney disease.

Parathyroid hormone

Parathyroid hormone (PTH) is a single-chain, 84-amino acid peptide hormone produced by the parathyroid glands in response to a decrease in the extracellular concentration of ionized calcium, its main role being to increase plasma calcium concentration. It is cleaved both within the parathyroid gland and after secretion into amino (N)-terminal, carboxy (C)-terminal, and mid-region fragments, which are metabolized in the liver and kidney.

The bony complications of kidney failure, driven by phosphate retention and failure of vitamin D activation, have been known to nephrologists for many years. With the advent of easily obtainable PTH measurements it appeared that a suitable marker to detect and manage chronic kidney disease-mineral bone disorder (CKD-MBD), as it has now been termed, was finally available. The last decade has also seen intense interest in the vascular calcification that characterizes renal failure, with attempts being made to relate this complication to PTH concentrations.

There has been an evolution of increasingly specific PTH assays (Fig. 104.4). Beginning in 1963 (Berson et al., 1963) and continuing through the 1980s, radioimmunoassays (RIAs) were used: these are now considered 'first-generation' PTH assays. RIA techniques involved a single antibody directed towards epitopes primarily located in the mid-region or C-terminal regions of the molecule. These assays proved to be unreliable because of different characteristics of the antisera used and the realization that PTH circulates not only in the form of the intact peptide but also as multiple fragments. Most RIAs for PTH thus cross-reacted with and detected a variety of C-terminal PTH fragments as well as full-length PTH(1–84), yielding a wide variety of results. Furthermore, measurements of PTH using C-terminal RIAs were inaccurate in patients with CKD as a result of impaired renal excretion of these fragments, resulting in marked elevation compared to subjects with normal kidney function.

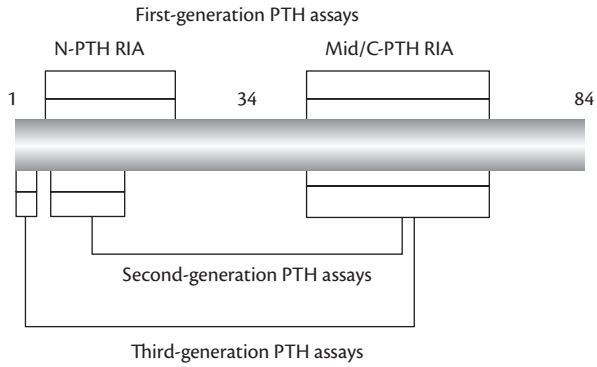


Fig. 104.4 Reactivity of PTH assays with differing fractions of circulating PTH. Early radioimmunoassays (RIAs) used a single antibody targeted against the N-, mid-, or C-terminal portion of the molecule. Second-generation assays used two antibodies ('sandwich assays') targeted against both the N- and mid/C-terminal portion of the molecule. Third-generation assays also use two antibodies but the N-terminal antibody is directed against the first few N-terminal amino acids, hence not capturing N-terminally truncated molecules, for example, PTH(7–84).

Reproduced with permission from Kidney Disease Improving Global Outcomes (KDIGO) (2009). KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*, S1–130.

The development of a second generation of PTH assays from 1987, the two-site immunoradiometric assays (IRMAs), improved upon many of the inadequacies of the single-antibody RIAs (Brown et al., 1987; Nussbaum et al., 1987). A capture antibody binds near the N-terminus and a second solid phase-coupled antibody binds to the C-terminus. Such assays were more reproducible than RIAs, particularly among patients requiring treatment with dialysis. These so-called intact PTH assays were thought to detect predominantly full length PTH(1–84). They remain the most widely used methods for measuring PTH clinically today, although they now commonly employ non-radioactive (e.g. chemiluminometric) detection systems.

In the mid 1990s, a Canadian research group discovered that another molecular form of PTH, thought to be PTH(7–84), was being detected by the second-generation assays (Lepage et al., 1998; D'Amour et al., 2005b). As would be predicted, given earlier experiences with RIAs, this fragment accumulates as GFR declines (Brossard et al. 2000), typically accounting for approximately half of the PTH measured by second-generation assays in patients with kidney failure. Discrete biological activities of PTH(7–84) (Huan et al., 2006), antagonistic to PTH(1–84), have been mooted, as have diagnostic uses of its measurement (Herberth et al., 2010): the significance of these remain uncertain at present.

The discovery that the second-generation 'intact' PTH assays measure other PTH molecules has led to the development of specific PTH(1–84) assays, referred to as third-generation assays. These are defined by their ability to measure whole intact PTH(1–84) without cross-reacting with PTH(7–84). Exploitation of the difference between the two N-terminal regions has provided an antibody that exclusively detects PTH(1–84); polyclonal antibodies are targeted to epitopes within the first four amino acids from the N-terminal (Gao et al., 2001). Third-generation assays are at present expensive and very few are automated: consequently they are not widely available in clinical practice.

As for urinary total protein and albumin discussed above, there is no reference method for PTH measurement. Significant intermethod variability exists (Fig. 104.5), to influence clinical decision-making (Fig. 104.6) (Lamb et al. 2007). Joly et al. compared PTH concentrations measured with 15 commercial immunoassays in samples of pooled plasma from dialysis patients (Joly et al., 2008). They used the Nichols Allegro PTH assay as the reference, since it was upon this assay that KDOQI guidelines were predominantly based; however this assay is no longer available. The median bias ranged from −45 to +123%. Similar results have been observed by others (Cantor et al., 2006).

Intermethod variability may be explained in part by problems of antibody specificity and lack of common standardization (D'Amour et al., 2005a). Commercially available assays show differing recovery of PTH(1–84), and differing cross-reactivity with PTH(7–84): data from the United Kingdom National External Quality Assessment Scheme (UKNEQAS) estimated between 69% and 102% cross-reactivity with PTH(7–84) for commercially available second-generation assays (Lamb et al., 2007). This reflects

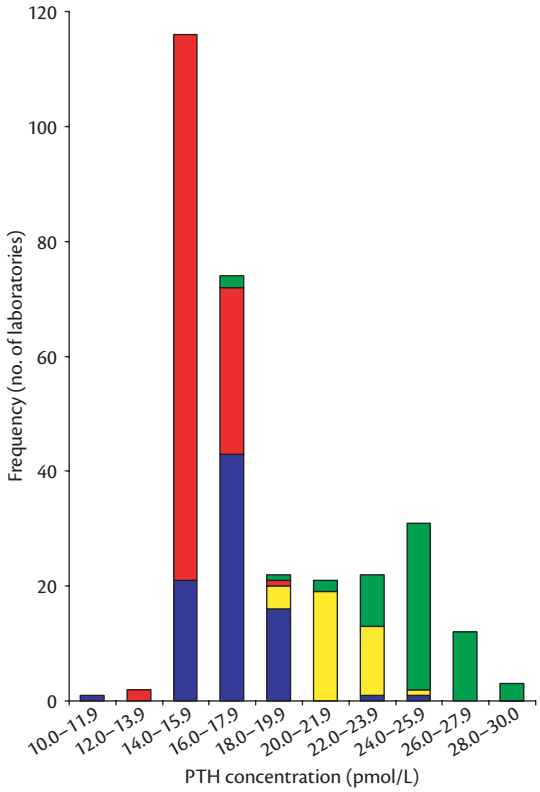


Fig. 104.5 Variability of plasma PTH results using a variety of commercial PTH assays. A pool of plasma obtained from patients with renal failure was distributed to laboratories participating in the UKNEQAS. The histogram shows results for all methods. The green boxes indicate results obtained from laboratories using the Siemens Immulite method, red the Roche ElecSys method, yellow patterning the Abbott Architect method and blue patterning other methods. Data supplied by UK NEQAS (exercise dated January 2010). To convert PTH in pmol/L to ng/L divide by 0.11.

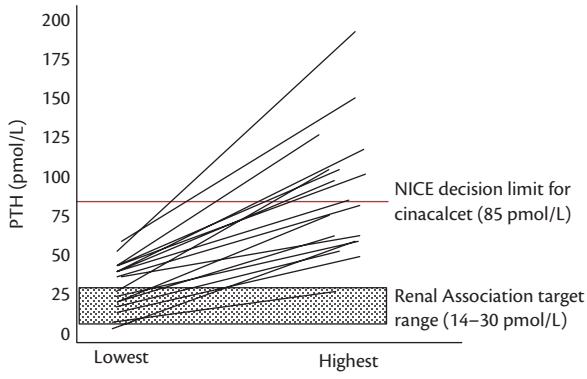


Fig. 104.6 Potential treatment variation attributable to analytical variation. The highest and lowest PTH concentrations in 18 patients measured using a range of commercially available assays is shown. Each line represents a single study patient (shaded area, Renal Association (4th edition, 2007) target range for PTH in CKD patients; red line, National Institute for Health and Care Excellence decision limit for eligibility for cinacalcet). CKD = chronic kidney disease; PTH = parathyroid hormone. To convert PTH in pmol/L to ng/L divide by 0.11.

Reproduced with permission from Almond et al. (2012), Current parathyroid hormone immunoassays do not adequately meet the needs of patients with chronic kidney disease. *Ann Clin Biochem*, 49(Pt 1), 63–7.

differences in antibody specificities and affinities, which are individual to each manufacturer. The problem is further compounded by the differential retention and accumulation of PTH(7–84) and other PTH fragments in CKD.

Nearly 50 years after the first PTH immunoassays were developed, there remains no agreed common standard between PTH assays, that is, the human PTH(1–84) calibrators present in the assays differ from company to company. A reference preparation of purified human PTH for PTH immunoassays (WHO 79/500) was prepared in 1981 (Zanelli and Gaines-Das, 1983). However, its content was formally defined in international units (0.1 IU/ampoule) whereas PTH measurements tend to be expressed in mass or molar units. Some manufacturers have claimed traceability to 79/500 but its nominal mass concentration was probably inaccurate and did not provide a sound basis for conversion to the use of mass units for reporting PTH. A newer preparation based on recombinant PTH and defined in mass units has been prepared by the National Institute of Biological Standards and Controls (NIBSC/WHO 95/646, <http://www.nibsc.ac.uk/documents/ifu/95-646.pdf>) and its commutability between assays is being established (<http://whqlibdoc.who.int/hq/2009/WHO_BS_09.2115_eng.pdf>). It is hoped that the introduction of this material will lead to significant improvement in assay comparability (Sturgeon et al., 2011).

Measured PTH concentration is also affected by a variety of pre-analytical factors. Assay results can differ if samples are measured in plasma or serum, and depending on the temperature and speed at which they are processed. Many studies have found that, at room temperature, PTH is more stable in blood samples collected into ethylendiaminetetraacetic acid (EDTA)-preserved tubes than in tubes containing no preservative (Teal et al., 2003, 2004; English et al., 2007). Changes in measured PTH concentrations as a result of different storage conditions are sufficient to affect clinical decision-making in many cases (Joly et al., 2008). There is preliminary evidence that PTH measured by third-generation assays is more stable than when measured by second-generation assays (i.e. suggesting that PTH(1–84) is more stable *ex vivo* than PTH(7–84)) (Teal et al., 2004; Cavalier et al., 2012).

Other contributors to PTH variability are also poorly appreciated. For example, central venous catheter PTH concentrations in haemodialysis patients are reported to be 30% higher than those in peripheral blood samples (Vulpio et al., 2010).

Reported CV_I for PTH is 26% in healthy individuals (Ankrah-Tetteh et al., 2008) with a similar value being reported in stable haemodialysis patients (Gardham et al., 2010). Given this high value, not unexpected for a hormone under dynamic feedback control and with a short half-life, most modern, automated methods can achieve desirable and even optimal analytical precision. However, in terms of interpreting the data that is generated, it should be noted that this produces an RCV required to be 95% certain of a true change in value having occurred of 72%; in other words, a PTH concentration of 300 ng/L followed by one of 500 ng/L would *not* necessarily be truly different from each other. Further, ideally 26 specimens are required to estimate a dialysis patient's PTH homeostatic set-point within ±10% (Gardham et al., 2010). In practice, what this means is that whilst extreme values of PTH probably do indicate adynamic or hyperparathyroid bone disease, most results fall in an indefinite zone where biological and analytical variability precludes meaningful interpretation. It should be noted that the high CV_I of PTH renders interpretation against

reference ranges, upon which clinical targets have been based, of little value: most information can be gained by monitoring an individual's trend in concentration, as recently suggested (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009).

PTH has been used as a surrogate marker of underlying bone status in patients with kidney disease for many years. National and international guideline groups even suggest targets of PTH concentration that should be aimed for. There are many reasons why PTH is unsuitable for this purpose (Drueke, 2008): in this section we have reviewed the technical limitations of PTH in this setting. The current lack of standardization is an absolute impediment to the development of any meaningful clinical targets. However, as we have seen earlier with serum creatinine, even standardization fails to circumvent the problems of non-specificity. Third-generation PTH assays are probably suitably specific, but their wider availability will first require clear demonstration of their clinical benefit. Currently such advantages have not been shown (Inaba et al., 2004) although suggestions of improved stability of measured PTH are clearly a strong argument. Once a standardized, specific assay is available, it will be imperative to strictly define pre-analytical conditions of sampling and storage (Hanon et al., 2013). Only then will we be able to ascertain whether PTH really provides useful information in the assessment of CKD-MBD.

General conclusions

In the assessment of their complex patients, nephrologists rely heavily on objective, quantitative laboratory data. It is unreasonable to expect practitioners to fully understand the methodology, traceability, and variability that underlie every single result that a laboratory produces: that is the role of laboratory professionals. Interpretation of data should be underpinned by traceability to a higher-order reference method and calibration linked to a standardized reference material. Without these prerequisites, accuracy cannot really exist and clinicians using differing methods are not dealing in the same 'currency'. Once 'trueness' is established, as it is now for serum creatinine, for example, we need to understand how normal biological variability influences our interpretation and laboratories need to ensure that assays are fit for purpose and able to meet performance targets. A critical component of this is participation in external quality assessment schemes, which provide ongoing reassurance of the validity, or otherwise, of laboratory outputs.

Nephrologists may be unaware that 'routine' clinical assays that have been in use for many years remain non-standardized and incompletely characterized. Nephrologists and pathologists need to work together to ensure that laboratory data better serves patients.

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References

Ankrah-Tetteh, T., Wijeratne, S., and Swaminathan, R. (2008). Intraindividual variation in serum thyroid hormones, parathyroid hormone and insulin-like growth factor-1. *Ann Clin Biochem*, 45, 167–9.

Berson, S. A., Yalow, R. S., Aurbach, G. D., *et al.* (1963). Immunoassay of bovine and human parathyroid hormone. *Proc Natl Acad Sci U S A*, 49, 613–17.

Blaabjerg, O. and Hyltoft Petersen, P. (1979). Effect of aggregates on albumin standardization. *Scand J Clin Lab Invest*, 39, 751–7.

Bowie, L., Smith, S., and Gochman, N. (1977). Characteristics of binding between reagent-strip indicators and urinary proteins. *Clin Chem*, 23, 128–30.

Brossard, J. H., Lepage, R., Cardinal, H., *et al.* (2000). Influence of glomerular filtration rate on non-(1-84) parathyroid hormone (PTH) detected by intact PTH assays. *Clin Chem*, 46, 697–703.

Brown, R. C., Aston, J. P., Weeks, I., *et al.* (1987). Circulating intact parathyroid hormone measured by a two-site immunochemiluminometric assay. *J Clin Endocrinol Metab*, 65, 407–14.

Cameron, J. S., Turner, A. N., (2015). Richard Bright and the discovery of renal disease. History of Nephrology blog. http://historyofnephrology.blogspot.com/2015/07/richard-bright-and-discovery-of-kidney.html

Cantor, T., Yang, Z., Caraiani, N., and Ilamathi, E. (2006). Lack of comparability of intact parathyroid hormone measurements among commercial assays for end-stage renal disease patients: implication for treatment decisions. *Clin Chem*, 52, 1771–6.

Carter, J. L., Tomson, C. R., Stevens, P. E., *et al.* (2006). Does urinary tract infection cause proteinuria or microalbuminuria? A systematic review. *Nephrol Dial Transplant*, 21, 3031–7.

Cavalier, E., Carlisi, A., Bekaert, A. C., *et al.* (2012). New insights on the stability of the parathyroid hormone as assayed by an automated 3rd generation PTH assay. *Clin Chim Acta*, 413(1–2), 353–4.

Chambers, R. E., Bullock, D. G., and Whicher, J. T. (1991). External quality assessment of total urinary protein estimation in the United Kingdom. *Ann Clin Biochem*, 28 (Pt 5), 467–73.

Coresh, J., Astor, B. C., Mcquillan, G., *et al.* (2002). Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis*, 39, 920–9.

D'amour, P., Brossard, J. H., Rakel, A., *et al.* (2005a). Evidence that the amino-terminal composition of non-(1-84) parathyroid hormone fragments starts before position 19. *Clin Chem*, 51, 169–76.

D'amour, P., Brossard, J. H., Rousseau, L., *et al.* (2005b). Structure of non-(1-84) PTH fragments secreted by parathyroid glands in primary and secondary hyperparathyroidism. *Kidney Int*, 68, 998–1007.

De Keijzer, M. H., Klasen, I. S., Branten, A. J., *et al.* (1999). Infusion of plasma expanders may lead to unexpected results in urinary protein assays. *Scand J Clin Lab Invest*, 59, 133–7.

Dodder, N. G., Tai, S. S., Sniegoski, L. T., *et al.* (2007). Certification of creatinine in a human serum reference material by GC-MS and LC-MS. *Clin Chem*, 53, 1694–9.

Drueke, T. B. (2008). Is parathyroid hormone measurement useful for the diagnosis of renal bone disease? *Kidney Int*, 73, 674–6.

English, E., Mcfarlane, I., Taylor, K. P., *et al.* (2007). The effect of potassium EDTA on the stability of parathyroid hormone in whole blood. *Ann Clin Biochem*, 44, 297–9.

Fraser, C. G. and Harris, E. K. (1989). Generation and application of data on biological variation in clinical chemistry. *Crit Rev Clin Lab Sci*, 27, 409–37.

Gao, P., Scheibel, S., D'amour, P., *et al.* (2001). Development of a novel immunoradiometric assay exclusively for biologically active whole parathyroid hormone 1-84: implications for improvement of accurate assessment of parathyroid function. *J Bone Miner Res*, 16, 605–14.

Gardham, C., Stevens, P. E., Delaney, M. P., *et al.* (2010). Variability of parathyroid hormone and other markers of bone mineral metabolism in patients receiving hemodialysis. *Clin J Am Soc Nephrol*, 5, 1261–7.

Gosling, P. (1995). Microalbuminuria: a sensitive indicator of non-renal disease? *Ann Clin Biochem*, 32 (Pt 5), 439–41.

Gowans, E. M. and Fraser, C. G. (1988). Biological variation of serum and urine creatinine and creatinine clearance: ramifications for interpretation of results and patient care. *Ann Clin Biochem*, 25 (Pt 3), 259–63.

Graziani, M. S., Gambaro, G., Mantovani, L., *et al*. (2009). Diagnostic accuracy of a reagent strip for assessing urinary albumin excretion in the general population. *Nephrol Dial Transplant*, 24, 1490–4.

Guy, M., Newall, R., Borzomato, J., *et al*. (2009). Use of a first-line urine protein-to-creatinine ratio strip test on random urines to rule out proteinuria in patients with chronic kidney disease. *Nephrol Dial Transplant*, 24, 1189–93.

Gyure, W. L. (1977). Comparison of several methods for semiquantitative determination of urinary protein. *Clin Chem*, 23, 876–9.

Hanon, E. A., Sturgeon, C. M., and Lamb, E. J. (2013). Sampling and storage conditions influencing the measurement of parathyroid hormone in blood samples: a systematic review. *Clin Chem Lab Med*, 51, 1925–41.

Heick, H. M., Begin-Heick, N., Acharya, C., *et al*. (1980). Automated determination of urine and cerebrospinal fluid proteins with Coomassie Brilliant Blue and the Abbott ABA-100. *Clin Biochem*, 13, 81–3.

Herberth, J., Branscum, A. J., Mawad, H., *et al*. (2010). Intact PTH combined with the PTH ratio for diagnosis of bone turnover in dialysis patients: a diagnostic test study. *Am J Kidney Dis*, 55, 897–906.

Huan, J., Olgaard, K., Nielsen, L. B., *et al*. (2006). Parathyroid hormone 7-84 induces hypocalcemia and inhibits the parathyroid hormone 1-84 secretory response to hypocalcemia in rats with intact parathyroid glands. *J Am Soc Nephrol*, 17, 1923–30.

Inaba, M., Nakatsuka, K., Imanishi, Y., *et al*. (2004). Technical and clinical characterization of the bio-PTH (1-84) immunochemiluminometric assay and comparison with a second-generation assay for parathyroid hormone. *Clin Chem*, 50, 385–390.

James, G. P., Bee, D. E., and Fuller, J. B. (1978). Proteinuria: accuracy and precision of laboratory diagnosis by dip-stick analysis. *Clin Chem*, 24, 1934–9.

Joly, D., Drueke, T. B., Alberti, C., *et al*. (2008). Variation in serum and plasma PTH levels in second-generation assays in hemodialysis patients: a cross-sectional study. *Am J Kidney Dis*, 51, 987–95.

Keen, H. and Chlouverakis, C. (1963). An immunoassay method for urinary albumin at low concentrations. *Lancet*, 2, 913–14.

Keen, H. and Chlouverakis, C. (1964). Urinary albumin excretion and diabetes mellitus. *Lancet*, 2, 1155–6.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009). KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*, 113, S1–130.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*, 3, 1–150.

Kronborg, J., Solbu, M., Njolstad, I., *et al*. (2008). Predictors of change in estimated GFR: a population-based 7-year follow-up from the Tromso study. *Nephrol Dial Transplant*, 23, 2818–26.

Lamb, E. J., Mackenzie, F., and Stevens, P. E. (2009). How should proteinuria be detected and measured? *Ann Clin Biochem*, 46, 205–17.

Lamb, E. J., Vickery, S., and Ellis, A. R. (2007). Parathyroid hormone, kidney disease, evidence and guidelines. *Ann Clin Biochem*, 44, 1–4.

Lamb, E. J., Wood, J., Stowe, H. J., *et al*. (2005). Susceptibility of glomerular filtration rate estimations to variations in creatinine methodology: a study in older patients. *Ann Clin Biochem*, 42, 11–18.

Lepage, R., Roy, L., Brossard, J. -H., *et al*. (1998). A non-(1–84) circulating parathyroid hormone (PTH) fragment interferes significantly with intact PTH commercial assay measurements in uremic samples. *Clin Chem*, 44, 805–9.

Levey, A. S., Bosch, J. P., Lewis, J. B., *et al*. (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*, 130, 461–70.

Levey, A. S., Eckardt, K. U., Tsukamoto, Y., *et al*. (2005). Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*, 67, 2089–100.

Lowry, O. H., Rosebrough, N. J., Farr, A. L., *et al*. (1951). Protein measurement with the Folin phenol reagent. *J Biol Chem*, 193, 265–75.

Marshall, T. and Williams, K. M. (2000). Total protein determination in urine: elimination of a differential response between the Coomassie blue and pyrogallol red protein dye-binding assays. *Clin Chem*, 46, 392–8.

Marshall, T. and Williams, K. M. (2004). Extent of aminoglycoside interference in the pyrogallol red-molybdate protein assay depends on the concentration of sodium oxalate in the dye reagent. *Clin Chem*, 50, 934–5.

Matsushita, K., Van Der Velde, M., Astor, B. C., *et al*. (2010). Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*, 375, 2073–81.

McDowell, T. L. (1985). Benzethonium chloride method for proteins adapted to centrifugal analysis. *Clin Chem*, 31, 864–6.

McElderry, L. A., Tarbit, I. F., and Cassells-Smith, A. J. (1982). Six methods for urinary protein compared. *Clin Chem*, 28, 356–60.

Miller, W. G. (2008). Urine albumin: recommendations for standardization. *Scand J Clin Lab Invest Suppl*, 241, 71–2.

Miller, W. G. (2009). Estimating glomerular filtration rate. *Clin Chem Lab Med*, 47, 1017–9.

Miller, W. G., Bruns, D. E., Hortin, G. L., *et al*. (2009). Current issues in measurement and reporting of urinary albumin excretion. *Clin Chem*, 55, 24–38.

Miller, W. G., Myers, G. L., Ashwood, E. R., *et al*. (2005). Creatinine measurement: state of the art in accuracy and interlaboratory harmonization. *Arch Pathol Lab Med*, 129, 297–304.

Miller, W. G., Myers, G. L., Lou Gantzer, M., *et al*. (2011). Roadmap for harmonization of clinical laboratory measurement procedures. *Clin Chem*, 57, 1108–17.

Murthy, K., Stevens, L. A., Stark, P. C., *et al*. (2005). Variation in the serum creatinine assay calibration: a practical application to glomerular filtration rate estimation. *Kidney Int*, 68, 1884–7.

Myers, G. L., Miller, W. G., Coresh, J., *et al*. (2006). Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem*, 52, 5–18.

National Institute for Health and Clinical Excellence. (2004). *Type 1 Diabetes: Diagnosis and Management of Type 1 Diabetes in Children, Young People and Adults*. Clinical Guideline 15. London: National Institute for Health and Clinical Excellence.

National Institute for Health and Clinical Excellence. (2008a). *Chronic Kidney Disease: National Clinical Guideline for Early Identification and Management in Adults in Primary and Secondary Care*. Clinical Guideline 73. London: National Institute for Health and Clinical Excellence.

National Institute for Health and Clinical Excellence. (2008b). *Type 2 Diabetes: the Management of Type 2 Diabetes*. Clinical Guideline 66. London: National Institute for Health and Clinical Excellence.

National Kidney Foundation (2002). K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*, 39, S1–266.

Newman, D. J., Pugia, M. J., Lott, J. A., *et al*. (2000). Urinary protein and albumin excretion corrected by creatinine and specific gravity. *Clin Chim Acta*, 294, 139–55.

Newman, D. J., Thakkar, H., Medcalf, E. A., *et al*. (1995). Use of urine albumin measurement as a replacement for total protein. *Clin Nephrol*, 43, 104–9.

Nishi, H. H. and Elin, R. J. (1985). Three turbidimetric methods for determining total protein compared. *Clin Chem*, 31, 1377–80.

Nussbaum, S. R., Zahradnik, R. J., Lavigne, J. R., *et al*. (1987). Highly sensitive two-site immunoradiometric assay of parathyrin, and its clinical utility in evaluating patients with hypercalcemia. *Clin Chem*, 33, 1364–7.

Obermayr, R. P., Temml, C., Knechtelsdorfer, M., *et al*. (2008). Predictors of new-onset decline in kidney function in a general middle-european population. *Nephrol Dial Transplant*, 23, 1265–73.

Panteghini, M., Myers, G. L., Miller, W. G., *et al*. (2006). The importance of metrological traceability on the validity of creatinine measurement as an index of renal function. *Clin Chem Lab Med*, 44, 1287–92.

Peitzman, S. (2007). *Dropsy, Dialysis, Transplant*. Baltimore, MD: John Hopkins University Press.

Preiss, D. J., Godber, I. M., Lamb, E. J., *et al.* (2007). The influence of a cooked-meat meal on estimated glomerular filtration rate. *Ann Clin Biochem*, 44, 35–42.

Ralston, S. H., Caine, N., Richards, I., *et al.* (1988). Screening for proteinuria in a rheumatology clinic: comparison of dipstick testing, 24 hour urine quantitative protein, and protein/creatinine ratio in random urine samples. *Ann Rheum Dis*, 47, 759–63.

Rehberg, P. (1926). Studies on kidney function: II. The excretion of urea and chloride analyzed according to a modified filtration reabsorption theory. *Biochem J*, 20, 461–82.

Rumley, A. (2000). Urine dipstick testing: comparison of results obtained by visual reading and with the Bayer CLINITEK 50. *Ann Clin Biochem*, 37 (Pt 2), 220–1.

Scotti Da Silva-Colombeli, A. and Falkenberg, M. (2007). Analytical interferences of drugs in the chemical examination of urinary protein. *Clin Biochem*, 40, 1074–6.

Sedmak, J. J. and Grossberg, S. E. (1977). A rapid, sensitive, and versatile assay for protein using Coomassie brilliant blue G250. *Anal Biochem*, 79, 544–52.

Shepherd, J., Warner, M. H., and Kilpatrick, E. S. (2007). Stability of creatinine with delayed separation of whole blood and implications for eGFR. *Ann Clin Biochem*, 44, 384–7.

Spencer, K. (1986). Analytical reviews in clinical biochemistry: the estimation of creatinine. *Ann Clin Biochem*, 23 (Pt 1), 1–25.

Sturgeon, C. M., Sprague, S. M., and Metcalfe, W. (2011). Variation in parathyroid hormone immunoassay results—a critical governance issue in the management of chronic kidney disease. *Nephrol Dial Transplant*, 26, 3440–5.

Teal, T. K., Reed, M., Stevens, P. E., *et al.* (2003). Stability of parathyroid hormone ex vivo in haemodialysis patients. *Ann Clin Biochem*, 40, 191–3.

Teal, T. K., Wood, J. L., Stevens, P. E., *et al.* (2004). Stability of Bio-Intact (1-84) parathyroid hormone ex vivo in serum and EDTA plasma from hemodialysis patients. *Clin Chem*, 50, 1713–4.

Turner, A. N. (2013). Proteinuria: a bad thing since 400 BC. History of Nephrology blog. http://historyofnephrology.blogspot.co.uk/2013/01/proteinuria-bad-thing-since-400-bc.html

Van Der Velde, M., Halbesma, N., De Charro, F. T., *et al.* (2009). Screening for albuminuria identifies individuals at increased renal risk. *J Am Soc Nephrol*, 20, 852–62.

Viberti, G. C., Hill, R. D., Jarrett, R. J., *et al.* (1982). Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet*, 1, 1430–2.

Vulpio, C., Bossola, M., Speranza, D., *et al.* (2010). Influence of blood sampling site on intact parathyroid hormone concentrations in hemodialysis patients. *Clin Chem*, 56, 489–90.

Watanabe, N., Kamei, S., Ohkubo, A., *et al.* (1986). Urinary protein as measured with a pyrogallol red-molybdate complex, manually and in a Hitachi 726 automated analyzer. *Clin Chem*, 32, 1551–4.

Waugh, J. J., Bell, S. C., Kilby, M. D., *et al.* (2005). Optimal bedside urinalysis for the detection of proteinuria in hypertensive pregnancy: a study of diagnostic accuracy. *BJOG*, 112, 412–7.

Waugh, J. J., Clark, T. J., Divakaran, T. G., *et al.* (2004). Accuracy of urinalysis dipstick techniques in predicting significant proteinuria in pregnancy. *Obstet Gynecol*, 103, 769–77.

Weber, J. A. and Van Zanten, A. P. (1991). Interferences in current methods for measurements of creatinine. *Clin Chem*, 37, 695–700.

Wimsatt, D. K. and Lott, J. A. (1987). Improved measurement of urinary total protein (including light-chain proteins) with a Coomassie brilliant blue G-250-sodium dodecyl sulfate reagent. *Clin Chem*, 33, 2100–6.

Yilmaz, F. M. and Yucel, D. (2006). Effect of addition of hemolysate on urine and cerebrospinal fluid assays for protein. *Clin Chem*, 52, 152–3.

Zanelli, J. M. and Gaines-Das, R. E. (1983). The first international reference preparation of human parathyroid hormone for immunoassay: characterization and calibration by international collaborative study. *J Clin Endocrinol Metab*, 57, 462–9.

CHAPTER 105

Effect of lifestyle modifications on patients with chronic kidney disease

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Lifestyle and disease progression

Lifestyle plays an important role in the development and management of chronic kidney disease (CKD). Sedentary lifestyles as well as diet and obesity are all contributors to the development of CKD and associated comorbidities, type 2 diabetes, and cardiovascular disease (CVD). The role of lifestyle factors (Fig. 105.1) including physical inactivity, diet, and obesity in the development and progression of CKD are discussed in the following sections.

Physical inactivity and low exercise capacity

Physical inactivity leading to low exercise capacity is common in CKD patients and is associated with reduced glomerular filtration rate (GFR) (Finkelstein et al., 2006) as well as CVD and diabetes, common comorbidities in CKD. In end-stage renal disease (ESRD) patients, an exercise capacity below 17.5 mL/kg/min is associated with an increased mortality (Sietsema et al., 2004). However, while CKD patients are at increased risk of cardiovascular (CV) death (Foley et al., 1998), the relationship between exercise capacity and mortality has not been reported.

Diet

(See Chapter 101.)

Protein

The recommended level of dietary protein for a healthy adult is approximately 0.8 g/kg body weight (Anonymous, 1985). However, the average Western diet contains up to 2.0 g/kg body weight. The use of high-protein diets has led to the conjecture that they may contribute to the development of CKD by sustained increase in intraglomerular pressure and hyperfiltration. This is supported by a study (De Miguel et al., 2011), where rats fed a high-protein (30%) and salt diet developed elevated urine albumin:creatinine ratio compared to those fed a normal- or low-protein diet (18% or 6% respectively). Despite a lack of evidence linking high-protein diets with renal damage in healthy adults, the same argument has been proposed to recommend dietary protein restriction in CKD patients. Multiple trials have investigated the role of dietary protein in the progression of CKD. Meta-analyses of these studies indicate that although dietary protein restriction reduces renal mortality (Fouque and Laville, 2009), the rate of GFR decline was only 0.53 mL/min/year (Kasiske et al., 1998) leading to the conclusion that better therapies are needed to slow the rate of CKD progression.

Salt

Sodium retention occurs in most patients with CKD. This is discussed in Chapter 101.

Phosphate

In CKD there is impaired excretion of phosphate leading to hyperphosphataemia. This is discussed further in Chapter 101.

Alcohol

Several epidemiological studies have attempted to identify the role of alcohol consumption in development of CKD. Inverse trends have been reported between alcohol consumption and CKD in Japanese men (Funakoshi et al., 2012), and between alcohol consumption and development of elevated creatinine levels or decreased GFR over a 14-year follow-up period (Schaeffner et al., 2005) leading to the conclusion that moderate alcohol consumption (up to two standard drinks per day) may actually decrease the risk of renal dysfunction. However alcohol consumption was not related to CKD incidence in the National Health and Nutrition Examination Survey study (Stengel et al., 2003). Excessive alcohol, through an effect on blood pressure, will have an adverse effect on CKD.

Obesity

Obesity may be considered a risk factor for the development of CKD. A recent meta-analysis of cross-sectional and case–control studies (Wang et al., 2008) reported that in industrialized countries, 16.5% of CKD in men and 26.3% in women could be related to excess weight and obesity. In addition, overweight people have

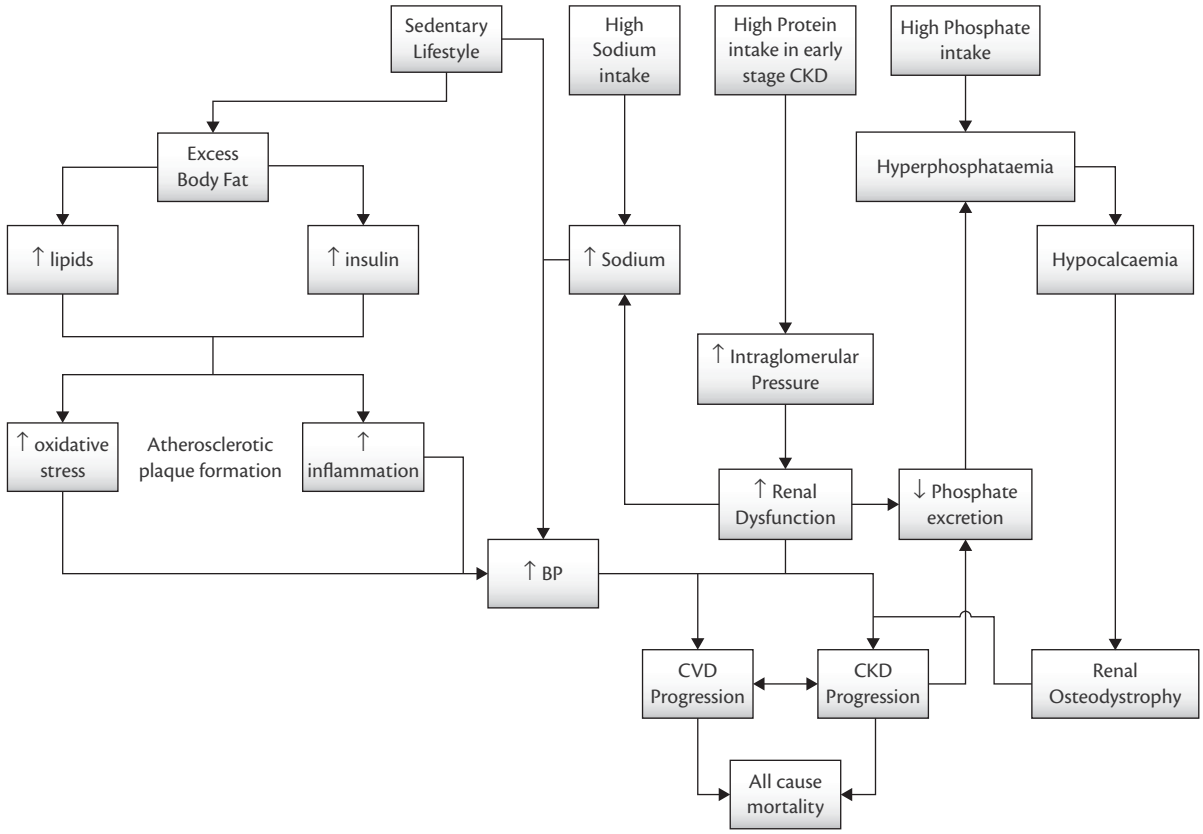

Fig. 105.1 Lifestyle factors influencing CKD development and progression leading to all-cause mortality.

a 40% higher risk of developing CKD, and obese people an 83% higher risk, which is independent of incidence of diabetes and hypertension (Wang et al., 2008). The relationship between obesity and progression of CKD (as well as mortality) is less obvious. This may be due to the common use of body mass index to indicate obesity (Teta, 2010). Increased visceral fat has been linked with higher fasting plasma insulin and triglyceride levels and greater prevalence of atherosclerosis in dialysis patients (Yamauchi et al., 2003), while the detrimental effects of oxidative stress and inflammation noted with obesity are augmented in patients with CKD and may contribute to decrements in renal function (Ramos et al., 2008).

Evidence for lifestyle in the management of chronic kidney disease

Exercise

While the benefit of exercise training in patients with ESRD has been investigated widely, with observed improvements in CV fitness, physical functioning, and decreases in CV risk (Segura-Orti and Johansen, 2010), the potential benefits of exercise in less severe CKD have not been well investigated (Howden et al., 2012). The Kidney Disease Improving Global Outcomes clinical practice guidelines (2013) emphasize that regular physical activity should be strongly encouraged, especially to manage CV risk.

Aerobic exercise

Aerobic exercise capacity has strong independent associations with mortality in both healthy and chronic disease populations. Specifically in ESRD, VO_2 peak is a strong predictor of survival and is thought to provide additional prognostic information (Sietsema et al., 2004). A Cochrane review of CKD in adults found that aerobic exercise training improved exercise capacity in both patients with CKD and ESRD (Heiwe and Jacobson, 2011). Aerobic exercise training also improves physical function (Boyce et al., 1997), reduces resting blood pressure (Boyce et al., 1997), arterial stiffness (Mustata et al., 2011) and markers of oxidative stress (Pechter et al., 2003), and may improve renal function (Pechter et al., 2003; Toyama et al., 2010). In patients with ESRD, aerobic exercise training improves health-related quality of life (HRQOL) (Segura-Orti and Johansen, 2010) and reduces insulin resistance (Goldberg et al., 1983), oxidative stress biomarkers (Wilund et al., 2010), and inflammation (Afshar et al., 2010).

Resistance exercise

CKD causes a progressive reduction in muscle strength and skeletal muscle mass. In ESRD the effects of protein wasting are more pronounced and therefore the rationale for inclusion of this type of training is stronger. The effects of resistance exercise training in CKD have been investigated in a small number of studies (Segura-Orti and Johansen, 2010; Heiwe and Jacobson,

2011). Whilst there is only low-level evidence at present in CKD patients, the results suggest improvement in muscle function and strength, functional mobility, and inflammatory status are possible. In a meta-analysis (Segura-Orti and Johansen, 2010) the potential benefits of exercise in HD patients were described. This review identified moderate-level evidence for increases in HRQOL, large non-significant increases in strength following resistance training, and encouraging findings in terms of increased muscle cross-sectional area in two separate studies following resistance training. Two other studies have investigated the effect of intradialytic resistance training on inflammatory markers with inconsistent findings. Afshar et al. (2010) reported reductions in C-reactive protein following 8 weeks of intradialytic exercise training, and Cheema and colleagues (Cheema et al., 2011) reported no change in any pro- or anti-inflammatory cytokines following 12 weeks of high-intensity, progressive intradialytic resistance training.

Combination exercise training

Three studies (Clyne et al., 1991; Cook et al., 2008; Howden et al., 2013) have investigated the effect of the combination of aerobic and resistance training in CKD patients, but only one of these was a randomized controlled trial (Howden et al., 2013). While all studies reported that exercise capacity and muscle endurance were increased with combination training, the effects on kidney function and blood pressure are less clear. One uncontrolled study reported no change in kidney function (Clyne et al., 1991) while in the other estimated GFR decreased in a subgroup of 12 of 32 patients (Cook et al., 2008). In comparison, the most recent study reported significant improvements following 12 months of exercise and lifestyle intervention in CV parameters including left ventricular function in patients with moderate CKD (Howden et al., 2013). In ESRD the benefits reported from this type of training include improvements in VO_2 peak (Deligiannis et al., 1999; van Vilsteren et al., 2005), muscle strength, dialysis adequacy and general health perception (van Vilsteren et al., 2005), and heart rate variability and the incidence of arrhythmias (Deligiannis et al., 1999). The 2011 Cochrane review reported that combination high-intensity exercise training results in a significant decrease in resting systolic and diastolic blood pressure of between 4 to 7 mmHg in adults with CKD. This finding is clinically important given that even small reductions in blood pressure in the general population can reduce coronary heart disease, stroke and all-cause mortality (Heiwe and Jacobson, 2011).

Interdialytic exercise has been reported to be superior to intradialytic exercise in terms of outcomes (Moinuddin and Leehey, 2008). However, there is a role for intradialytic exercise as there is generally a lower withdrawal rate when this type of exercise is used.

Exercise recommendations

The 2011 Cochrane review on CKD in adults suggests that the current level of scientific evidence supports the recommendation that exercising regularly for > 30 minutes/session three times/week will improve physical fitness, walking capacity, CV function, and HRQOL (Heiwe and Jacobson, 2011). A recent position statement (Smart et al., 2013) suggests that exercise training include aerobic, resistance, and flexibility activities. While individual recommendations by stage and/or treatment modality of kidney disease do not exist at present, Table 105.1 is suggested to guide exercise prescription.

To improve adherence to exercise training and reduce the risk of injury, it is suggested that exercise programmes should be prescribed and supervised by exercise physiologists and other appropriately trained health professionals. Special considerations include the recommendation that HD patients who perform intradialytic exercise only do so in the first 2 hours of the HD session, peritoneal patients perform exercise without fluid in the peritoneal cavity, and all patients be counselled on the effects of exercise on their medication and co-morbidities (Smart et al., 2013).

Dietary interventions

Diet may affect the development and progression of renal disease either by directly affecting the kidneys or through secondary mechanisms including affecting metabolic disease parameters such as hypertension.

Protein and calorie control

Protein energy malnutrition (PEM), as indicated by low serum albumin and/or pre-albumin levels, is present in up to 70% of dialysis patients (Fouque et al., 2007), and is one of the strongest predictors of mortality in patients with CKD (Kalantar-Zadeh et al., 2011). Diagnostic criteria for PEM include unintentional

Table 105.1 Exercise training recommendations for CKD patients

	Aerobic	Resistance	Flexibility	Comment
Frequency (week)	5	2	5–7	Resistance training should be performed on non-consecutive days
Intensity	Moderate to vigorous (RPE 11–16/20)	10–15 repetitions of 60–70% 1 RM	–	Pre-exercise screening is suggested, especially in patients planning to exercise at higher intensity
Duration	≥ 30 to < 90min	≥ 30min to < 90min	10 min	Low fitness: suggest start at 10 min continuous
Example	Walking, jogging, cycling, swimming	Exercise against gravity, therabands, machine and free weights	Combine with aerobic and resistance session	Inclusion of balance exercises for those at risk of falls

RM = repetition maximum; RPE = rating of perceived exertion.

weight loss, low serum albumin, and sarcopenia, and there is increasing evidence that PEM is associated with increased morbidity, mortality, and impaired quality of life (Kalantar-Zadeh et al., 2011). The European Best Practice Guidelines on nutrition states that dietary protein intake in clinically stable chronic HD patients should be at least 1.1 g protein/kg ideal body weight (IBW)/day while energy intake should be at least 30 kcal/kg IBW/day in order to prevent wasting (Fouque et al., 2007). In pre-dialysis patients the protein recommendations are lower, reflecting the possible relationship between protein intake and CKD progression. The Dietitians Association of Australia guidelines for the nutritional management of CKD (Ash et al., 2006) recommend a protein intake of between 0.75 and 1.0 g protein/kg IBW/day in stage 3 CKD and 0.75 g/kg IBW/day with at least 50% coming from high-biological value sources in stage 4. The same body recommend a minimum energy intake of at least 146 kJ/kg IBW/day in patients with stage 4 CKD and that energy intake be determined as for healthy individuals in less advanced disease (Ash et al., 2006).

Dietary salt intake

(See Chapter 101)

Phosphate and calcium

(See Chapter 101)

Alcohol

While the direct evidence for a link between alcohol consumption and CKD is low, there is evidence from observational studies that alcohol intake may have a dose-dependent relationship with blood pressure, particularly at levels above two drinks per day (Xin et al., 2001). In addition, a meta-analysis (Xin et al., 2001) reported that decreased alcohol consumption in previously heavy drinkers resulted in decreases in systolic blood pressure and diastolic blood pressure by 3.3 and 2.0 mmHg respectively. Given the link between hypertension and the development and progression of CKD (Hanratty et al., 2011), the results suggest that heavy drinking may be detrimental to blood pressure and thereby renal function.

Antioxidant and anti-inflammatory supplements

Omega-3 fatty acids have been investigated for their role in reducing inflammation shown in animal (Peake et al., 2011) and human (Zhao et al., 2004) models. Supplementation studies in pre-dialysis CKD patients have reported improvements in surrogate CVD markers including 24-hour ambulatory heart rate and blood pressure. In dialysis patients, similar supplementation studies have reported decreased C-reactive protein and interleukin 6 levels, attenuation of adrenergic activity, and decreased insulin resistance. No study has, however, investigated CVD outcomes in CKD patients after omega-3 fatty acid supplementation. An overview of the evidence for and against supplementation is provided in a review (Fassett et al., 2010).

A number of small trials (many with a non-randomized open-label design and in ESRD patients) have been conducted to determine the potential benefits of supplementation with the antioxidants vitamins C and E or *N*-acetylcysteine (NAC) on oxidative stress. The outcomes of studies investigating the benefits of antioxidant supplementation have been summarized previously (Del Vecchio et al., 2011; Coombes and Fassett, 2012). Briefly, the balance of evidence indicates that supplementation with vitamin E or NAC reduce oxidative stress but the evidence for a benefit from vitamin C is equivocal.

There is accumulating evidence for the efficacy of soy protein as an alternative protein source with studies showing reductions in plasma urea levels following a soy-based diet in mice with surgically induced uraemia (Tomayko et al., 2011), improved kidney function in rats with renal failure (Yang et al., 2008), and trends towards decreases in C-reactive protein levels in HD patients (Fanti et al., 2006).

Bariatric surgery

(See Chapter 106).

Summary and recommendations for lifestyle management

Lifestyle is an important contributor to the development and progression of CKD. Sedentary lifestyles and unhealthy diets contribute directly to the obesity that appears to contribute to increases in oxidative stress and inflammation that may trigger or progress CKD. The effect of lifestyle interventions such as increased physical activity and weight loss have been widely researched particularly in patients with ESRD and shown to reduce disease progression and improve quality of life in CKD patients. Similarly surgical interventions designed to restrict nutrient intake to assist weight loss have also been reported to improve markers of CKD progression.

References

Afshar, R., Shegarfy, L., Shavandi, N., *et al.* (2010). Effects of aerobic exercise and resistance training on lipid profiles and inflammation status in patients on maintenance hemodialysis. *Indian J Nephrol*, 20, 185–9.

Anonymous (1985). Energy and protein requirements. Report of a joint FAO/WHO/UNU Expert Consultation. *World Health Organ Tech Rep Ser*, 724, 1–206.

Ash, S., Campbell, K., MacLaughlin, H., *et al.* (2006). Evidence based practice guidelines for the nutritional management of chronic kidney disease. *Nutr Diet*, 63, S35–45.

Block, G. A., Klassen, P. S., Lazarus, J. M., *et al.* (2004). Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*, 15, 2208–18.

Boyce, M. L., Robergs, R. A., Avasthi, P. S., *et al.* (1997). Exercise training by individuals with predialysis renal failure: cardiorespiratory endurance, hypertension, and renal function. *Am J Kidney Dis*, 30, 180–92.

Cheema, B. S., Abas, H., Smith, B. C., *et al.* (2011). Effect of resistance training during hemodialysis on circulating cytokines: a randomized controlled trial. *Eur J Appl Physiol*, 111, 1437–45.

Clyne, N., Ekholm, J., Jogestrand, T., *et al.* (1991). Effects of exercise training in predialytic uremic patients. *Nephron*, 59, 84–9.

Cook, S. A., MacLaughlin, H., and MacDougall, I. C. (2008). A structured weight management programme can achieve improved functional ability and significant weight loss in obese patients with chronic kidney disease. *Nephrol Dial Transplant*, 23, 263–8.

Coombes, J. S. and Fassett, R. G. (2011). Antioxidant therapy in hemodialysis patients: a systematic review. *Kidney Int*, 81(3), 233–46.

Currie, A., Chetwood, A., and Ahmed, A. R. (2011). Bariatric surgery and renal function. *Obes Surg*, 21, 528–39.

Del Vecchio, L., Locatelli, F., and Carini, M. (2011). What we know about oxidative stress in patients with chronic kidney disease on

dialysis—clinical effects, potential treatment, and prevention. *Semin Dial*, 24, 56–64.
Deligiannis, A., Kouidi, E., and Tourkantonis, A. (1999). Effects of physical training on heart rate variability in patients on hemodialysis. *Am J Cardiol*, 84, 197–202.
De Miguel, C., Lund, H., and Mattson, D. L. (2011). High dietary protein exacerbates hypertension and renal damage in Dahl SS rats by increasing infiltrating immune cells in the kidney. *Hypertension*, 57, 269–74.
Fanti, P., Asmis, R., Stephenson, T. J., *et al.* (2006). Positive effect of dietary soy in ESRD patients with systemic inflammation—correlation between blood levels of the soy isoflavones and the acute-phase reactants. *Nephrol Dial Transplant*, 21, 2239–46.
Fassett, R. G., Gobe, G. C., Peake, J. M., *et al.* (2010). Omega-3 polyunsaturated fatty acids in the treatment of kidney disease. *Am J Kidney Dis*, 56, 728–42.
Finkelstein, J., Joshi, A., and Hise, M. K. (2006). Association of physical activity and renal function in subjects with and without metabolic syndrome: a review of the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis*, 48, 372–82.
Foley, R. N., Parfrey, P. S., and Sarnak, M. J. (1998). Epidemiology of cardiovascular disease in chronic renal disease. *J Am Soc Nephrol*, 9, S16–23.
Fouque, D. and Laville, M. (2009). Low protein diets for chronic kidney disease in non diabetic adults. *Cochrane Database Syst Rev*, 3, CD001892.
Fouque, D., Vennegoor, M., Ter Wee, P., *et al*, R. (2007). EBPG guideline on nutrition. *Nephrol Dial Transplant*, 22 Suppl 2, ii45–87.
Funakoshi, Y., Omori, H., Onoue, A., *et al.* (2012). Association between frequency of drinking alcohol and chronic kidney disease in men. *Environ Health Prev Med*, 17(3), 199–204.
Goldberg, A. P., Geltman, E. M., Hagberg, J. M., *et al.* (1983). Therapeutic benefits of exercise training for hemodialysis patients. *Kidney Int Suppl*, 16, S303–9.
Hanratty, R., Chonchol, M., Havranek, E. P., *et al.* (2011). Relationship between blood pressure and incident chronic kidney disease in hypertensive patients. *Clin J Am Soc Nephrol*, 6(11), 2605–11.
Heiwe, S. and Jacobson, S. H. (2011). Exercise training for adults with chronic kidney disease. *Cochrane Database Syst Rev*, 10, CD003236.
Howden, E. J., Fassett, R. G., Isbel, N. M., *et al.* (2012). Exercise training in chronic kidney disease patients. *Sports Med*, 42, 473–88.
Howden, E. J., Leano, R., Petchey, W., *et al.* (2013). Effects of exercise and lifestyle intervention on cardiovascular function in CKD. *Clin J Am Soc Nephrol*, 8, 1494–501.
Joy, M. S., Karagiannis, P. C., and Peyerl, F. W. (2007). Outcomes of secondary hyperparathyroidism in chronic kidney disease and the direct costs of treatment. *J Manag Care Pharm*, 13, 397–411.
Kalantar-Zadeh, K., Cano, N. J., Budde, K., *et al.* (2011). Diets and enteral supplements for improving outcomes in chronic kidney disease. *Nat Rev Nephrol*, 7, 369–84.
Kasiske, B. L., Lakatua, J. D., Ma, J. Z., *et al.* (1998). A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am J Kidney Dis*, 31, 954–61.
Kestenbaum, B., Sampson, J. N., Rudser, K. D., *et al.* (2005). Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol*, 16, 520–8.
Kidney Disease Improving Global Outcomes (2013). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*, 3, 1–150.
Krikken, J. A., Laverman, G. D., and Navis, G. (2009). Benefits of dietary sodium restriction in the management of chronic kidney disease. *Curr Opin Nephrol Hypertens*, 18, 531–8.
Levin, A., Hemmelgarn, B., Culleton, B., *et al.* (2008). Guidelines for the management of chronic kidney disease. *CMAJ*, 179, 1154–62.
Moinuddin, I. and Leehey, D. J. (2008). A comparison of aerobic exercise and resistance training in patients with and without chronic kidney disease. *Adv Chronic Kidney Dis*, 15, 83–96.
Mustata, S., Groeneveld, S., Davidson, W., *et al.* (2011). Effects of exercise training on physical impairment, arterial stiffness and health-related quality of life in patients with chronic kidney disease: a pilot study. *Int Urol Nephrol*, 43(4), 1133–41.
Navaneethan, S. D., Yehnert, H., Moustarah, F., *et al.* (2009). Weight loss interventions in chronic kidney disease: a systematic review and meta-analysis. *Clin J Am Soc Nephrol*, 4, 1565–74.
O'Shaughnessy, K. M. and Karet, F. E. (2006). Salt handling and hypertension. *Annu Rev Nutr*, 26, 343–65.
Peake, J. M., Gobe, G. C., Fassett, R. G., *et al.* (2011). The effects of dietary fish oil on inflammation, fibrosis and oxidative stress associated with obstructive renal injury in rats. *Mol Nutr Food Res*, 55, 400–10.
Pechter, U., Ots, M., Mesikepp, S., *et al.* (2003). Beneficial effects of water-based exercise in patients with chronic kidney disease. *Int J Rehabil Res*, 26, 153–6.
Ramos, L. F., Shintani, A., Ikizler, T. A., *et al.* (2008). Oxidative stress and inflammation are associated with adiposity in moderate to severe CKD. *J Am Soc Nephrol*, 19, 593–9.
Schaeffner, E. S., Kurth, T., De Jong, P. E., *et al.* (2005). Alcohol consumption and the risk of renal dysfunction in apparently healthy men. *Arch Intern Med*, 165, 1048–53.
Segura-Orti, E. and Johansen, K. L. (2010). Exercise in end-stage renal disease. *Semin Dial*, 23, 422–30.
Sietsema, K. E., Amato, A., Adler, S. G., *et al.* (2004). Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. *Kidney Int*, 65, 719–24.
Smart, N. A., Williams, A. D., Levinger, I., *et al.* (2013). Exercise & Sports Science Australia (ESSA) position statement on exercise and chronic kidney disease. *J Sci Med Sport*, 16(5), 406–11.
Stengel, B., Tarver-Carr, M. E., Powe, N. R., *et al.* (2003). Lifestyle factors, obesity and the risk of chronic kidney disease. *Epidemiology*, 14, 479–87.
Suckling, R. J., He, F. J., and MacGregor, G. A. (2010). Altered dietary salt intake for preventing and treating diabetic kidney disease. *Cochrane Database Syst Rev*, 12, CD006763.
Teta, D. (2010). Weight loss in obese patients with chronic kidney disease: who and how? *J Ren Care*, 36 Suppl 1, 163–71.
Tomayko, E. J., Chung, H. R., and Wilund, K. R. (2011). Soy protein diet and exercise training increase relative bone volume and enhance bone microarchitecture in a mouse model of uremia. *J Bone Miner Metab*, 29(6), 682–90.
Toyama, K., Sugiyama, S., Oka, H., *et al.* (2010). Exercise therapy correlates with improving renal function through modifying lipid metabolism in patients with cardiovascular disease and chronic kidney disease. *J Cardiol*, 56, 142–6.
Uribarri, J. (2007). Phosphorus homeostasis in normal health and in chronic kidney disease patients with special emphasis on dietary phosphorus intake. *Semin Dial*, 20, 295–301.
Van Vilsteren, M. C., De Greef, M. H., and Huisman, R. M. (2005). The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in The Netherlands: results of a randomized clinical trial. *Nephrol Dial Transplant*, 20, 141–6.
Wang, Y., Chen, X., Song, Y., *et al.* (2008). Association between obesity and kidney disease: a systematic review and meta-analysis. *Kidney Int*, 73, 19–33.
Wilund, K. R., Tomayko, E. J., Wu, P. T., *et al.* (2010). Intradialytic exercise training reduces oxidative stress and epicardial fat: a pilot study. *Nephrol Dial Transplant*, 25, 2695–701.
Xin, X., He, J., Frontini, M. G., *et al.* (2001). Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension*, 38, 1112–17.

Yamauchi, T., Kuno, T., Takada, H., *et al.* (2003). The impact of visceral fat on multiple risk factors and carotid atherosclerosis in chronic haemodialysis patients. *Nephrol Dial Transplant*, 18, 1842–7.
Yang, H. Y., Chen, J. R., and Chang, L. S. (2008). Effects of soy protein hydrolysate on blood pressure and angiotensin-converting enzyme activity in rats with chronic renal failure. *Hypertens Res*, 31, 957–63.
Zhao, Y., Joshi-Barve, S., Barve, S., *et al.* (2004). Eicosapentaenoic acid prevents LPS-induced TNF-alpha expression by preventing NF-kappaB activation. *J Am Coll Nutr*, 23, 71–8.
Zhao, Y., Joshi-Barve, S., Barve, S., *et al.* (2004). Eicosapentaenoic acid prevents LPS-induced TNF-alpha expression by preventing NF-kappaB activation. *J Am Coll Nu*tr, 23, 71–8.

CHAPTER 106

Malnutrition, obesity, and undernutrition in chronic kidney disease

Navneet Kumar, Heather Henderson, Beverly D. Cameron, and Peter A. McCullough

Obesity

By the World Health Organization's definition of obesity as a body mass index (BMI) > 30kg/m^2, 33.8% of adults (> 19 years of age) and 17% of children and adolescents in the United States (aged 2–19 years) are obese (Centers for Disease Control and Prevention, 2011). There is evidence that obesity is an independent risk factor for both chronic kidney disease (CKD) and end-stage renal disease (ESRD) (Iseki et al., 2004; Hsu et al., 2006; Munkhaugen et al., 2009). Obesity also independently increases progression of native CKD from other causes and in those who have received renal allografts (Meier-Kriesche et al., 2002; Ducloux et al., 2005). Obese men and morbidly obese women have a three- to fourfold increase in lifetime risk for advanced CKD (Ejerblad et al., 2006). Compared to lean incident dialysis patients, the overweight and obese have 17% and 40% odds for a family history of ESRD (Speckman et al., 2006).

Most studies used surrogate markers of renal disease, mainly proteinuria, albuminuria, and estimated glomerular filtration rate (eGFR) to examine the impact of obesity on renal outcomes. Data from the African American Study of Kidney Disease and Hypertension (AASK) cohort showed that BMI is independently associated with both urine total protein:creatinine and urine albumin:creatinine ratios in African Americans (particularly those aged < 61) with baseline hypertensive nephrosclerosis (Toto et al., 2010). Patients with higher BMI had higher urine total protein and albumin excretion rates. This association was independent of blood pressure, level of kidney function, glycaemia, and hyperuricaemia. These findings have also been supported by the Kidney Early Evaluation Program (KEEP) which has consistently found an association between BMI and microalbuminuria in all non-Caucasian ethnic groups (Jolly et al., 2010). In the Framingham Study, a higher BMI was independently associated with an increased risk of developing proteinuria (Foster et al., 2008). With decreased urinary protein excretion, metabolic improvement and a decline in cardiovascular risks are seen (Mykkanen et al., 1998; Hsu et al., 2009). For a 50% decrease in albuminuria, cardiovascular risk declines by 18% and heart failure risk by 27% (De Zeeuw et al., 2004).

The metabolic syndrome is independently associated with decreased eGFR (Kawamoto et al., 2008). Waist:hip ratio and individual components of the metabolic syndrome are also independently associated with CKD and ESRD (Elsayed et al., 2008; Savica et al., 2010). BMI, waist circumference, or fat mass are each associated with increased risk of rapid eGFR loss (in those aged > 65), after adjustment for age, gender, race, and smoking (De Boer et al., 2009). Risk was larger for those with eGFR < 60 mL/min/1.73 m^2 at baseline.

Obesity-related kidney disease includes albuminuria, glomerulomegaly, and obesity-related glomerulopathy (ORG) (Mathew et al., 2011), a form of secondary focal segmental glomerulosclerosis (Fig. 106.1), the incidence of which is increasing in the obesity pandemic (Kambham et al., 2001; Eknoyan, 2007). ORG does not usually cause nephrotic syndrome, has a more benign course, and slower progression to renal failure. Podocyte density and number are decreased, and correlate with the degree of proteinuria and renal function impairment (Chen et al., 2006). Obesity-related renal dysfunction may be due to glomerular capillary hypertension, and mediated by transforming growth factor-beta (Torun et al., 2007), and adipocyte-derived cytokines like leptin, interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), resistin, macrophage colony simulating protein-1 (MCP-1), and plasminogen activator inhibitor-1 (PAI-1) which increase protein permeability in glomerular capillaries and enhance renal fibrosis (Henegar et al., 2001; Zhang et al., 2005; Wahba and Ma, 2007). Adipokines, like adiponectin, have been associated with proteinuria and increased glomerular permeability to plasma proteins (Ahima, 2008; Sharma et al., 2008). There is an alteration in renal haemodynamics leading to hyperfiltration (Wuerzner et al., 2010) and upregulation of the renin–angiotensin system (Agrawal et al., 2009). Compared to normal healthy subjects, severely obese, non-diabetic individuals (BMI > 38 kg/m^2) have 51% and 31% higher GFR and renal plasma flow (RPF) respectively (Chagnac et al., 2000). Another recent study in non-diabetic subjects of African descent showed that a high BMI (> 25) is associated with increased GFR, effective RPF, and filtration fraction (Wuerzner et al., 2010). But after adjustment of body surface area (BSA), no association was found between BMI and GFR, questioning the appropriateness of indexing GFR for BSA in high BMI (> 25) population.

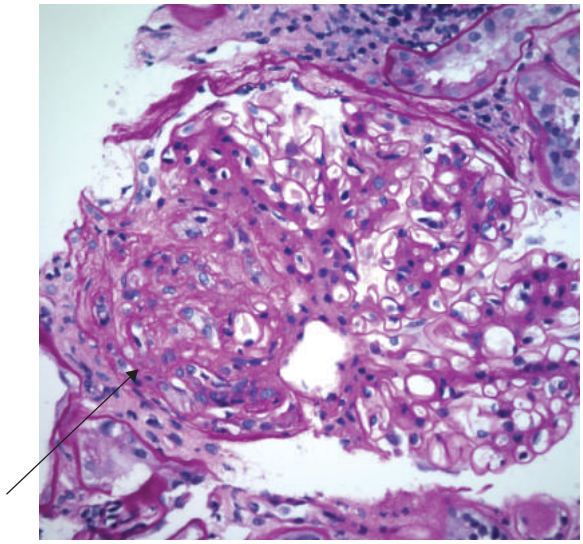

Fig. 106.1 A light microscope photograph of obesity-related glomerulopathy: a hypertrophied glomeruli with discrete lesion (arrow) of segmental sclerosis with hyalinosis and adhesion to Bowman's capsule.
With help from Hong Qu, MD, Pathologist, St John Hospital and Medical Center, Detroit, MI, USA.

Weight loss is associated with a decrease in albuminuria. However, it has been associated with lower eGFR possibly because the decreased muscle mass reduces creatinine production (Agrawal et al., 2008). Voluntary weight loss is associated with a decline in albuminuria (Shen et al., 2010). A meta-analysis showed that every 1 kg weight loss results in 110 mg or a 4% decrease in urinary protein excretion, independent of baseline weight and decline in mean arterial pressure (Afshinnia et al., 2010). Even after adjusting for angiotensin-converting enzyme inhibitor use, similar results were obtained. Interestingly, a 0.7 mg decrease in microalbuminuria was seen with every week of weight loss intervention. Both surgical and non-surgical weight loss reduce proteinuria and blood pressure, but only surgical interventions showed normalization of creatinine clearance (Navaneethanet al., 2009). In extreme obesity stage 3 CKD patients who had undergone bariatric surgery, decrease in the BMI from 49.8 kg/m^2 to 34.5 kg/m^2 had an improvement of mean GFR from 47.9 to 61.6 mL/min/1.73 m^2 at 12 months after surgery (Navaneethan and Yehner, 2009). eGFR was used and the study could not exclude a serum creatinine decline due to a decrease in muscle mass and creatinine generation. It should be noted that the current methods of estimating GFR were based on lean subjects (Eknoya, 2011). In obese individuals, the Modification of Diet in Renal Disease (MDRD) Study equation is more dependable than the Cockcroft–Gault formula which grossly overestimates creatinine clearance (bias of 86 mL/min). The MDRD equation also has an error of 11.7 mL/min in obese subjects (Friedman et al., 2010). This study used a simple and accurate iohexol-based protocol for comparison.

Education of patients about the risks of obesity, periodic assessment for excess body fat (weight and waist circumference), and continual brief advice on healthy diet and exercise is an important task for healthcare providers including nephrologists. Blood pressure, HbA1c, eGFR, lipids, and glucose, and urine albumin:creatinine ratio should be measured in obese subjects attending a pre-dialysis clinic.

Large studies with longer follow-up are needed to assess the effect of weight loss on the risk of progression to ESRD. The existing evidence showing the potential for slowing or reversing the progression of CKD with weight loss, medically supervised weight loss, or bariatric surgery means that these measures should be considered in obese individuals (Praga and Morales, 2010).

Undernutrition

Nutrition is a vital contributing factor in the morbidity and mortality of CKD patients. It is well recognized that a low serum albumin at the time of initiation of dialysis and throughout a patient's time on dialysis is associated with increased morbidity and mortality (Lowrie et al., 1994; Iseki et al., 1996; Pifer et al., 2002; Amaral et al., 2008; Fouque et al., 2008a). In a study of > 13,000 dialysis patients, a serum albumin of 3.5–3.9 g/dL had an odds ratio of death of 1.48 compared to 3.13 for an albumin concentrations of 3.0–3.4 g/dL (Owen et al., 1993). Similar results have been seen in adolescents. Amaral and colleagues studied 675 adolescents requiring haemodialysis and found those with a serum albumin > 4.0 g/dL had a 57% decreased risk for death and fewer hospitalizations per time at risk compared to those with lower albumin concentrations (Amaral et al., 2008). Hypoalbuminaemia was once considered an indicator of malnutrition; however, chronic inflammation is the more important cause of hypoalbuminaemia. The multiple variables that contribute to the phenomenon of undernutrition and resultant cachexia are shown in Fig. 106.2.

Malnutrition or protein calorie malnutrition is often inadequate in describing the muscle wasting, skin and hair changes, and premature ageing seen with uraemia. Malnutrition only refers to inadequate diet; however, this is rarely the sole problem identified in kidney disease patients. In 2008, the International Society of Renal Nutrition and Metabolism (ISRNM) defined the term protein energy wasting (PEW) to define the loss of body protein mass and fuel reserves (Fig. 106.2) (Praga and Morale, 2010). Three diagnostic criteria must be present: low serum albumin (or low transthyretin or cholesterol), reduced body mass, and reduced muscle mass (sarcopenia). Reports show 18–75% of CKD patients on maintenance haemodialysis has some form of wasting (Kalanter-Zadeh et al., 2003; Praga and Morale, 2010). Using this classification emphasizes that it is not only an inadequate diet, but also systemic inflammation and oxidative stress that causes increased protein catabolism and decreased anabolism. Many believe initiating dialysis earlier would mitigate some of the proinflammatory cytokines and improve survival. However, the IDEAL study showed no difference between early (eGFR 10–14 mL/min) or late (5–7 mL/min) dialysis initiation (Cooper et al., 2010). Only when clear signs of uraemia are present does initiation of dialysis early improve outcomes.

Pathophysiology of protein energy wasting

Many processes contribute to PEW: low nutrient intake, acidaemia, inflammation, anaemia, oxidative stress, altered responses to anabolic hormones, increased levels of retained toxins, and nutrient losses in the dialysate. There is a survival paradox in dialysis in that a higher BMI is associated with decreased mortality, in contrast to the general population (Meuwese et al., 2011). This may be secondary to increased prevalence of PEW and inflammation in patients with lower BMI ultimately leading to increase

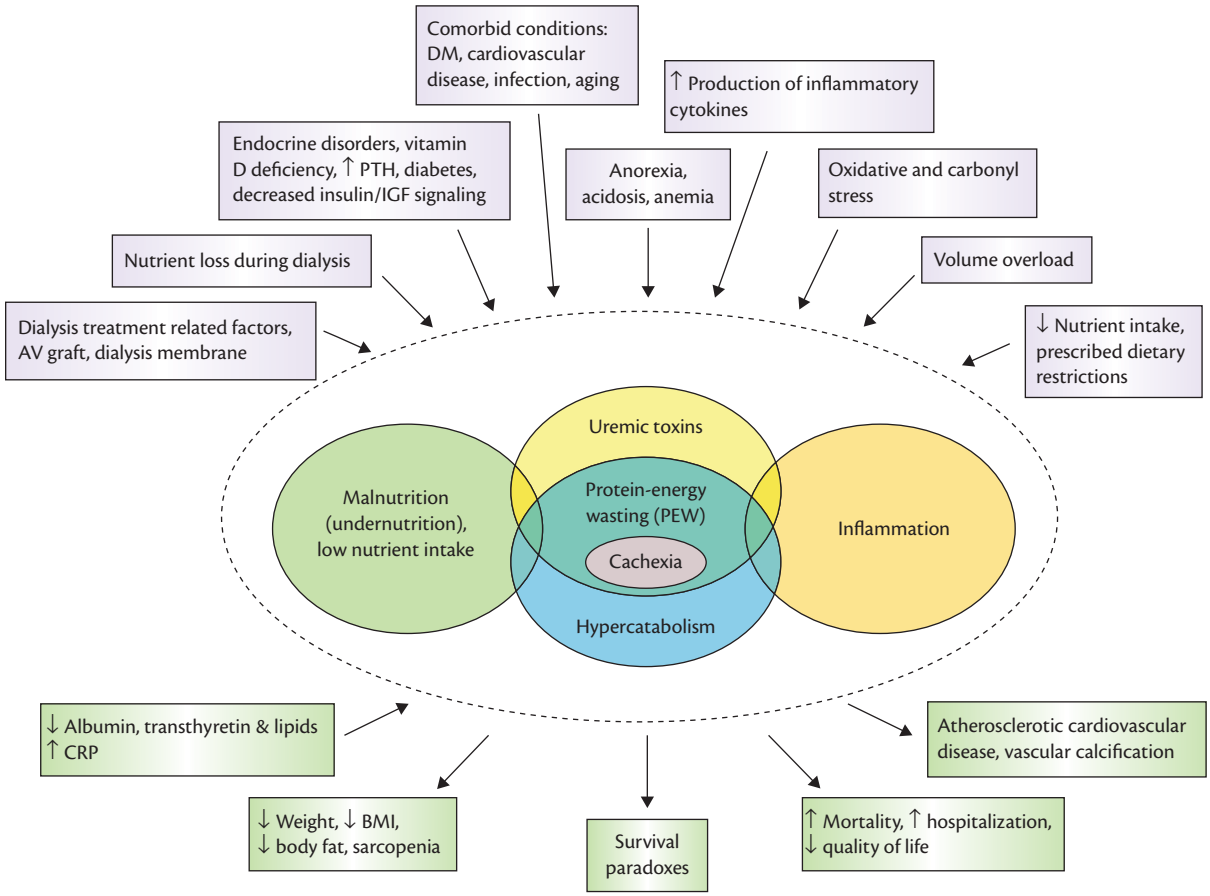

Fig. 106.2 Schematic representation of the causes and manifestations of the protein energy wasting syndrome in kidney disease.
Reproduced with permission from Foque, D et al. A proposed nomenclature and diagnostic criteria for protein energy wasting in acute and chronic kidney disease. *Kidney International*, 73, 391–398.

atherosclerotic cardiovascular disease and vascular disease leading to increased morbidity and mortality, especially after reaching dialysis (Kalanter-Zadeh et al., 2003; Friedman et al., 2010).

Comorbid conditions may also contribute to the decreased nutrient intake observed in CKD. Diabetics are prone to poor dietary intake due to dietary restrictions, gastroparesis, pancreatic insufficiency, and bacterial overgrowth (Noori and Kopple, 2010). Depression, gastrointestinal side effects of multiple medications, and restricted mobility also contribute to anorexia. Patients with nephrotic syndrome also have increased PEW from renal losses of albumin leading to further progression of CKD. Higher levels of albuminuria are associated with higher all-cause mortality and increased need for renal replacement therapy (Hemmelgarn et al., 2010). The Chronic Kidney Disease in Children (CKiD) study found proteinuria is linked to worsening GFR, which leads to growth restriction during childhood development (Copelovitch et al., 2011).

Metabolic acidosis contributes to the hypercatabolic state by increasing oxidation of branched-chain amino acids: leucine, valine, and isoleucine (Stein et al., 1997; Qureshi et al., 1998; Chiu et al., 2009). The concentrations of these amino acids are decreased in CKD patients, especially in chronic dialysis. Increased parathyroid hormone concentrations (secondary hyperparathyroidism) enhance muscle release of amino acids. Vitamin K and 25-hydroxy vitamin D have been shown to be deficient in patients with CKD stages 3–5 and sufficient levels correlated with improved nutritional status and higher serum albumin levels (Holden et al., 2010).

Dialysis therapy itself compounds the negative nitrogen balance seen in kidney disease patients. Amino acids are lost during haemodialysis and peritoneal dialysis (PD), 5–8 g/session and 5–12 g/day respectively, increasing catabolism and resting energy expenditure (Fouque et al., 2011). The glucose contents of PD fluid may contribute to early satiety and decreased oral intake. Stankovic-Popovic and colleagues found that patients using biocompatible peritoneal dialysis solutions (neutral solutions with lower glucose and calcium) had lower C-reactive proteinss, less left ventricular hypertrophy, thinner intima media thickness of the carotid, and improved nutritional status (Stankovic-Popovic et al., 2011). Continuous ambulatory PD patients supplemented with high alkali dialysate had fewer hospitalizations and an increase in body weight and mid-arm circumference at 1 year (Chiu et al., 2009). The dose of dialysis influences the nutritional status of patients. Until recently, adequacy of dialysis was judged mainly on Kt/V; 1.2 for thrice weekly haemodialysis and 2.0 for PD. Dialysis hours were only considered if 'adequacy' was not achieved. There is now less focus on Kt/V and more on clinical parameters and treatment time as predictors of improved morbidity and mortality (Zsom et al., 2008). Increasing dialysis time from the standard 3.5 hours to > 4 hours

was associated with lower relative risk (RR) of death (0.81) and for every additional 30 minutes of dialysis time there was a 7% lower risk of death. Ultrafiltration rates > 10 mL/kg/hour were associated with higher risk of intradialytic hypotension and higher mortality. This may explain why longer dialysis times improve outcomes. Longer times allow slower ultrafiltration (Saran et al., 2006). Before the widespread use of biocompatible dialysis membranes a greater induction of the inflammatory cascade occurred with increasing hours and this induced catabolism (Parker et al., 1996). Daily and overnight dialysis regimens also appear to improve nutritional status and morbidity and mortality (Chazot and Jean, 2009; Sikkes et al., 2009). The type of dialysis access is also associated with clinical and laboratory parameters of PEW. In a study by Wystrychowski et al., those with central venous access which changed to arteriovenous fistula or graft showed improvements in their serum albumin concentrations, decreased white blood cell counts, and increasing haemoglobin levels (Wystrychowski et al., 2009).

The increased production of the proinflammatory cytokines (TNF-α and IL-6) and oxidative stress in CKD increases resting energy expenditure when compared to normal controls and these may induce anorexia. IL-6 also enhances muscle protein breakdown via the nuclear factor kappa B pathway (Qureshi et al., 1998; Kalanter-Zadeh et al., 2003; Friedman et al., 2010; Miyamoto et al., 2011). Inflammation reduces insulin-like growth factor-1 variability and synthesis thereby decreasing anabolic actions of growth hormone contributing to muscle atrophy (Garibotto et al., 2008; Friedman et al., 2010).

Diagnosis

The diagnosis of obesity is obvious but PEW requires tools that allow identification of those at risk. The consensus statement from ISRNM recommended the use of serum chemistries (albumin < 3.8 g/dL, pre-albumin < 30 g/dL, cholesterol < 100 mg/dL); body mass (BMI < 23 kg/m^2; unintended weight loss > 5% over 3 months or > 10% over 6 months; total body fat percentage < 10%); reduced muscle mass (loss of muscle mass > 5% over 3 months or > 10% over 6 months); reduced mid arm circumference area (> 10% less than 50th percentile for reference population); creatinine production; and dietary intake (unintentional low dietary protein intake < 0.8 g/kg/day or unintentional low dietary energy intake < 25 kcal/kg/day for at least 2 months) (Friedman et al., 2010). These markers are not universally accepted. Serum albumin, for example, is affected not only by nutrient intake, but also inflammation. The use of nutrition scales has been proposed to identify patients with PEW, however other than the Subjective Global Assessment (SGA) scale, none have been tested and are not at present recommended for use. Current guidelines recommend measurement of body weight and albumin at least monthly and SGA scale at least every 6 months (National Kidney Foundation, 2000; Mutsert et al., 2009).

The eGFR, which relies on plasma creatinine, will be affected by patients' muscle mass and protein intake. Relying on 24-hour urine creatinine may overestimate 'GFR' because creatinine is secreted by the proximal tubule. The Cockcroft–Gault equation, an estimate of creatinine clearance, also commonly overestimates the GFR. The MDRD and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations are now preferred. The extended version of MDRD includes age, sex, race, creatinine, BUN (blood urea nitrogen), and albumin. CKD-EPI has been shown to be more accurate than MDRD at a higher GFR (Levey et al., 2009). Cystatin C, a variable felt to be more accurate than creatinine to assess kidney function, is not affected by protein intake, but is not widely available (Tangri et al., 2011). Other common laboratory abnormalities seen in undernourished patients include low urea and a normal anion gap despite a metabolic acidosis.

Treatment

Many treatment strategies have been used to prevent the worsening of PEW. Targeting albumin levels of > 40 g/L improves survival in both adults and adolescents, with as high as 57% decreased risk of death when achieved (Fouque et al., 2008a). Increased resting energy expenditure in CKD stages 4 and 5 requires an energy intake of 35 kcal/kg body weight in subjects < 60 years old or 30–35 kcal/kg body weight in those > 60 years to compensate for increased catabolism (Qureshi et al., 1998; Miyamoto et al., 2011; Wright and Jones, 2011). Patients who start renal replacement therapy without continual assessment and advice may present later with symptoms of malnutrition. Care of nutrition as part of patients' CKD management appears to be the main protective factor against progressive wasting (Qureshi et al., 1998). Oral protein supplements improved SGA score, but are limited by high non-compliance rates (Fouque et al., 2008b). Administering these during dialysis sessions improves adherence and increases serum albumin (Moretti et al., 2009).

Limiting protein consumption also in the hope of preventing progression of CKD need not affect nutritional status. The MDRD Study group showed protein restriction from the typical Western diet of 1.3 g/kg ideal body weight (IBW)/day to 0.58 g/kg/day slowed decline in GFR during follow-up (Klahr et al., 1994). Current guidelines allow patients to restrict their protein intake to 0.6 g/kg IBW/day until CKD stages 4–5 at which time should be increased to 0.75 g/kg IBW/day. To prevent sarcopenia, elderly patients should not be protein restricted < 0.8 g/kg IBW/day. Once patients are started on dialysis, protein restrictions should be discontinued and a liberal protein intake encouraged to prevent further PEW (at least 1.2 g/kg IBW/day) (Qureshi et al., 1998; Miyamoto et al., 2011).

Correcting metabolic acidosis is an important component of the treatment in CKD patients because this improves nitrogen balance. Kidney Disease Outcomes Quality Initiative guidelines recommend maintaining serum bicarbonate at >22 mmol/L in CKD patients. The results of recent studies in dialysis patients led to recommendation of even higher concentrations: the goal is > 24 mmol/L. If serum bicarbonate falls below the normal ranges, patients should be supplemented with oral sodium bicarbonate (Hemmelgarn et al., 2010; Miyamoto et al., 2011).

Water-soluble vitamins are lost during dialysis treatment so patients with poor nutrition should be supplemented (Tangri et al., 2011). Specifically, vitamin B_6, folate, and ascorbic acid can be depleted, and monitoring these levels in severe PEW or cachexia should be considered (Miyamoto et al., 2011).

Role of renal dietitian and medical nutrition therapy

CKD patients require specific dietary advice by a renal dietitian (Boxes 106.1 and 106.2). A medical nutrition therapy for kidney disease patients is a healthcare benefit covered by Medicare and most HMO insurance plans in the United States.

Box 106.1 When to refer a CKD patient to a renal dietitian

- BMI > 35
- Uncontrolled blood glucose levels (pre-diabetes or confirmed diabetes)
- Hypertension
- Recent weight changes of ≥ 10% within past 3 months
- Serum albumin ≤ 35 g/L
- Hyperlipidaemia or hypertriglyceridaemia
- Hypophosphataemia.

The obesity–cachexia continuum in paediatric chronic kidney disease

Data on demographic and clinical characteristics of CKD in a paediatric population come from large prospective studies including The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) and the ItalKid Project. The CKiD study started in 2005. It has enrolled > 600 children of ages 1–16 years with mild to moderate CKD; 25% of these children were overweight or obese. The important outcomes being examined include the CKiD equation (a more precise and accurate GFR estimate), CKiD bedside equation (bedside-applicable update to original Schwartz formula), the finding that > 50% of children were hypertensive, and 39% of these were not being treated, and in 48% of those receiving treatment the blood pressure was not controlled (Copelovitch et al., 2011). Seventeen per cent of children had left ventricular hypertrophy, with 9% having concentric left ventricular remodelling. A lower GFR, obesity, and nephrotic-range proteinuria were associated with increased prevalence of dyslipidaemia.

Box 106.2 Services offered by renal dietitians

- Initial assessment of current caloric, protein, fat, sodium, fibre, and fluid intake
- Evaluation of laboratory parameters
- Evaluation of food diaries
- Evaluation of physical activity
- Evaluation of weight, BMI, and body fat analysis (as appropriate)
- Development of individualized meal plans
- Coordinating the management plan with family members or caregivers
- Follow-up visits for evaluating progress (food journals, weight changes, blood glucose levels, and care plan adjustments)
- Minimizing risk factors such as hyperglycaemia, hyperlipidaemia, hypertriglyceridemia, smoking, physical inactivity, obesity, and malnutrition
- Active communication regarding management plan with primary care physician and other team members.

References

Afshinnia, F., Wilt, T. J., Duval, S., *et al.* (2010). Weight loss and proteinuria: systemic review of clinical trials and comparative cohorts. *Nephrol Dial Transplant*, 25, 1173–83.

Agrawal, V., Khan, I., Rai, B., *et al.* (2008). The effect of weight loss after bariatric surgery on albuminuria. *Clin Nephrol*, 70(3), 194–202.

Agrawal, V., Shah, A., Rice, C., *et al.* (2009). Impact of treating the metabolic syndrome on chronic kidney disease. *Nat Rev Nephrol*, 5(9), 520–8.

Ahima, R. S. (2008). Linking adiponectin to proteinuria. *J Clin Invest*, 118(5), 1619–22.

Amaral, S., Hwang, W., Fivush, B., *et al.* (2008). Serum albumin level and risk for mortality and hospitalization in adolescents on haemodialysis. *Clin J Am Soc Nephrol*, 3, 759–67.

Centers for Disease Control and Prevention (2011). *U.S. Obesity Trends*. [Online] <http://www.cdc.gov/obesity/data/trends.html#National>

Chagnac, A., Weinstein, T., Korzets, A., *et al.* (2000). Glomerular hemodynamics in severe obesity. *Am J Physiol Ren Physiol*, 278, F817–22.

Chazot, C. and Jean, G. (2009). The advantages and challenges of increasing the duration and frequency of maintenance dialysis sessions. *Nat Clin Pract Nephrol*, 5(1), 34–44.

Chen, H. M., Liu, Z. H., Zeng, C. H., *et al.* (2006). Podocyte lesions in patients with obesity-related glomerulopathy. *Am J Kidney Dis*, 48(5), 772–9.

Chiu, Y. W., Kopple, J. D., and Mehrotra, R. (2009). Correction of metabolic acidosis to ameliorate wasting in chronic kidney disease: goals and strategies. *Semin Nephrol*, 29 (1), 67–74.

Cooper, B., Branley, P., Bulfone, L., *et al.* (2010). A randomized- controlled trial of early versus late initiation of dialysis. *N Engl J Med*, 7, 609–19.

Copelovitch, L., Warady, B. A., and Furth, S. L. (2011). Insights from the Chronic Kidney Disease in Children (CKiD) Study. *Clin J Am Soc Nephrol*, 6, 2047–53.

De Boer, I. H., Katz, R., Fried, L. F., *et al.* (2009). Obesity and change in estimated GFR among older adults. *Am J Kidney Dis*, 54(6), 1043–51.

De Zeeuw, D., Remuzzi, G., Parving, H. H., *et al.* (2004). Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation*, 110, 921–27.

Ducloux, D., Kazory, A., Simula-Faivre, D., *et al.* (2005). One year post-transplant weight gain is a risk factor for graft loss. *Am J Transplant*, 5, 2922–8.

Ejerblad, E., Fored, C. M., Lindblad, P., *et al.* (2006). Obesity and risk for chronic renal failure. *J Am Soc Nephrol*, 17, 1695–702.

Eknoyan, G. (2007). Obesity, diabetes and chronic kidney disease. *Curr Diabet Rep*, 7, 449–53.

Eknoyan, G. (2011). Obesity and chronic kidney disease. *Nefrologia*, 31(4), 397–403.

Elsayed, E. F., Tighiouart, H., Weiner, D. E., *et al.* (2008). Waist hip ratio and body mass index as risk factors for cardiovascular events in chronic kidney disease. *Am J Kidney Dis*, 52(1), 49–57.

Foster, M. C., Hwang, S. J., Larson, M. G., *et al.* (2008). Overweight, obesity, and the development of stage 3 CKD: The Framingham Heart Study. *Am J Kidney Dis*, 52(1), 39–48.

Fouque, D., Kalantar-Zadeh, K., Kopple, J., *et al.* (2008a). A proposed nomenclature and diagnostic criteria for protein energy wasting in acute and chronic kidney disease. *Kidney Int*, 73, 391–8.

Fouque, D., McKenzie, J., de Mutsert, R., *et al.* (2008b). Renilon Multicentre Trial Study Group: use of a renal specific oral supplement by haemodialysis patients with low protein intake does not increase the need for phosphate binders and may prevent a decline in nutritional status and quality of life. *Nephrol Dial Transplant*, 23, 2902–10.

Fouque, D., Pelletier, S., Mafra, D., *et al.* (2011). Nutrition and chronic kidney disease. *Kidney Int*, 80, 348–57.

Friedman, A. N., Strother, M., Quinney, S. K., *et al.* (2010). Measuring the glomerular filtration rate in obese individuals without overt kidney disease. *Nephron Clin Pract*, 116 (3), 224–34.

Garibotto G, Russo R, Sofia A, *et al.* (2008). Effects of uraemia and inflammation on growth hormone resistance in patients with chronic kidney disease. *Kidney Int*, 74, 937–45.

Hemmelgarn, B. R., Manns, B. J., Lloyd, A., *et al.* (2010). Relation between kidney function, proteinuria, and adverse outcomes. *JAMA*, 303(5), 423–9.

Henegar, J. R., Bigler, S. A., Henegar, L. K., *et al.* (2001). Functional and structural changes in the kidney in the early stages of obesity. *J Am Soc Nephrol*, 12(6), 1211–17.

Holden, R. M., Morton, A. R., Garland, J. S., *et al.* (2010). Vitamins K and D status in stages 3-5 chronic kidney disease. *Clin J Am Soc Nephrol*, 5, 590–7.

Hsu, C. Y., Iribarren, C., McCulloch, C. E., *et al.* (2009). Risk factors for end-stage renal disease. *Arch Intern Med*, 169(4), 342–50.

Hsu, C., McCulloch, C. E., Iribarren, C., *et al.* (2006). Body mass index and risk for end-stage renal disease. *Ann Intern Med*, 144(1), 21–8.

Iseki, K., Ikemiya, Y., Kinjo, K., *et al.* (2004). Body mass index and the risk of development of end-stage renal disease in a screened cohort. *Kidney Int*, 65, 1870–6.

Iseki, K., Uehara, H., Nishime, K., *et al.* (1996). Impact of the initial levels of laboratory variables on survival in chronic dialysis patients. *Am J Kidney Dis*, 28, 541–8.

Jolly, S. E., Burrows, N. R., Chen, S. C., *et al.* (2010). Racial and ethnic differences in albuminuria in individuals with estimated GFR greater than 60 mL/min/1.73 m^2: results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis*, 55(3 Suppl 2), S15–22.

Kalanter-Zadeh, K., Ikizler, T. A., Block, G., *et al.* (2003). Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. *Am J Kidney Dis*, 42(5), 864–81.

Kambham, N., Markowitz, G. S., Valeri, A. M., *et al.* (2001). Obesity-related glomerulopathy: an emerging epidemic. *Kidney Int*, 59, 1498–509.

Kawamoto, R., Kohara, K., Tabara, Y., *et al.* (2008). An association between metabolic syndrome and the estimated glomerular filtration rate. *Intern Med*, 47, 1399–406.

Klahr, S., Levey, A. S., Beck, G. J., *et al.* (1994). The effects of dietary protein restriction and blood pressure control on the progression of chronic renal disease. *N Engl J Med*, 330 (13), 877–84.

Levey, A., Stevens, L., Schmid, C., *et al.* (2009). A new equation to estimate glomerular filtration rate. *Ann Internal Med*, 150(9), 604–12.

Lowrie, E. G., Huang, W. H., Lew, N. L., *et al.* (1994). The relative contribution of measured variable to death risk among haemodialysis patients. In E. A. Freidman (ed.) *Death on Haemodialysis*, pp. 121–41. Amsterdam: Kluwer Academic Publishers.

Mathew, A. V., Okada, S., and Sharma, K. (2001). Obesity related kidney disease. *Curr Diabet Rev*, 7(1), 41–9.

Meier-Kriesche, H. U., Arndorfer, J. A., and Kaplan, B. (2002). The impact of body mass index on renal transplant outcomes: a significant independent risk factor for graft failure and patient death. *Transplantation*, 73, 70–4.

Meuwese, C. L., Carrero, J. J., and Stenvinkel, P. (2011). Recent insights in inflammation-associated wasting in patients with chronic kidney disease. *Contrib Nephrol*, 171, 120–6.

Miyamoto, T., Carrero, J. J., and Stenvinkel, P. (2011). Inflammation as a risk factor and target for therapy in chronic kidney disease. *Curr Opin Nephrol Hypertens*, 20, 662–8.

Moretti, H. D., Johnson, A. M., and Keeling-Hathaway, T. J. (2009). Effects of protein supplementation in chronic hemodialysis and peritoneal dialysis patients. *J Ren Nutr*, 19, 298–303.

Munkhaugen, J., Lydersen, S., Wideroe, T. E., *et al.* (2009). Prehypertension, obesity, and risk of kidney disease: 20-year follow up of the HUNT I study in Norway. *Am J Kidney Dis*, 54, 638–46.

Mutsert, R., Grootendorst, D., Boeschoten, E., *et al.* (2009). Subjective global assessment of nutritional status is strongly associated with mortality in chronic dialysis patients. *Am J Clin Nutr*, 89, 787–93.

Mykkanen, L., Zaccaro, D. J., Wagenknecht, L. E., *et al.* (1998). Microalbuminuria is associated with insulin resistance in nondiabetic subjects: the Insulin Resistance Atherosclerosis Study. *Diabetes*, 47, 793–800.

National Kidney Foundation (2000). K/DOQI clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis*, 6 Suppl, S1–140.

Navaneethan, S. D. and Yehnert, H. (2009). Bariatric surgery and progression of chronic kidney disease. *Surg Obes Relat Dis*, 5(6), 662–5.

Navaneethan, S. D., Yehnert, H., Moustarah, F., *et al.* (2009). Weight loss interventions in chronic kidney disease: a systemic review and meta-analysis. *Clin J Am Soc Nephrol*, 4(10), 1565–74.

Noori, N. and Kopple, J. D. (2010). Effect of diabetes mellitus on protein energy wasting and protein wasting in end stage renal disease. *Semin Dial*, 23(2), 178–84.

Owen, W. F., Lew, N. L., Lin, Y., *et al.* (1993). The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing haemodialysis. *N Engl J Med*, 329, 1001–6.

Parker, T. F., Wingard, R. L., Husni, L., *et al.* (1996). Effect of the membrane biocompatibility on nutritional parameters in chronic haemodialysis patients. *Kidney Int*, 49, 551–6.

Pifer, T. B., McCullough, K. P., Port, F. K., *et al.* (2002). Mortality risk in haemodialysis patients and changes in nutritional indicators: DOPPS. *Kidney Int*, 62(6), 2238–45.

Praga, M. and Morales, E. (2010). Obesity-related renal damage. *Kidney Int*, 78(7), 633–5.

Qureshi, A. R., Alvestrand, A., Danielsson, A., *et al.* (1998). Factors predicting malnutrition in haemodialysis patients: a cross sectional study. *Kidney Int*, 53, 773–82.

Saran, R., Bragg-Gresham, J. L., Levin, N. W., *et al.* (2006). Longer treatment time and slower ultrafiltration in haemodialysis: associations with reduced mortality in the DOPPS. *Kidney Int*, 69, 1222–8.

Savica, V., Bellinghieri, G., and Kopple, J. (2010). The effect of nutrition on blood pressure. *Ann Rev Nutr*, 30, 365–401.

Sharma, K., Ramachandrarao, S., Qiu, G., *et al.* (2008). Adiponectin regulates albuminuria and podocyte function in mice. *J Clin Invest*, 118(5), 1645–56.

Shen, W. W., Chen, H. M., Chen, H., *et al.* (2010). Obesity-related glomerulopathy: body mass index and proteinuria. *Clin J Am Soc Nephrol*, 5, 1401–9.

Sikkes, M. E., Kooistra, M. P., and Weijs, P. J. (2009). Improved nutrition after conversion to nocturnal home haemodialysis. *J Ren Nutr*, 19(6), 494–9.

Speckman, R. A., McClellan, W. M., Volkova, N. V., *et al.* (2006). Obesity is associated with family history of ESRD in incident dialysis patients. *Am J Kidney Dis*, 48(1), 50–8.

Stankovic-Popovic, V., Nesic, V., Popovic, D., *et al.* (2011). Effects of conventional versus biocompatible peritoneal dialysis solutions on peritoneal and systemic inflammation, malnutrition, and atherosclerosis in CAPD patients. *Clin Nephrol*, 76, 314–22.

Stein, A., Moorehouse, J., Iles-Smith, H., *et al.* (1997). Role of an improvement in acid-base status and nutrition in CAPD patients. *Kidney Int*, 52, 1089–95.

Tangri, N., Stevens, L. A., Schmid, C. H., *et al.* (2011). Chages in dietary protein intake has no effect on serum cystatin C levels independent of the glomerular filtration rate. *Kidney Int*, 79, 471–7.

Torun, D., Ozelsancak, R., Turan, I., *et al.* (2007). The relationship between obesity and transforming growth factor beta on renal damage in essential hypertension. *Int Heart J*, 48(6), 733–41.

Toto, R. D., Greene, T., Hebert, L. A., *et al.* (2010). Relationship between body mass index and proteinuria in hypertensive nephrosclerosis: results from the African American Study of Kidney Disease and Hypertension (AASK) cohort. *Am J Kidney Dis*, 56(5), 896–906.

Wahba, I. M. and Mak, R. H. (2007). Obesity and obesity-initiated metabolic syndrome: mechanistic links to chronic kidney disease. *Clin J Am Soc Nephrol*, 2, 550–62.

Wright, M. and Jones, C. (2011). Renal Association Clinical Practice Guideline on Nutrition in CKD. *Nephron Clin Pract*, 118 Suppl 1, 154–64.

Wuerzner, G., Pruijm, M., Maillard, M., *et al.* (2010). Marked association between obesity and glomerular hyperfiltration: a cross sectional study in an African population. *Am J Kidney Dis*, 56(2), 303–12.

Wystrychowski, G., Kitzler, T. M., Thijssen, S., *et al.* (2009). Impact of switch of vascular access type on key clinical and laboratory parameters in chronic haemodialysis patients. *Nephrol Dial Transplant*, 24, 2194–200.

Zhang, Z., Shahinfar, S., Keane, W. F., *et al.* (2005). Importance of baseline distribution of proteinuria in renal outcomes trial: lessons from the reduction of endpoints in NIDDM with angiotensin II antagonist losartan (RENAAL) study. *J Am Soc Nephrol*, 16(6), 1775–80.

Zsom, L., Zsom, M., Fulop, T., *et al.* (2008). Treatment time, chronic inflammation and hemodynamic stability: the overlooked parameters in haemodialysis Quantification. *Semin Dial*, 21(5), 395–400.

CHAPTER 107

Left ventricular hypertrophy in chronic kidney disease

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Introduction

Chronic kidney disease (CKD) is a major risk factor for cardiovascular (CV) disease (Matsushita et al., 2010). CKD patients who progress to kidney failure (stage 5), are at particularly high risk. Although CV disease in these patients is similar to that in the general population (Zoccali, 2008), their absolute risk for fatal CV events is over 10 times higher than that in in the general population (de Jager et al., 2009). Congestive heart failure (CHF), the terminal stage of left ventricular (LV) disorders including LV hypertrophy (LVH) and LV systolic and diastolic dysfunction, has a 30% prevalence in CKD-5 patients on dialysis (CKD-5D) and 3-year survival in these patients is only 17% (Trespalacios et al., 2003). Even mild to moderate reductions in the glomerular filtration rate (GFR) signal an increased risk for LVH in essential hypertension (Perticone et al., 2008) and in the general population (Moran et al., 2008) and the prevalence of this disorder in CKD patients increases progressively as renal function deteriorates (Levin, 2003; Park et al., 2012).

Clinical epidemiology of left ventricular hypertrophy and left ventricular dysfunction in chronic kidney disease

LV mass indexing in CKD

LV mass is proportional to body size. To make an allowance for this relationship, LV mass is indexed to body surface area (BSA) or height (either crude height or height to the power of 2.71) (de Simone et al., 1995). Indexing by BSA is problematic in CKD because weight, a basic parameter for the calculation of BSA, decreases in malnourished patients and is proportionally higher in those who are volume expanded (Zoccali et al., 2001). Decrease in body weight by loss of lean and fat mass determines an overestimation of LV mass when this is indexed to BSA. On the contrary, increase in body weight by volume expansion leads to an underestimation of LV mass by the same indexing. Thus, measurements of LV mass indexed by BSA in CKD can be distorted in an unpredictable way and in opposite directions by malnutrition and extracellular volume expansion. The decision on whether to index LV mass by BSA or by height$^{2.71}$ can influence estimates of the prevalence of LVH in CKD-5D, and, more importantly, its capacity to predict cardiac risk. Indeed in these patients the height$^{2.71}$-based method is superior to the BSA-based method for predicting death and CV events (Zoccali et al., 2001) (see 'Pathophysiology of left ventricular hypertrophy in chronic kidney disease'). Furthermore, the prognostic value of subcategorizing patients according to concentric or eccentric LVH becomes apparent only when LVM is indexed to height$^{2.71}$ (Zoccali et al., 2001). Although no study has specifically investigated this issue in patients with stage 2–4 CKD, it appears likely that the superiority of the indexing by height extends also to these stages. Renal physicians should ask cardiologists and echocardiography technicians to index LVM by height in echocardiography reports in CKD-5D patients and perhaps also in patients at earlier stages of CKD.

LVH and CKD stages

LVH as measured by nuclear magnetic resonance (NMR) imaging has a 12% prevalence in stage 2 CKD patients (Moran et al., 2008). The prevalence in stage 3–5 CKD varies from 27% to 74% (Tucker et al., 1997; Levin, 2003; Paoletti et al., 2005; Stewart et al., 2005; Peterson et al., 2007; Eckardt et al., 2009; Nardi et al., 2009) (Fig. 107.1), a phenomenon depending on differences in background risk factors and comorbidities. The study reporting the lowest LVH prevalence (27%) included patients with an average age of 50 years and without cerebrovascular, peripheral vascular, cardiac valvular, or coronary disease and with satisfactory compliance to antihypertensive drugs prescription (Tucker et al., 1997). The study with the highest prevalence (74%) focused on a series of non-diabetic patients with an average age of 63 years and excluded only patients with very severe ischaemic heart disease (Paoletti et al., 2005). Similarly, the study which detected the second highest prevalence (64%) was based on elderly, high-risk patients enrolled in the African American Study of Kidney disease (AASK) (Peterson et al., 2007). With the exception of a survey (prevalence 16.4%) which did not adopt pre-specified echocardiographic criteria but relied simply on the diagnosis of LVH (Stack and Saran, 2002), LVH has been found to be highly prevalent in stage CKD-5D patients (Greaves et al., 1994; Foley et al., 1998; Zoccali et al., 2001) (Fig. 107.1). Among 3487 participants of the Chronic Renal Insufficiency Cohort (CRIC) Study (Park et al., 2012), by far the largest survey on LVH in CKD performed so far, the prevalence of LVH was 32% in patients with a GFR > 60 mL/min/1.73m^2 and rose stepwise at more advanced stages to reach a prevalence of 75% in stage 4–5

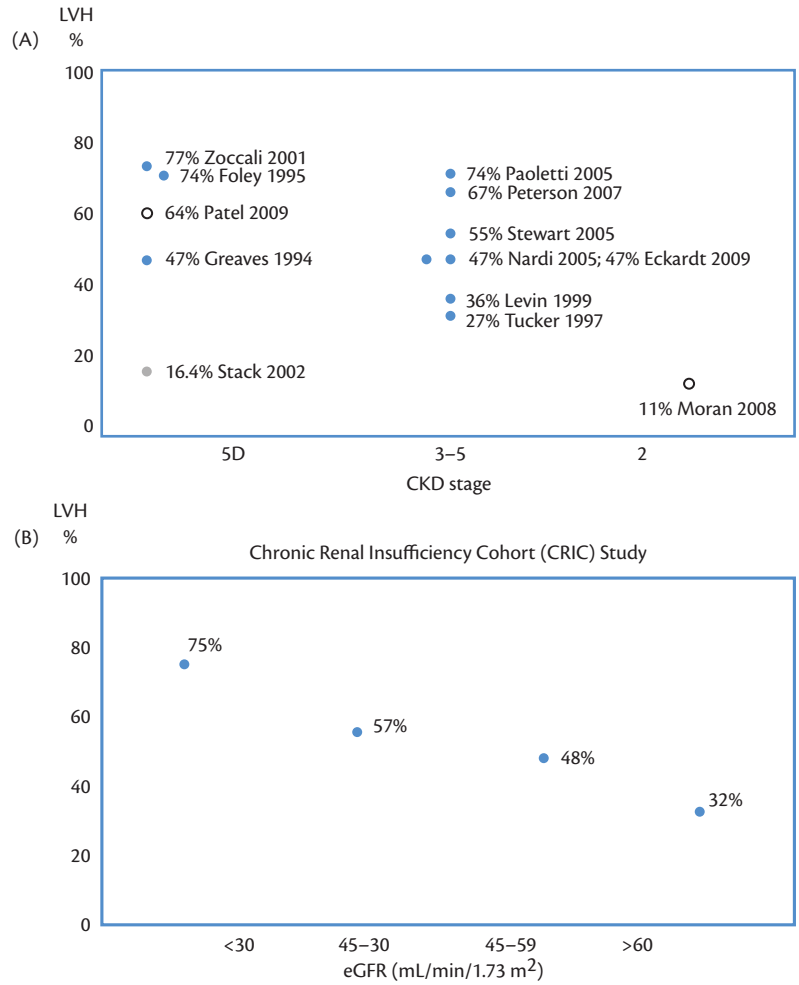

Fig. 107.1 (A) Relationship between CKD stages and LV mass index in studies in CKD patients. (B) Prevalence of LVH at various GFR levels in the CRIC study. Studies applying echocardiography (●), NMR (O) and electrocardiography (●).
Redrawn from Park et al. (2012).

CKD, a figure close to that in previous studies in stage 5D CKD patients (Foley et al., 1998; Zoccali et al., 2001). Echocardiography overestimates LV mass as compared to NMR (Stewart et al., 1999). Yet the prevalence of LVH by this very accurate and precise technique was only slightly lower (64%) (Patel et al., 2009) (Fig. 107.1) than that observed in the two studies in the same population that relied on echocardiography (74% and 77%). Even though disorders of LV mass and LV function are mainly seen as a consequence of CKD, it was hypothesized that the presence of this alteration may act as a factor accelerating renal function loss in CKD (Shlipak et al., 2009; Chen et al., 2011; Paoletti et al., 2011). However, this phenomenon may simply reflect shared risk factors for heart and kidney disease.

Cardiomyopathy in stage 3–5 CKD patients

In the CRIC study which enrolled a cohort of CKD patients without heart failure, the prevalence of concentric LVH rose stepwise at progressively severe CKD stages to 50% in patients with stage 4–5 CKD (Park et al., 2012), a proportion close to that registered in studies in stage 5D CKD patients (Zoccali et al., 2001). Alterations in left ventricular function are classically divided into two broad categories: diastolic dysfunction and systolic dysfunction. As to diastolic function, Doppler mitral flow velocities (E, early, and A, late atrial, and their ratio (E/A)) have long been used for the investigation of diastolic function. The ratio of early mitral flow velocity (E) to early mitral annulus velocity (E′), the E/E′ ratio, is now the preferred indicator of diastolic function. Impaired diastolic function is often the first detectable abnormality in many cardiac diseases and represents a frequent alteration in unselected patients with moderate to severe CKD. In fact, 65% of the latter display alterations in indices of diastolic function as determined by conventional echocardiographic methods, and as many as 82% show diastolic dysfunction by tissue velocity imaging (Hayashi et al., 2006). Quite surprisingly, in the CRIC study (Park et al., 2012) concentric LVH was not associated with progressively severe diastolic dysfunction (an obligatory sequel of concentric LVH (Paulus et al., 2007)). This phenomenon may depend on the poor sensitivity of the echocardiographic method adopted in CRIC for measuring LV diastolic function as compared to colour tissue Doppler velocity imaging (Hayashi et al., 2006). No excess risk for LV systolic dysfunction assessed by ejection fraction (EF) measured at endocardial level was observed in the same study (Park et al., 2012). However,

as discussed below, this measurement of LV may underestimate the degree of LV systolic dysfunction in patients with concentric LVH, the prevailing geometric pattern in the CRIC study.

Cardiomyopathy in dialysis (CKD-5D) patients

Diastolic dysfunction is very common in CKD (Pecoits-Filho et al., 2012). This abnormality as measured by the E/A ratio predicted mortality in a Japanese study in CKD-5D patients (Sharma et al., 2006), but because of the difficulty of grading diastolic function and the high frequency of this alteration in kidney failure, this measurement is unlikely to provide additional information beyond that given by LV mass indexing (LVMI) for risk stratification in this population. Left ventricular systolic function can be estimated by echocardiography based on measurements made at endocardial level, that is, by standard fractional shortening or EF (the most popular index of systolic function). As these methods can overestimate cardiac contractility in patients with concentric LVH, a geometry-independent index of myocardial contractile efficiency—midwall fractional shortening—was introduced 20 years ago (Shimizu et al., 1991).

Systolic dysfunction is the strongest predictor of recurring heart failure in dialysis patients. Furthermore, the mean time to death in patients with this abnormality is only 38 months (Parfrey et al., 1996). Because reversal of cardiomyopathy in kidney failure is difficult to achieve, it is important to focus attention on patients when they are at an asymptomatic phase. No study has, however, tested the prognostic value of systolic function indicators in asymptomatic patients at stage 3–5 CKD. In asymptomatic CKD-5D patients the proportion of patients with systolic dysfunction is at least seven times higher than in coeval cohorts in the community (Zoccali et al., 2004b).

Of note, midwall fractional shortening identifies a much greater proportion of kidney failure patients with abnormal systolic function than does standard EF (48% vs 22%) (Zoccali et al., 2004b) (Fig. 107.2). This phenomenon can be attributed to the high prevalence of concentric LVH (about 50%) in this population. As already noted in studies of individuals with essential hypertension, at comparable levels of midwall fractional shortening, both EF and fractional shortening at endocardial level systematically overestimate systolic function in stage 5D CKD patients with concentric LVH (Zoccali et al., 2004b). Importantly, LV systolic dysfunction, measured either by midwall fractional shortening or by standard EF, is a strong and independent predictor of incident CV complications in these patients (Zoccali et al., 2004b).

Collectively, these findings suggest that echocardiographic assessment of LVMI and myocardial contractility may be useful in secondary prevention in patients with kidney failure. Both progression of LVH (Zoccali et al., 2004a) and worsening systolic dysfunction (Zoccali et al., 2004b) predict CV events in kidney failure independently of baseline values and traditional and emerging risk factors.

Current Kidney Disease Outcomes Quality Initiative guidelines recommend that echocardiography be repeated at 3-year intervals in dialysis patients (K/DOQI Workgroup, 2005). However there is still no study testing whether treatment policies guided by measurement of LVMI and LV function actually produce better outcomes in this high-risk population.

Cardiomyopathy in renal transplant patients

After successful transplantation the risk for CV complications reduces from over 10 times higher to three to five times higher than that of the coeval general population (Jardine et al., 2011). Kidney transplantation attenuates some CV risk factors peculiar to CKD, including anaemia and arteriovenous fistula, and improves hyperparathyroidism and volume overload. Furthermore, some immunosuppressive drugs like mammalian target of rapamycin (mTor) inhibitors may promote the regression of LVH after transplantation (Paoletti et al., 2012). On the other hand after renal transplantation the prevalence of hypertension and hyperlipidaemia increases along with the risk of obesity and excess weight resulting in insulin resistance and diabetes (Jardine et al., 2011).

The prognostic value of LVH in transplant patients has not been properly studied. Persisting or *de novo* LVH as assessed by electrocardiography predicts death in transplant patients (Rigatto et al., 2003), as it does in the general population. Similarly, LVH, as assessed by echocardiography, predicted the risk for incident CV events in a small cohort of non-diabetic transplant patients (Arnol et al., 2010).

Whether renal transplantation has a beneficial effect on LVH is controversial. Improvement of LVH after transplantation was observed in some studies (Ferreira et al., 2002; Rigatto et al., 2003) but not in others (Hernandez et al., 1997; De Lima et al., 2002). Time-related

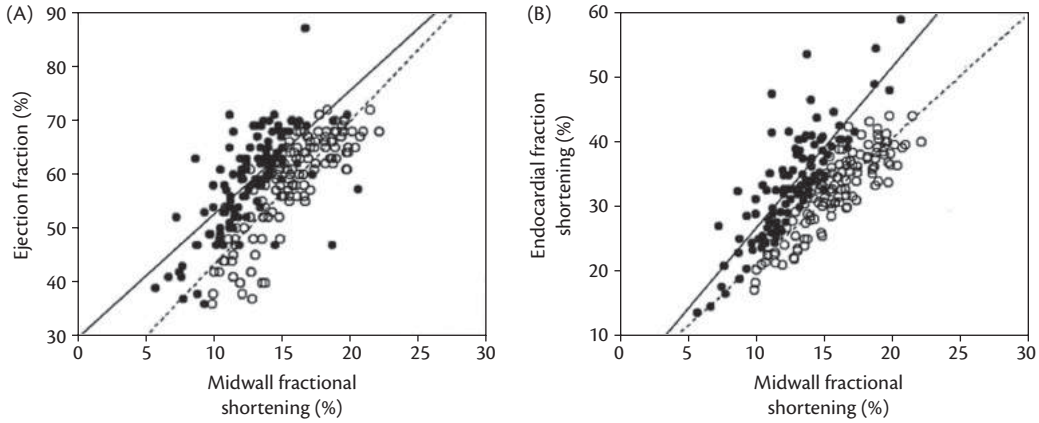

Fig. 107.2 Relationship between midwall fractional shortening with ejection fraction (A) and endocardial fractional shortening (B). (●), patients with concentric remodelling or concentric LVH; (○), patients with eccentric LVH or normal LV geometry.
From Sharma et al. (2006).

changes in LV mass from pre-dialysis stage to renal transplantation were analysed in a retrospective cohort study including 60 patients (Hernandez et al., 2007). In this study the prevalence of LVH in stage 3–5 CKD patients was 61% (37 patients). Twelve patients with initially normal LV mass developed *de novo* LVH, five after starting dialysis and seven after renal transplantation. Antecedent LVH persisted after transplantation in 29 cases. Only in eight patients with LVH at pre-dialysis stage did LVH regress after transplantation. Overall, 68% of transplant patients in this cohort had LVH. These results were confirmed by Patel et al. (2008) who applied NMR to measure LV mass in a matched cohort study comparing 25 patients studied before and after transplantation with 25 patients studied twice while remaining on chronic dialysis treatment. There was no significant change in LVMI between patients who underwent renal transplantation and those who remained on dialysis.

Even though LVH may regress after renal transplantation in some cases, the prevalence of LVH after transplantation remains close to that seen in dialysis patients and a functioning renal graft should not be seen as a guarantee of LVH regression. Predictors for LVH reversal in renal transplant recipients are the use of angiotensin-converting enzyme inhibitors (ACEIs) but age, the presence of LVH before transplantation, anaemia, hypertension, and poor renal function after transplantation are all predictors of persistence of LVH after transplantation (Hernandez et al., 2007).

Pathophysiology of left ventricular hypertrophy in chronic kidney disease

LVH is an adaptive mechanism aimed at compensating increased cardiac work demand (Selvetella et al., 2004). However, such a physiological mechanism may be maladaptive in disease states because the persistence of stimuli to myocyte growth may eventually translate into myocardial disease. From an anatomical point of view, myocardial hypertrophy can be classified as concentric or eccentric (Ganau et al., 1992) (Fig. 107.3).

In concentric hypertrophy, the muscular component of the LV (LV wall) predominates over the cavitary component (LV volume). As a consequence, the end-diastolic volume is small and inadequate to maintain cardiac output under varying physiological demands. Furthermore, thick LV walls reduce ventricular compliance (diastolic dysfunction).

In eccentric hypertrophy, tensile stress elongates myocardiocytes and increases LV end-diastolic volume. The LV walls are relatively thinner and with reduced ability to contract (systolic dysfunction).

In CKD, diverse casual factors concur in generating LVH and due to the frequent coexistence of volume expansion, hypertension and exposure to various myocardial growth factors (see below), myocardial hypertrophy (thicker LV wall) often goes along with cavity enlargement (increased LV end-diastolic volume). Defective neovascularization and sustained myocardial hypertrophy in CKD leads to cardiomyocyte ischaemia and activates biological signals promoting extracellular matrix expansion and myocardial fibrosis (Amann et al., 1992). Fibrosis and ischaemia in turn exacerbate cardiac wall stiffness and impair cardiac contractility leading to LV dysfunction and, ultimately, CHF. Fibrosis also disturbs the physiologic transmission of electric conduction within the myocardium producing anomalous re-entry pathways and arrhythmias. These are a leading cause of death in stages 5 and 5D CKD (Roberts and Green, 2011). The pathophysiology of LVH in CKD is shown in Fig. 107.4.

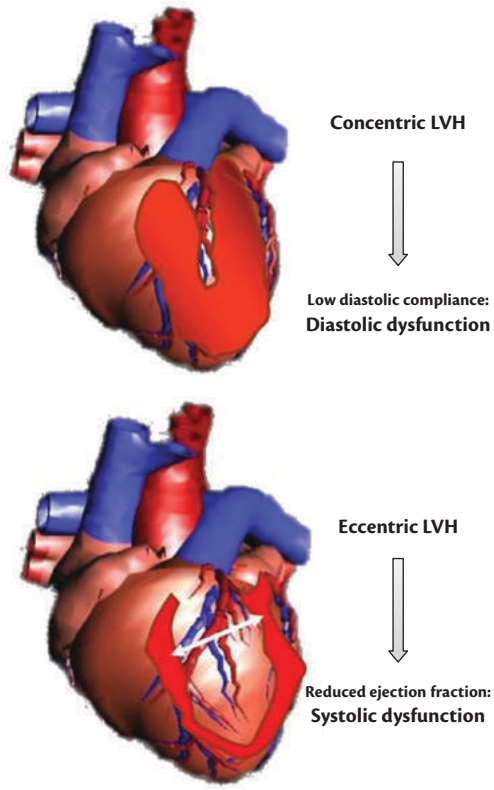

Fig. 107.3 Anatomical classification of myocardial hypertrophy.

Pathogenesis of concentric left ventricular hypertrophy in chronic kidney disease

Afterload-related risk factors

Hypertension and arterial stiffness, two factors imposing a high afterload to cardiac work, are the main causal risk factors for LVH in CKD patients (London, 1998). High afterload triggers the expression of embryonic genes altering the myocardial cell phenotype (Toischer et al., 2010). Activation of the intracardiac renin–angiotensin system (RAS) by a high afterload is crucial in LVH (Lijnen and Petrov, 1999) but angiotensin II and aldosterone can elicit myocardial cell hypertrophy and fibrosis also independently of their effect on blood pressure (BP) and arterial compliance (Ritz, 2009).

CKD bone-mineral disorders

In experimental models, low vitamin D levels are causally involved in LVH via activation of the intracardiac RAS (Strozecki et al., 2001). Vitamin D supplementation effectively reduces LVH, cardiac fibrosis, and microvascular remodelling in these models (Bodyak et al., 2007). However, the implication of these findings for the treatment of CKD patients remains uncertain because a recent clinical trial with paricalcitol, an active form of vitamin D, produced a reduction in left atrial volume but no effect on LV mass in these patients (Thadhani et al., 2012). Hyperphosphataemia has been associated with LVH in CKD-5D patients (Achinger and Ayus, 2006) and the adverse effect of phosphate on the myocardium is suspected to be mediated by fibroblast growth factor 23 (FGF23, see Chapter 117), a bone-hormone with a constellation

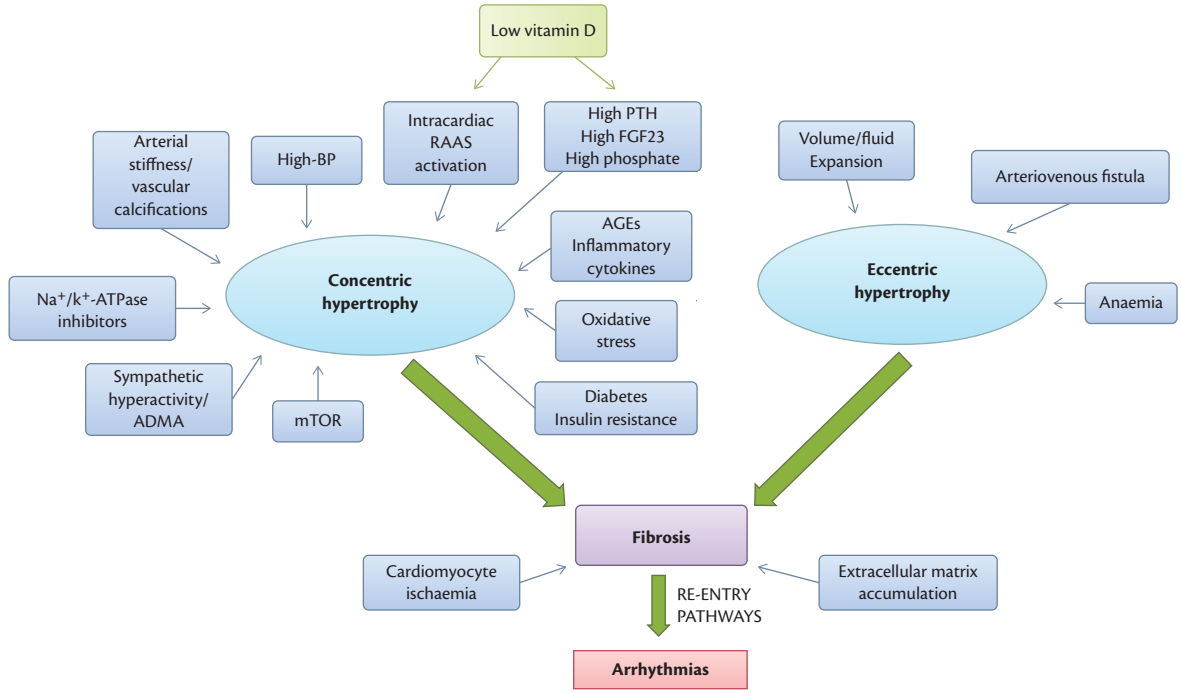

Fig. 107.4 Pathophysiology of LVH in CKD.

of effects on Ca-P metabolism including 1,25 dihydroxy-vitamin D downregulation. Intramyocardial or intravenous injection of FGF23 causes concentric LVH in normal mice and FGF23 antagonism prevents LVH in mice with 5/6 ablation of renal mass (Faul et al., 2011). Accordingly, high plasma levels of FGF23 associate with LVH in CKD patients (Gutierrez et al., 2009; Faul et al., 2011). Parathyroid hormone (PTH)-induced arterial rigidity and increased afterload are additional plausible mechanisms for LVH in CKD (Walker et al., 2010). However, interventions targeting PTH levels, such as calcimimetics, improve cardiac fibrosis but do not cause regression of LVH (Koleganova et al., 2009).

Sympathetic overactivity and nitric oxide inhibition

High sympathetic activity is a risk factor in CKD (Neumann et al., 2004). Well beyond hypertension and arterial stiffness (Chapter 111), norepinephrine (noradrenaline) per se stimulates myocardial growth *in vitro* in a dose–response fashion (Simpson, 1983). Elevated norepinephrine is a hallmark of concentric LVH in CKD-5D patients (Zoccali et al., 2002b) and elevated sympathetic activity predicts LVH in moderate to severe CKD (Siddiqi et al., 2010). Sympathetic activity is closely related to the nitric oxide (NO) system (Sartori et al., 2005). LV mass in CKD is associated both with asymmetric dimethyl arginine (ADMA; an endogenous NO synthase inhibitor) and with sympathetic nerve firing in pre-dialysis CKD patients (Grassi et al., 2011) and with ADMA and circulating norepinephrine in stage 5D CKD patients (Zoccali et al., 2002a, 2002b). Rats with aortic banding, an experimental intervention increasing afterload, develop concentric LVH that can be prevented by the administration of a β_1-blocker. However, blockade of the NO synthase activity by LNMA completely abolishes the protective effects of β_1-blockade on the left ventricle (Liao et al., 2004). These experimental findings are in line with the observation that NO blockade by ADMA and high norepinephrine are in same pathway leading to adverse clinical outcomes in stage 5D CKD patients (Mallamaci et al., 2004).

Inflammation, oxidative stress, Na^+/K^+-ATPase inhibition, and the mTOR pathway

Inflammation, high levels of endothelin-1, and oxidative stress are all relevant factors implicated in LVH (Ritz, 2009). Advanced glycation end products (AGEs), a series of pro-inflammatory compounds which exert toxic effects on various organ systems, trigger LVH in a rat model (Candido et al., 2003) and high levels of the decoy receptor of these compounds (RAGEs) are inversely correlated with LVMI in CKD patients (Leonardis et al., 2012). These finding suggest that effective endogenous blocking of AGEs by RAGEs may attenuate the effect of these compounds on LVH. The inhibition of xanthine oxidase, a key enzyme implicated in reactive oxygen species generation, attenuates systolic overload-induced left ventricular hypertrophy and dysfunction in mice (Xu et al., 2008). The relevance of this pathway in CKD patients is now supported by a clinical trial showing that xanthine oxidase inhibition by allopurinol induces regression of LVH in this population (Kao et al., 2011). Inhibition of Na^+/K^+-ATPase sarcolemmal activity is another relevant mechanism operating via oxidative stress (Kennedy et al., 2006) via activation of the extracellular signal-regulated kinase (ERK), a strong pro-oxidant kinase. Marino-bufagenin, circulating inhibitor of Na^+/K^+-ATPase which accumulates in advanced CKD, causes LVH and diastolic dysfunction in experimental models (Kennedy et al., 2006). Ouabain, another endogenous inhibitor of Na^+/K^+-ATPase which reaches high plasma levels in CKD, is directly related to LV mass and LV volume in CKD-5D patients (Stella et al., 2008). Na^+/K^+-ATPase apart, ERK signalling can be also stimulated by the activation of mTOR (Lee et al., 2007). The role of mTOR in determining LVH has been extensively examined in cardiomyocyte cultures as well as in a variety of experimental models of cardiac hypertrophy (Lee et al.,

2007), including a mouse model of CKD (Siedlecki et al., 2009). In this model, LVH can be prevented by the mTOR inhibitor rapamycin. However, the relevance of this pathway in CKD is still unclear. Everolimus reduced LV mass in a small trial in transplant patients (Paoletti et al., 2012). Yet, trials testing mTOR inhibitors in autosomal polycystic kidney disease have been disappointing (Huber et al., 2011). New-generation mTOR inhibitors, specifically targeting this receptor at the organ level like folate-conjugated rapamycin (Shillingford et al., 2012) in the kidney, will soon allow organ benefit at minimal systemic toxicity in humans.

Diabetes and insulin resistance

LVH and LV systolic and diastolic dysfunction are highly prevalent in diabetic patients (Tenenbaum et al., 2003; Boonman-de Winter et al., 2012). Although abnormal glucose homeostasis plays a major role in pathological cardiac remodelling (Poornima et al., 2006), other metabolic factors, such as insulin resistance (Spoto et al., 2012) and increased non-esterified fatty acids (Liu et al., 2001) may significantly alter cardiac structure and function.

Pathogenesis of eccentric left ventricular hypertrophy in chronic kidney disease

Volume overload, a pervasive complication of CKD at all stages, is the major driver of eccentric remodelling, particularly in CKD-5D patients (Ozkahya et al., 1998). Chronic fluid volume expansion imposes a sustained tensile stress to the ventricular wall which activates specific gene pathways leading to asymmetric growth of myocytes, apoptosis, and fibrosis (Du et al., 2010). Interdialysis fluid gain goes along with LVH in a dose–response fashion (London et al., 1997) and the intensification of ultrafiltration by frequent haemodialysis (HD) improves myocardial mechanics and the cardiac gene expression profile (Chan et al., 2012a). Furthermore, frequent HD attenuates LVH and reduces mortality as compared to standard dialysis in CKD-5D patients (Chan et al., 2012b). An arteriovenous fistula triggers sustained haemodynamic adaptations including reduced systemic vascular resistances and increased venous return and cardiac output. Severity of LV dilation in HD patients correlates with AV fistula flow (London et al., 1997). Partial regression of LVH in transplanted patients has been attributed to AV closure (Cridlig et al., 2008). Severe (Foley et al., 1996), but not mild to moderate (Drueke et al., 2006) anaemia leads to eccentric LVH in CKD, predicts new-onset cardiac failure, and death. Accordingly, partial correction of severe anaemia improves LV dilation (Evans et al., 1990; Beusterien et al., 1996; Foley et al., 2000) while haemoglobin (Hb) normalization in CKD patients with mild to moderate anaemia does not modify either LV end diastolic volume or LV mass (Drueke et al., 2006).

Treatment of left ventricular disorders in chronic kidney disease

Notwithstanding the fact that LVH and LV dysfunction are so frequent in pre-dialysis CKD patients and almost universal in CKD-5D patients, few randomized trials aimed at testing treatments for these disorders have been performed. Available trials are shown in Tables 107.1 and 107.2. Trials are grouped on the basis of the main study outcome (either LVH or LV systolic dysfunction) and according to the target population, that is, pre-dialysis CKD patients and CKD-5D patients. The same trials are discussed below according to the pharmacological intervention made.

Drug treatment of left ventricular hypertrophy and left ventricular dysfunction in chronic kidney disease and CKD-5D patients

Angiotensin-converting enzyme inhibitors

In patients with CKD, LVH is a risk factor for death and CV complications independent of BP (Zoccali et al., 2004a). A substantial number of CKD patients display LV dilatation and dysfunction, that is, alterations frequently associated with a history of myocardial infarction (MI) and cardiac ischaemia. CKD-5D patients with LV dysfunction are at high risk of death even if asymptomatic (Zoccali et al., 2004b). Because at comparable BP reductions ACEIs are superior to other drugs for causing regression of LVH in patients with heart disease and, because the RAS is hyperactivated in CKD, ACE inhibition represents the first choice in these patients.

Until now, no specific trial has tested the effect of ACEIs on the regression of LVH in pre-dialysis CKD patients. A randomized trial (FOSDIAL, Fosinopril in Dialysis) (Zannad et al., 2006), tested fosinopril in CKD-5D patients with echocardiographic LVH. Regression of LVH was not considered as an endpoint in this study, which was based on clinical events only. The drug produced only a minor decrease (−7%) in the combined endpoint including CV death, non-fatal stroke, heart failure, MI, or revascularization. Of note, Fosinopril produced a −5/−3 mmHg BP fall as compared to placebo in hypertensive patients but it did not modify arterial pressure in normotensive patients. No detailed data on LV mass and function in patients enrolled in the FOSDIAL study (Zannad et al., 2006) were reported. ACEIs are unlikely to induce favourable effects on LV mass when administered to normotensive dialysis patients. Indeed, ramipril had no influence on this outcome measure in a randomized controlled trial (RCT) in dialysis patients with LVH by echocardiography and optimal BP control (average BP = 125/69 mmHg) (Yu et al., 2006).

In another RCT (Yilmaz et al., 2010) in 112 HD patients randomized to amlodipine or ramipril, LVMI progressed in both treatment groups despite the achievement of a stable BP control. Subgroup analyses in this study showed that the effect of these drugs on LVMI depends on the underlying geometry of the LV because a significant decrease occurs in patients with concentric remodelling only.

In the SAVE trial (Survival and Ventricular Enlargement) in asymptomatic patients with LVEF < 40% after MI, captopril was associated with a 19% reduction in all-cause mortality and a 37% decrease in the risk of progressing to heart failure (Pfeffer et al., 1992). Importantly, these beneficial effects were registered in all patients groups including those with moderate CKD and those with adjunctive therapies such as thrombolytics, aspirin, and/or β-blockers.

Angiotensin II receptor blockers

When added to ACEIs, angiotensin II type 1 receptor blockers (ARBs) exert favourable effects on LV remodelling, haemodynamic measurements, neurohumoral activity, and CV mortality in patients with CHF (McKelvie et al., 1999; Pfeffer et al., 2003). Secondary analyses in CHARM (Candesartan in Heart Failure: Assessment of Reduction

Table 107.1 Randomized controlled trials of drug interventions on LVH

RCTs of stage 1 to stage 5 CKD (pre-dialysis)							
Authors, year, country	**Type of study**	**Population**	**Intervention**	**Comparator**	**Follow-up**	**Results**	**Notes**
Zamboli et al., 2011 Italy	RCT Open-label	40 hypertensive patients with mild to moderate CKD	Furosemide 25–75 mg/day	Non-diuretic antihypertensive treatments	52 weeks	LVMI by Echo was more reduced in patients receiving furosemide (−7.9, interquartile range (IQR) −15.8 to −1.4 g/h$^{2.7}$) than in controls (0.0, IQR −6.2 to +9.5 g/h$^{2.7}$, P = 0.013)	Absolute reduction of LVMI correlated with reduction in extracellular water in furosemide-treated patients (r = 0.458, P = 0.042) but not in controls
Thadhani et al., 2012 Multicentre	RCT Double-blind	227 CKD patients with mild to moderate LVH, and normal LVEF	Paricalcitol 2 micrograms/day	Placebo	48 weeks	Changes in LVMI were not different between groups (paricalcitol 0.34 g/m$^{2.7}$ (95% CI, −0.14 to 0.83 g/m$^{2.7}$) vs placebo −0.07 g/m$^{2.7}$ (95% CI, −0.55 to 0.42 g/m$^{2.7}$))	No differences were observed also in Doppler measures of diastolic function including peak early diastolic lateral mitral annular tissue velocity
Kao et al., 2011 UK	RCT Double-blind	134 CKD stage 3 patients with LVH	Allopurinol 300 mg/day	Placebo	9 months	After treatment, ΔLVMI was more significantly reduced in allopurinol than in placebo group (-1.42 ± 4.67 g/m^2 vs −1.28 ± 4.45 g/m^2; P = 0.036)	End-systolic volume and ejection fraction did not change with treatment of allopurinol. Changes in LVMI correlated with flow-mediated dilation, PWV, end-diastolic volume, and urine protein:creatinine ratio
Chen et al., 2008 Taiwan	RCT Open-label	69 patients with CKD stage 4-5	Darbepoetin alfa (DA) or epoetin alfa (EPO)	No EPO therapy	24 weeks	LVMI decreased significantly in both the EPO (−5.7 ± 14.2 g/m^2) and DA groups (−5.6 ± 15.8 g/m^2). The decrease in LVMI was not different between groups	The ejection fraction increased in both treatment groups (EPO group: 2.45% ± 2.28%, DA group: 1.64% ± 2.95%) and decreased in controls (-1.15% ± 3.69%) (P = 0.004 among groups)
Akizawa et al., 2011 Japan	RCT Open-label	321 CKD patients	Darbepoetin alfa (DA)	Recombinant EPO (rHuEPO)	48 weeks	LVM remained stable in the rHuEPO group and significantly decreased in the DA group (−7.8 g/m^2; 95% CI: −12.1 to −3.6 g/m^2, P < 0.001)	No significant differences in the incidence of CV and adverse events between the two groups
Paoletti et al., 2012 Italy	RCT Open-Label	30 non-diabetic renal transplant recipients (RTRs)	Everolimus (EVL) plus reduced-exposure cyclosporin A (CsA)	Standard dose CsA	12 months	LVMI significantly decreased in the EVL group (difference between groups: 9.2 ± 3.1 g/m$^{2.7}$, p = 0.005)	Changes in BP were similar in the two groups

(*Continued*)

Table 107.1 Continued

RCTs of stage CKD-5D							
Authors, year, country	**Type of study**	**Population**	**Intervention**	**Comparator**	**Follow-up**	**Results**	**Notes**
Zannad et al., 2006 France	RCT Double-blind	397 HD patients	Fosinopril 5–20 mg daily	Placebo	24 months	In those patients who were hypertensive at baseline, SBP and DBP were significantly decreased in the fosinopril as compared to the placebo group	Patients in the fosinopril group had a higher baseline LVM, higher rates of diabetes, disease, peripheral artery disease and stroke
Yu et al., 2006 Taiwan	RCT Double-blind	46 normotensive HD patients	Ramipril 2.5 mg 3 times/week	Placebo	12 months	No significant within-group or between-group differences in LVM at entry, 6 and 12 months after treatment, and 1 month after washout	In the ramipril group, BP decreased significantly at 6 and 12 months after treatment
Mitsuhashi et al., 2009 Japan	RCT Double-blind	40 hypertensive HD patients	Losartan	Placebo	12 months	Compared with the control group, losartan significantly decreased LVMI and pulse wave-velocity	Significant correlations between changes in LVMI and changes in night-time short-term BP variability
Yilmaz et al., 2010 Turkey	RCT Blinding not stated	112 HD patients	Amlodipine	Ramipril	12 months	LVMI progressed in both treatment groups: 15.2% in amlodipine vs 10.3% in ramipril group (P = 0.38)	In patients with concentric LVH, LVMI regressed −13.2% in ramipril and −9.8% in amlodipine group. In patients with eccentric LVH, LVMI increased 3.4% in ramipril and 5.2% in amlodipine group
Li and Wang, 2011 China	RCT Blinding not stated	144 HD patients	Isosorbide 30–120 mg/day	Standard therapy not including nitrates	24 weeks	LVMI decreased more in the nitrate group (−14 $g/m^{2.7}$) than in controls (−7.6 $g/m^{2.7}$). The prevalence of LVH in the nitrate and control groups decreased 17.2% and 9.8%, respectively	The incidence of acute LV failure was 1.4% in the nitrate group and 11.1% in the non-nitrate group (P = 0.03)

Table 107.2 Randomized controlled trials of drug interventions on LV dysfunction

RCTs of stage 1 to stage 5 CKD (pre-dialysis)							
Authors, year, country	**Type of study**	**Population**	**Intervention**	**Comparator**	**Follow-up**	**Results**	**Notes**
Pfeffer et al., 1992 USA	RCT Double blind	2221 patients with recent AMI and LVEF < 40%	Captopril 6.25–12.5 mg daily	Placebo	42 months	Patients on captopril were less likely to reach a composite endpoint of progressive LV dysfunction and all-cause mortality (P = 0.006)	19% reduction in all-cause mortality and 37% in the risk of progressing to heart failure after treatment with captopril. These effects were registered also in patients with moderate kidney failure
Hillege et al., 2006 Multicentre	RCT Double blind (secondary analysis of CHARM trial)	2743 patients with symptomatic HF (NYHA class II–IV) with LVEF ≤ 40% or > 40%	Candesartan 4–32 mg daily	Placebo	48 months	Cardiovascular death, CHF hospitalization and all causes mortality were lower in the candesartan group	No interaction between renal function and beneficial effects of candesartan, indicating that the effect of treatment is similar in CKD and non-CKD patients
Edwards et al., 2009, 2010 UK	RCT Doubleblind	112 CKD patients stage 2–3	Spironolactone 25 mg/day	Placebo	40 weeks	Compared with placebo, spironolactone improved LVM by Echo (−14 ± 13 g vs −3 ± 11 g, P < 0.01) and various indexes of LV function	Spironolactone improved also pulse wave velocity, augmentation index, and aortic distensibility
Wali et al., 2011 Multicentre	Pooled analysis of data from two double-blinded RCTs	1959 post-AMI patients with LVEF < 40% (CAPRICORN) and 2289 CHF patients with LVEF < 25% (COPERNICUS)	Carvedilol 12.5–50 mg daily (CAPRICORN) Carvedilol 6.25–25 mg daily (COPERNICUS)	Placebo	4–8 weeks	Carvedilol decreases by 24% the risk of all-cause and CV mortality.	The majority (60.8%) of patients had moderate to severe CKD (eGFR < 60 mL/min). In patients with CKD stage 3B (eGFR < 45mL/min), the efficacy of carvedilol was not significantly different from placebo
RCTs of stage 5D-CKD							
Cice et al., 2001, 2003 Italy	RCT Doubleblind	114 HD patients with chronic heart failure and dilated cardiomyopathy	Carvedilol 6.25–50 mg/day	Placebo	24 months	Carvedilol significantly improved LVEF, LV end-diastolic volume and end-systolic volume	Carvedilol significantly reduced all cause (−21.5%) and CV mortality (−38.6%) and hospitalization rate (−24.4%)
Cice et al., 2010 Italy	RCT Double blind	332 HD patients with CHF (NYHA class II–III), LVEF < 40%	Telmisartan (progressively increased to 80 mg/day)	Placebo	36 months	Telmisartan improved LV diastolic diameter: −0.12 ± 0.6 in telmisartan vs −0.04 ± 0.3 (cm/m^2) in placebo (P < 0.0001); and LVEF: 5.8 ± 6.7% in telmisartan vs 3.1 ± 4.4% in placebo (P < 0.0001)	Telmisartan significantly reduced all-cause mortality (35.1% vs 54.4%; P < 0.001), CV death (30.3% vs 43.7%; P < 0.001), and hospital admission for CHF (33.9% vs 55.1%; P < 0.0001)
Taheri et al., 2009 Iran	RCT Double blind	16 HD patients with CHF and LVEF < 45%	Spironolactone 25 mg/3 times a week	Placebo	6 months	Mean LVEF increased more in spironolactone than in placebo group (6.2 ± 1.64 vs 0.83 ± 4.9; P < 0.05)	Mean LVM decreased significantly in the spironolactone group but increased in the placebo group (−8.4 ± 4.72 vs 3 ± 7.97; P = 0.02)

in Mortality and Morbidity) (Hillege et al., 2006), a trial which enrolled 269 patients with eGFR < 60 mL/min, showed no interaction between renal function and the beneficial effect of candesartan, indicating that the benefit of this angiotensin II blocker extends to CKD patients with heart failure. In hypertensive HD patients, losartan added to calcium antagonists and other drugs (Mitsuhashi et al., 2009), decreased LVMI and pulse wave velocity (PWV) with reduced BP variability during the night. Telmisartan, added to ACEIs and β-blockers in CKD-5D patients with heart failure (New York Heart Association (NYHA) stages II–IV) and LVEF < 40%, reduced mortality by 49% (Cice et al., 2010). This remarkable risk reduction may depend on the peculiarly favourable effect of telmisartan on the parasympathetic–sympathetic balance, a key issue in kidney failure. Indeed, telmisartan increases parasympathetic activity while leaving sympathetic activity unmodified (Karas et al., 2005). Interventions aimed at countering hypertension, LVH, and systolic dysfunction in CKD patients care demand special attention at maintaining BP at the best tolerated level, particularly so in dialysis patients. Indeed about 10% of patients enrolled in the telmisartan study had to be excluded because of excessive BP reduction (Cice et al., 2010).

Aldosterone antagonists

Aldosterone is one of the most potent factors implicated in LVH and in myocardial fibrosis. ACEIs and ARBs do not completely suppress aldosterone production. The addition of aldosterone receptor blockers might therefore potentiate the protective effect of ACEIs and ARBs on LV remodelling and LV function. In a randomized trial in 112 patients with CKD stages 2 and 3, the addition of spironolactone to ACEIs and ARBs improved LVMI, as well as LV systolic and diastolic function, PWV, and aortic distensibility (Edwards et al., 2009, 2010). In a small, randomized study of 16 CKD-5D patients on HD with moderate to severe heart failure, spironolactone reduced LVMI and produced a significant increase in the mean EF without increasing the risk of episodes of hyperkalaemia as compared to the placebo group (Taheri et al., 2009).

The impact of spironolactone treatment on hard CV outcomes, such as mortality or major CV events in CKD patients, is still unknown. The fact that mineralocorticoid receptor antagonists increased mortality by 40% (P = 0.005) in a recent trial (O'Meara et al., 2012) in patients with heart failure and atrial fibrillation (including 46.5% with moderate to severe CKD) is a reason for concern. A phase II clinical trial testing a novel, non-steroidal mineralocorticoid receptor antagonist in patients with heart failure and CKD is underway (Pitt, 2012). This study will provide answers on the safety and efficacy of this novel compound as compared to spironolactone in CKD patients with compromised LV function.

β-blockers

Prescription of β-blockers is formally recommended in patients who have suffered an MI because these drugs reduce the rate of sudden death and recurrent MI. A post hoc analysis of the SAVE trial suggested that β-blockers may also retard the progression of ventricular disease because the use of these drugs was associated with a 30% reduction in the risk of CV death and with a 21% reduction in the risk of heart failure. This retrospective analysis is in line with the results of the CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) study (Dargie et al., 2001) which prospectively tested the effect of carvedilol in patients with EF < 40% that were being treated with an ACEI. In a recent meta-analysis (Wali et al., 2011) based on individual data of patients with LV dysfunction and estimated GFR (eGFR) < 60 mL/min (N = 4217) pooled from the CAPRICORN (Dargie et al., 2001) and COPERNICUS (Carvedilol Prospective Randomized, Cumulative Survival study) studies (Packer et al., 2002), carvedilol decreased the risks of all-cause and CV mortality by 24% but apparently had no effect on sudden cardiac death. However, in a sensitivity analysis among heart failure subjects with CKD stage 3B (eGFR < 45 mL/min), the efficacy of carvedilol was not significantly different from placebo.

β-blockade may be particularly relevant in stage CKD-5D patients with LV disorders because sympathetic activity assessed by plasma norepinephrine increases in proportion to the severity of LV systolic dysfunction these patients (Zoccali et al., 2002b). The beneficial effect of carvedilol in this population was demonstrated in a randomized, placebo-controlled trial that showed a consistent improvement in LV volumes, LV function, and cardiac arrhythmia (Cice et al., 2001) and longer survival in patients treated with this β-blocker (Cice et al., 2003).

The use of BP lowering agents in stage CKD-5D patients with LV disorders demands strict surveillance. Indeed, as in the telmisartan trial (Cice et al., 2010) and in the carvedilol trial (Cice et al., 2001, 2003) about 5% of patients dropped out from the study because of intolerable hypotension.

Furosemide

Volume expansion and positive sodium balance is a dominant cause of LVH in CKD patients (Agarwal, 2011). In stage CKD-5D patients the adoption of a clinical policy emphasizing ultrafiltration (UF) intensification and reduction of salt intake produced impressive reductions in LVH in this population (Ozkahya et al., 1998; Agarwal et al., 2011). While it is beyond question that volume-dependent hypertension can be corrected by loop diuretics, the effect of these drugs on LVMI in CKD patients has been tested in only one study. In this open-label trial (Zamboli et al., 2011), 40 patients with mild to moderate CKD were randomized to furosemide or non-diuretic antihypertensive treatments. After 52 weeks, LVMI reduced more in patients receiving furosemide than in controls (P = 0.001) and the absolute reduction of LVMI correlated with achieved extracellular water decrease.

Other antihypertensive drugs

Sustained-release nitrate isosorbide was more effective than standard antihypertensive therapy for reducing LVH in a RCT of 144 HD patients (Li and Wang, 2011).

Correction of anaemia with erythropoiesis-stimulating agents

The effect of anaemia correction on LVH in CKD patients on conservative or renal replacement therapy has been examined in various studies with contrasting results (Foley et al., 2000; Roger et al., 2004; Ayus et al., 2005; Levin et al., 2005; Parfrey et al., 2005; MacDougall et al., 2007; Cianciaruso et al., 2008). A meta-analysis (Parfrey et al., 2009) including 15 trials (five of which were randomized and controlled) collected data from 1731 patients. The correction of anaemia with erythropoiesis-stimulating agents reduced LVMI only in those subjects with severe anaemia at baseline (Hb < 10 g/dL) who were treated to increase Hb to levels not exceeding 12 g/dL. No further benefit was registered above this

threshold. Another trial previous to the meta-analysis (Chen et al., 2008) demonstrated that epoetin alfa and darbepoetin alfa have a similar effect in lowering LVMI in patients with CKD stage 4–5 not yet on dialysis, contradicting the hypothetical superiority of darbepoetin alfa over recombinant human erythropoietin (rHuEPO) for causing regression in LVH in CKD patients (Akizawa et al., 2011).

Vitamin D

Vitamin D deficiency is a CV risk factor in the general population (Hsia et al., 2007; Wang et al., 2008). In CKD patients, the use of calcitriol or other active forms of vitamin D predicts a lower risk for CV events (Teng et al., 2003, 2005). Experimental models in Dahl rats (Bodyak et al., 2007) and in the 1α-hydroxylase knockout mice (Zhou et al., 2008) have consistently demonstrated that these compounds reduce LVMI and improve LV diastolic function.

Vitamin D deficiency triggers hyperparathyroidism, which itself may be another factor implicated in LVH. Parathyroidectomy leads to a significant improvement in LVMI in non-hypertensive patients with primary hyperparathyroidism (Stefenelli et al., 1997) and also in CKD-5D patients as well (Chow et al., 2003). However, lowering PTH levels by a calcimimetic (cinacalcet) decreases cardiac fibrosis but did not modify LV mass in an experimental study in rats with subtotal nephrectomy (Koleganova et al., 2009).

Two small, non-randomized, prospective studies support the hypothesis that vitamin D supplementation might improve LV function in CKD-5D patients (Matias et al., 2010; Bucharles et al., 2012). A randomized trial testing the effect of vitamin D on LVMI in CKD stages 3-5, OPERA, proved negative (Wang et al., 2014), as did the PRIMO study (Thadhani et al., 2012), in which paricalcitol at 2 micrograms/day (a dose sufficient to suppress PTH blood levels) failed to improve LVMI and diastolic function over a 48-week period, although it reduced CV disease-related hospitalizations and left atrial volume and prevented the increase in brain natriuretic peptide levels in subjects with higher baseline LVMI.

Allopurinol

The inhibition of xanthine oxidase activity promotes the regression of LVH in experimental models of CKD (Laakso et al., 2004; Xu et al., 2008). In a recent double-blind, placebo-controlled, parallel study in 67 patients with CKD stage 3, allopurinol significantly reduced LVH and improved endothelial function after 9 months of treatment (Kao et al., 2011). This requires further testing.

Drug treatment of left ventricular hypertrophy in renal transplant patients

There are few controlled trials aimed at assessing the effect of drug treatment on LVH in the transplant population. In the largest study, an ACEI (lisinopril) was compared with a calcium channel blocker (controlled-release nifedipine) (Midtvedt et al., 2001). Similar BP control was achieved in the two study arms and LVMI regressed by 15% in both groups indicating that hypertension control improves LVH independently of the antihypertensive agent used. Both ciclosporin and tacrolimus may exacerbate hypertension and LVH in transplant recipients. Ciclosporin augments sympathetic nerve activity, increases endothelin, and inhibits NO synthesis (Hoorn et al., 2012), all factors which may have BP-dependent and -independent effects on LV mass (see 'Left ventricular hypertrophy in chronic kidney disease pathophysiology'). In renal transplant recipients, the reduction of the dose of ciclosporin by 50% decreased the risk of hypertension without increasing rejection risk (Pascual et al., 2003). Tacrolimus has lower pro-hypertensive potential than ciclosporin (Margreiter, 2002). Yet used in combination with sirolimus it worsens hypertension. Observational studies show that that this combination has a negative impact upon graft survival (Meier-Kriesche et al., 2005). Everolimus reduced LV mass in a small trial in transplant patients (Paoletti et al., 2012). However, until now no beneficial effect of this drug on LVH has been shown in clinical trials in patients with adult polycystic kidney disease treated with this mTor inhibitor. Furthermore it remains to be seen whether the favourable effect of these drugs on LVH translates into better CV outcomes in renal transplant patients.

Treatment of left ventricular hypertrophy and left ventricular disorders in patients with kidney failure on dialysis (stage 5D-CKD)

Comparative trials between PD and HD pose virtually insurmountable difficulties (Korevaar et al., 2003) and until now no RCT comparing PD to HD in the management of LV disorders in patients with kidney failure has been performed (Table 107.3). US Renal Data System-based analyses including over 100,000 incident end-stage renal disease patients suggest that mortality is higher in PD patients with CHF and that the risk excess in PD patients becomes progressively more marked with increasing duration of follow-up (Stack et al., 2003). Subclinical extracellular fluid expansion is more common in peritoneal than in HD patients (Enia et al., 2001). Subtle volume expansion is associated with hypertension and LVH, both of which trigger LV systolic dysfunction.

Uncontrolled studies show that UF intensification and low dietary salt intake reduce LVMI considerably in HD patients (Ozkahya et al., 1998). In a secondary analysis of the DRIP (Dry-Weight Reduction in Hypertensive Hemodialysis Patients) trial, which tested whether additional volume reduction by UF intensification improves BP control in hypertensive HD patients, Agarwal et al. (2011) found that this intervention reduced the LVMI (–7.4 g/m^2 at 4 weeks; P = 0.005, and –6.3 g/m^2 at 8 weeks; P = 0.045). However, this change was mainly driven by a fall in LV end-diastolic volume rather than by a regression of the muscular component (LV wall thickness) of the LV (Zoccali et al., 2011).

In a randomized trial (Alvestrand et al., 2011) in 34 apparently CV disease-free patients comparing haemofiltration (HF) versus standard, low-flux HD, there was a more pronounced decrease in LVMI in patients randomized to HF. However the interpretation of this study is difficult because more patients in the HF arm were on antihypertensive treatment than in the control arm.

Culleton et al. (2007) were the first to compare the effects of a dialysis intensification regimen (nocturnal HD; five or six dialysis sessions per week, each lasting 6 hours) to conventional thrice-weekly HD in a randomized clinical trial including 51 patients. Nocturnal HD significantly reduced (by 8%) the LV mass as measured by NMR while no change was reported in the other study arm. This decline in LV mass was associated with a decrease, or discontinuation of, antihypertensive medications in about 60% of patients of the same arm.

In the FHN (Frequent Haemodialysis Network) trial (Chan et al., 2012), 245 patients were randomized either to six times per week

Table 107.3 Randomized controlled trials comparing different dialysis schedules or different extracorporeal treatments on LVH

Authors, year, country	Type of study	Population	Intervention	Comparator	Follow-up	Results	Notes
Culleton et al., 2007, Canada	RCT	52 HD patients	Frequent nocturnal HD (6 times/week)	Conventional HD (3 times/week)	6 months	Frequent nocturnal HD significantly improved LVM (mean difference between groups, 15.3 g; P = 0.04)	Frequent nocturnal HD was also associated with improved BP
Rocco et al., 2011, multicentre	RCT	87 HD patients	Frequent nocturnal HD (6 times/week)	Conventional HD (3 times/week)	12 months	No significant reduction in LVM (by NMR) and death between the two arms at the end of the study	Patients in the nocturnal arm had improved control of hypertension. There was a trend for increased vascular access events in the nocturnal arm
Agarwal et al., 2011, USA	RCT	113 hypertensive HD patients	Ultrafiltration intensification (UF)	Standard HD	8 weeks	In the control group, LVMI increased from baseline by +3.5 g/m^2 at 4 weeks and +0.3 g/m^2 at 8 weeks (P = NS). In the UF group, LVMI reduced by −7.4 g/m^2 at 4 weeks (P = 0.005) and −6.3 g/m^2 at 8 weeks (P = 0.045)	The change in LVM diameter was −10.9 g/m^2 more in UF than in the control group at 4 weeks (P = 0.012) but not significant at 8 weeks
Alvestrand et al., 2011, multicentre	RCT	34 incident HD patients	Haemofiltration (HF)	HD	24 months	In the HF group, LVMI decreased by 22 ± 48 g/m^2; in the HD group the decrease was 15 ± 57 g/m^2 (P = 0.03)	Blood pressure and other study variables did not differ between the two groups
Chan et al., 2012, multicentre	RCT	245 HD patients	Frequent (daily) HD (6 times/week)	Conventional HD (3 times/week)	12 months	Frequent HD reduced LVM index (6.9 g/m^2; P = 0.003) as measured by NMR	Changes in LVM were associated with changes in blood pressure (R = 0.54, P < 0.001). High rate of vascular access events in the FAD group

daily in-centre (frequent) HD, or to conventional HD. After 1 year, frequent HD resulted in a significant reduction of LVMI (−6.9 g/m^2; P = 0.003) and as a decline in mortality. Overall, a 39% decline in the occurrence of the composite primary endpoint of the study (either death or LVMI reduction) was registered in the frequent HD arm as compared to the control arm.

In another FHN trial (Rocco et al., 2011) comparing frequent nocturnal HD to conventional dialysis for the same composite endpoint, a 32% risk reduction was observed, but failed to achieve statistical significance because of the limited study power.

A meta-analysis (Susantitaphong et al., 2012) examined the effects of frequent or extended HD on cardiac morphology and function by including data from 38 single-arm studies, five crossover trials, and three RCTs. In the pooled analysis of these studies, frequent HD reduced LVMI by −31.2 g/m^2 (P < 0.001), which was a substantially greater effect than that registered in the three RCTs (−7.0 g/m^2; P < 0.001) mentioned above. Frequent or extended HD also reduced BP and improved to an important extent LV systolic function (+6.7%), indicating potential major effects of HD intensification for the prevention of CV complications in this high-risk population. In both FHN trials, there was an increase in adverse vascular access events in the active arms of these studies. Because of this problem, frequent HD treatments on LVM should be carefully balanced against the added burden of more frequent vascular access interventions.

Cardiac resynchronization

Cardiac resynchronization therapy (CRT) with or without ICD implantation is increasingly applied for the treatment of heart failure in selected cases. This device consists of a specialized pacemaker that synchronizes the pumping activity of the left and right ventricles. Indications for CRT implantation include EF < 35%, a QRS interval > 130 ms, and the presence of heart failure symptoms. CRT may be a valid treatment option in suitable CKD and in dialysis patients; however, there are still no studies based on clinical endpoints and the application of this treatment remains driven by clinical experience only.

Dysrhythmias

The incidence of sudden cardiac death is increased in CKD, but most markedly in dialysis patients. This is considered further in Chapter 108.

References

Achinger, S. G. and Ayus, J. C. (2006). Left ventricular hypertrophy: is hyperphosphatemia among dialysis patients a risk factor? *J Am Soc Nephrol*, 17(12 Suppl 3), S255–61.

Agarwal, R. (2011). Interdialytic hypertension – an update. *Adv Chronic Kidney Dis*, 18(1), 11–16.

Agarwal, R., Bouldin, J. M., Light, R. P., *et al.* (2011). Probing dry-weight improves left ventricular mass index. *Am J Nephrol*, 33(4), 373–80.

Akizawa, T., Gejyo, F., Nishi, S., *et al.* (2011). Positive outcomes of high hemoglobin target in patients with chronic kidney disease not on dialysis: a randomized controlled study. *Ther Apher Dial*, 15(5), 431–40.

Alvestrand, A., Ledebo, I., Hagerman, I., *et al.* (2011). Left ventricular hypertrophy in incident dialysis patients randomized to treatment with hemofiltration or haemodialysis: results from the ProFil study. *Blood Purif*, 32(1), 21–9.

Amann, K., Wiest, G., Zimmer, G., *et al.* (1992). Reduced capillary density in the myocardium of uremic rats—a stereological study. *Kidney Int*, 42(5), 1079–85.

Arnol, M., Knap, B., Oblak, M., *et al.* (2010). Subclinical left ventricular echocardiographic abnormalities 1 year after kidney transplantation are associated with graft function and future cardiovascular events. *Transplant Proc*, 42(10), 4064–8.

Ayus, J. C., Go, A. S., Valderrabano, F., *et al.* (2005). Effects of erythropoietin on left ventricular hypertrophy in adults with severe chronic renal failure and hemoglobin < 10 g/dL. *Kidney Int*, 68(2), 788–95.

Beusterien, K. M., Nissenson, A. R., Port, F. K., *et al.* (1996). The effects of recombinant human erythropoietin on functional health and well-being in chronic dialysis patients. *J Am Soc Nephrol*, 7(5), 763–73.

Bodyak, N., Ayus, J. C., Achinger, S., *et al.* (2007). Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in Dahl salt-sensitive animals. *Proc Natl Acad Sci U S A*, 104(43), 16810–15.

Boonman-de Winter, L. J., Rutten, F. H., Cramer, M. J., *et al.* (2012). High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia*, 55(8), 2154–62.

Bucharles, S., Barberato, S. H., Stinghen, A. E., *et al.* (2012). Impact of cholecalciferol treatment on biomarkers of inflammation and myocardial structure in haemodialysis patients without hyperparathyroidism. *J Ren Nutr*, 22(2), 284–91.

Candido, R., Forbes, J. M., Thomas, M. C., *et al.* (2003). A breaker of advanced glycation end products attenuates diabetes-induced myocardial structural changes. *Circ Res*, 92(7), 785–92.

Chan, C. T., Arab, S., Carasso, S., *et al.* (2012a). Impact of frequent nocturnal haemodialysis on myocardial mechanics and cardiomyocyte gene expression. *Circ Cardiovasc Imaging*, 5(4), 474–80.

Chan, C. T., Greene, T., Chertow, G. M., *et al.* (2012b). Determinants of left ventricular mass in patients on haemodialysis: Frequent Haemodialysis Network (FHN) Trials. *Circulation*, 5(2), 251–61.

Chen, H. H., Tarng, D. C., Lee, K. F., *et al.* (2008). Epoetin alfa and darbepoetin alfa: effects on ventricular hypertrophy in patients with chronic kidney disease. *J Nephrol*, (4), 543–9.

Chen, S. C., Su, H. M., Hung, C. C., *et al.* (2011). Echocardiographic parameters are independently associated with rate of renal function decline and progression to dialysis in patients with chronic kidney disease. *Clin J Am Soc Nephrol*, 6(12), 2750–8.

Chow, K. M., Szeto, C. C., Kum, L. C., *et al.* (2003). Improved health-related quality of life and left ventricular hypertrophy among dialysis patients treated with parathyroidectomy. *J Nephrol*, 16(6), 878–85.

Cianciaruso, B., Ravani, P., Barrett, B. J., *et al.* (2008). Italian randomized trial of hemoglobin maintenance to prevent or delay left ventricular hypertrophy in chronic kidney disease. *J Nephrol*, 21(6), 861–70.

Cice, G., Di Benedetto, A., D'Isa, S., *et al.* (2010). Effects of telmisartan added to angiotensin-converting enzyme inhibitors on mortality and morbidity in haemodialysis patients with chronic heart failure. *J Am Coll Cardiol*, 56(21), 1701–8.

Cice, G., Ferrara, L., D'Andrea, A., *et al.* (2003). Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol*, 41(9), 1438–44.

Cice, G., Ferrara, L., Di Benedetto, A., *et al.* (2001). Dilated cardiomyopathy in dialysis patients—beneficial effects of carvedilol: a double-blind, placebo-controlled trial. *J Am Coll Cardiol*, 37(2), 407–11.

Cridlig, J., Selton-Suty, C., Alla, F., *et al.* (2010). Cardiac impact of the arteriovenous fistula after kidney transplantation: a case-controlled, match-paired study. *Transplant Int*, 21(10), 948–54.

Culleton, B. F., Walsh, M., Klarenbach, S. W., *et al.* (2007). Effect of frequent nocturnal haemodialysis vs conventional haemodialysis on left ventricular mass and quality of life: a randomized controlled trial. *JAMA*, 298(11), 1291–9.

Dargie, H. J. (2001). Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*, 357(9266), 1385–90.

De Jager, D. J., Grootendorst, D. C., Jager, K. J., *et al.* (2009). Cardiovascular and noncardiovascular mortality among patients starting dialysis. *JAMA*, 302(16), 1782–9.

De Lima, J. J., Vieira, M. L., Viviani, L. F., *et al.* (2002). Long-term impact of renal transplantation on carotid artery properties and on ventricular hypertrophy in end-stage renal failure patients. *Nephrol Dial Transplant*, 17(4), 645–51.

De Simone, G., Devereux, R. B., Daniels, S. R., *et al.* (1995). Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. *J Am Coll Cardiol*, 25(5), 1056–62.

Drueke, T. B., Locatelli, F., Clyne, N., *et al.* (2006). Normalization of hemoglobin level in patients with chronic kidney disease and anaemia. *N Engl J Med*, 355(20), 2071–84.

Du, Y., Plante, E., Janicki, J. S., *et al.* (2010). Temporal evaluation of cardiac myocyte hypertrophy and hyperplasia in male rats secondary to chronic volume overload. *Am J Pathol*, 177(3), 1155–63.

Eckardt, K. U., Scherhag, A., Macdougall, I. C., *et al.* (2009). Left ventricular geometry predicts cardiovascular outcomes associated with anaemia correction in CKD. *J Am Soc Nephrol*, 20(12), 2651–60.

Edwards, N. C., Ferro, C. J., Kirkwood, H., *et al.* (2010). Effect of spironolactone on left ventricular systolic and diastolic function in patients with early stage chronic kidney disease. *Am J Cardiol*, 106(10), 1505–11.

Edwards, N. C., Steeds, R. P., Stewart, P. M., *et al.* (2009). Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease: a randomized controlled trial. *J Am Coll Cardiol*, 54(6), 505–12.

Enia, G., Mallamaci, F., Benedetto, F. A., *et al.* (2001). Long-term CAPD patients are volume expanded and display more severe left ventricular hypertrophy than haemodialysis patients. *Nephrol Dial Transplant*, 16(7), 1459–64.

Evans, R. W., Rader, B., and D.L. Manninen, D. L. (1990). The quality of life of haemodialysis recipients treated with recombinant human erythropoietin. Cooperative Multicenter EPO Clinical Trial Group. *JAMA*, 263(6), 825–30.

Faul, C., Amaral, A. P., Oskouei, B., *et al.* (2011). FGF23 induces left ventricular hypertrophy. *J Clin Invest*, 121(11), 4393–408.

Ferreira, S. R., Moisés, V. A., Tavares, A., *et al.* (2002). Cardiovascular effects of successful renal transplantation: a 1-year sequential study of left ventricular morphology and function, and 24-hour blood pressure profile. *Transplantation*, 74(11), 1580–7.

Foley, R. N., Parfrey, P. S., Harnett, J. D., *et al.* (1996). The impact of anaemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. *Am J Kidney Dis*, 28(1), 53–61.

Foley, R. N., Parfrey, P. S., Kent, G. M., *et al.* (1998). Long-term evolution of cardiomyopathy in dialysis patients. *Kidney Int*, 54(5), 1720–5.

Foley, R. N., Parfrey, P. S., Morgan, J., *et al.* (2000). Effect of hemoglobin levels in haemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int*, 58(3), 1325–35.

Ganau, A., Devereux, R. B., Roman, M. J., *et al.* (1992). Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol*, 19(7), 1550–8.

Grassi, G., Seravalle, G., Ghiadoni, L., *et al.* (2011). Sympathetic nerve traffic and asymmetric dimethylarginine in chronic kidney disease. *Clin J Am Soc Nephrol*, 6(11), 2620–7.

Greaves, S. C., Gamble, G. D., Collins, J. F., *et al.* (1994). Determinants of left ventricular hypertrophy and systolic dysfunction in chronic renal failure. *Am J Kidney Dis*, 24(5), 768–76.

Gutierrez, O. M., Januzzi, J. L., Isakova, T., *et al.* (2009). Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. *Circulation*, 119(19), 2545–52.

Hayashi, S. Y., Rohani, M., Lindholm, B., *et al.* (2006). Left ventricular function in patients with chronic kidney disease evaluated by colour tissue Doppler velocity imaging. *Nephrol Dial Transplant*, 21(1), 125–32.

Hernandez, D., González, A., Rufino, M., *et al.* (2007). Time-dependent changes in cardiac growth after kidney transplantation: the impact of pre-dialysis ventricular mass. *Nephrol Dial Transplant*, 22(9), 2678–85.

Hernandez, D., Lacalzada, J., Rufino, M., *et al.* (1997). Prediction of left ventricular mass changes after renal transplantation by polymorphism of the angiotensin-converting-enzyme gene. *Kidney Int*, 51(4), 1205–11.

Hillege, H. L., Nitsch, D., Pfeffer, M. A., *et al.* (2006). Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation*, 113(5), 671–8.

Hoorn, E. J., Walsh, S. B., McCormick, J. A., *et al.* (2012). Pathogenesis of calcineurin inhibitor-induced hypertension. *J Nephrol*, 25(3), 269–75.

Hsia, J., Heiss, G., Ren, H., *et al.* (2007). Calcium/vitamin D supplementation and cardiovascular events. *Circulation*, 115(7), 846–54.

Huber, T. B., Walz, G., and Kuehn, E. W. (2011). mTOR and rapamycin in the kidney: signaling and therapeutic implications beyond immunosuppression. *Kidney Int*, 79(5), 502–11.

Jardine, A. G., Gaston, R. S., Fellstrom, B. C., *et al.* (2011). Prevention of cardiovascular disease in adult recipients of kidney transplants. *Lancet*, 378(9800), 1419–27.

K/DOQI Workgroup (2005). K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis*, 45(4 Suppl 3), S1–153.

Kao, M. P., Ang, D. S., Gandy, S. J., *et al.* (2011). Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. *J Am Soc Nephrol*, 22(7), 1382–9.

Karas, M., Lacourcière, Y., LeBlanc, A. R., *et al.* (2005). Effect of the renin-angiotensin system or calcium channel blockade on the circadian variation of heart rate variability, blood pressure and circulating catecholamines in hypertensive patients. *J Hypertens*, 23(6), 1251–60.

Kennedy, D. J., Vetteth, S., Periyasamy, S. M., *et al.* (2006). Central role for the cardiotonic steroid marinobufagenin in the pathogenesis of experimental uremic cardiomyopathy. *Hypertension*, 47(3), 488–95.

Koleganova, N., Piecha, G., Ritz, E., *et al.* (2009). Interstitial fibrosis and microvascular disease of the heart in uremia: amelioration by a calcimimetic. *Lab Invest*, 89(5), 520–30.

Korevaar, J. C., Feith, G. W., Dekker, F. W., *et al.* (2003). Effect of starting with haemodialysis compared with peritoneal dialysis in patients new on dialysis treatment: a randomized controlled trial. *Kidney Int*, 64(6), 2222–8.

Laakso, J. T., Mervaala, E., Himberg, J. J., *et al.* (2004). Renal xanthine oxidoreductase activity during development of hypertension in spontaneously hypertensive rats. *J Hypertens*, 22(7), 1333–40.

Lee, C. H., Inoki, K., and Guan, K. L. (2007). mTOR pathway as a target in tissue hypertrophy. *Annu Rev Pharmacol Toxicol*, 47, 443–67.

Leonardis, D., Basta, G., Mallamaci, F., *et al.* (2012). Circulating soluble receptor for advanced glycation end product (sRAGE) and left ventricular hypertrophy in patients with chronic kidney disease (CKD). *Nutr Metab Cardiovasc Dis*, 22(9), 748–55.

Levin, A. (2003). Clinical epidemiology of cardiovascular disease in chronic kidney disease prior to dialysis. *Semin Dial*, 16(2), 101–5.

Levin, A., Djurdjev, O., Thompson, C., *et al.* (2005). Canadian randomized trial of hemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. *Am J Kidney Dis*, 46(5), 799–811.

Li, H. and Wang, S. X. (2011). Improvement of hypertension and LVH in maintenance haemodialysis patients treated with sustained-release isosorbide mononitrate. *J Nephrol*, 24(2), 236–45.

Liao, Y., Asakura, M., Takashima, S., *et al.* (2004). Celiprolol, a vasodilatory beta-blocker, inhibits pressure overload-induced cardiac hypertrophy and prevents the transition to heart failure via nitric oxide-dependent mechanisms in mice. *Circulation*, 110(6), 692–9.

Lijnen, P. and Petrov, V. (1999). Renin-angiotensin system, hypertrophy and gene expression in cardiac myocytes. *J Mol Cell Cardiol*, 31(5), 949–70.

Liu, G. X., Hanley, P. J., Ray, J., *et al.* (2001). Long-chain acyl-coenzyme A esters and fatty acids directly link metabolism to K(ATP) channels in the heart. *Circ Res*, 88(9), 918–24.

London, G. M. (1998). Heterogeneity of left ventricular hypertrophy—does it have clinical implications? *Nephrol Dial Transplant*, 13(1), 17–19.

London, G. M., Fabiani, F., Marchais, S. J., *et al.* (1987). Uremic cardiomyopathy: an inadequate left ventricular hypertrophy. *Kidney Int*, 31(4), 973–80.

MacDougall, I. C., Temple, R. M., and Kwan, J. T. (2007). Is early treatment of anaemia with epoetin-alpha beneficial to pre-dialysis chronic kidney disease patients? Results of a multicentre, open-label, prospective, randomized, comparative group trial. *Nephrol Dial Transplant*, 22(3), 784–93.

Mallamaci, F., Tripepi, G., Maas, R., *et al.* (2004). Analysis of the relationship between norepinephrine and asymmetric dimethyl arginine levels among patients with end-stage renal disease. *J Am Soc Nephrol*, 15(2), 435–41.

Margreiter, R. (2002). Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. *Lancet*, 359(9308), 741–6.

Matias, P. J., Jorge, C., Ferreira, C., *et al.* (2010). Cholecalciferol supplementation in haemodialysis patients: effects on mineral metabolism, inflammation, and cardiac dimension parameters. *CJASN*, 5(5), 905–11.

Matsushita, K., van der Velde, M., Astor, B. C., *et al.* (2010). Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*, 375(9731), 2073–81.

McKelvie, R. S., Yusuf, S., Pericak, D., *et al.* (1999). Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation*, 100(10), 1056–64.

Meier-Kriesche, H. U., Schold, J. D., Srinivas, T. R., *et al.* (2005). Sirolimus in combination with tacrolimus is associated with worse renal allograft survival compared to mycophenolate mofetil combined with tacrolimus. *Am J Transplant*, 5(9), 2273–80.

Midtvedt, K., Ihlen, H., Hartmann, A., *et al.* (2001). Reduction of left ventricular mass by lisinopril and nifedipine in hypertensive renal transplant recipients: a prospective randomized double-blind study. *Transplantation*, 72(1), 107–11.

Mitsuhashi, H., Tamura, K., Yamauchi, J., *et al.* (2009). Effect of losartan on ambulatory short-term blood pressure variability and cardiovascular remodeling in hypertensive patients on haemodialysis. *Atherosclerosis*, 207(1), 186–90.

Moran, A., Katz, R., Jenny, N. S., *et al.* (2008). Left ventricular hypertrophy in mild and moderate reduction in kidney function determined using cardiac magnetic resonance imaging and cystatin C: the multi-ethnic study of atherosclerosis (MESA). *Am J Kidney Dis*, 52(5), 839–48.

Nardi, E., Palermo, A., Mulè, G., *et al.* (2009). Left ventricular hypertrophy and geometry in hypertensive patients with chronic kidney disease. *J Hypertens*, 27(3), 633–41.

Neumann, J., Ligtenberg, G., Klein, I. I., *et al.* (2004). Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. *Kidney Int*, 65(5), 1568–76.

O'Meara, E., Khairy, P., Blanchet, M. C., *et al.* (2012). Mineralocorticoid receptor antagonists and cardiovascular mortality in patients with atrial fibrillation and left ventricular dysfunction: insights from the AF-CHF Trial. *Circ Heart Fail*, 5(5), 586–93.

Ozkahya, M., Ok, E., Cirit, M., *et al.* (1998). Regression of left ventricular hypertrophy in haemodialysis patients by ultrafiltration and reduced salt intake without antihypertensive drugs. *Nephrol Dial Transplant*, 13(6), 1489–93.

Packer, M., Fowler, M. B., Roecker, E. B., *et al.* (2002). Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. *Circulation*, 106(17), 2194–9.

Paoletti, E., Bellino, D., Cassottana, P., *et al.* (2005). Left ventricular hypertrophy in nondiabetic predialysis CKD. *Am J Kidney Dis*, 46(2), 320–7.

Paoletti, E., Bellino, D., Gallina, A. M., *et al.* (2011). Is left ventricular hypertrophy a powerful predictor of progression to dialysis in chronic kidney disease? *Nephrol Dial Transplant*, 26(2), 670–7.

Paoletti, E., Marsano, L., Bellino, D., *et al.* (2012). Effect of everolimus on left ventricular hypertrophy of de novo kidney transplant recipients: a 1 year, randomized, controlled trial. *Transplantation*, 93(5), 503–8.

Parfrey, P. S., Foley, R. N., Harnett, J. D., *et al.* (1996). Outcome and risk factors for left ventricular disorders in chronic uraemia. *Nephrol Dial Transplant*, 11(7), 1277–85.

Parfrey, P. S., Lauve, M., Latremouille-Viau, D., *et al.* (2009). Erythropoietin therapy and left ventricular mass index in CKD and ESRD patients: a meta-analysis. *CJASN*, 4(4), 755–62.

Parfrey, P.S., Foley, R. N., Wittreich, B. H., *et al.* (2005). Double-blind comparison of full and partial anaemia correction in incident haemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol*, 16(7), 2180–9.

Park, M., Hsu, C. Y., Li, Y., *et al.* (2012). Associations between kidney function and subclinical cardiac abnormalities in CKD. *J Am Soc Nephrol*, 23(10), 1725–34.

Pascual, M., Curtis, J., Delmonico, F. L., *et al.* (2003). A prospective, randomized clinical trial of ciclosporin reduction in stable patients greater than 12 months after renal transplantation. *Transplantation*, 75(9), 1501–5.

Patel, R. K., Oliver, S., Mark, P. B., *et al.* (2009). Determinants of left ventricular mass and hypertrophy in haemodialysis patients assessed by cardiac magnetic resonance imaging. *Clin J Am Soc Nephrol*, 4(9), 1477–83.

Patel, R. K., Mark, P. B., Johnston, N., *et al.* (2008). Renal transplantation is not associated with regression of left ventricular hypertrophy: a magnetic resonance study. *Clin J Am Soc Nephrol*, 3(6), 1807–11.

Paulus, W. J., Tschöpe, C., Sanderson, J. E., *et al.* (2007). How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J*, 28(20), 2539–50.

Pecoits-Filho, R., Bucharles, S., and Barberato, S. H. (2012). Diastolic heart failure in dialysis patients: mechanisms, diagnostic approach, and treatment. *Semin Dial*, 25(1), 35–41.

Perticone, F., Maio, R., Ruberto, C., *et al.* (2008). Kidney function and risk factors for left ventricular hypertrophy in untreated uncomplicated essential hypertension. *Am J Kidney Dis*, 52(1), 74–84.

Peterson, G. E., de Backer, T., Gabriel, A., *et al.* (2007). Prevalence and correlates of left ventricular hypertrophy in the African American Study of Kidney Disease Cohort Study. *Hypertension*, 50(6), 1033–9.

Pfeffer, M. A., Braunwald, E., Moyé, L. A., *et al.* (1992). Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*, 327(10), 669–77.

Pfeffer, M. A., Swedberg, K., Granger, C. B., *et al.* (2003). Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet*, 362(9386), 759–66.

Pitt, B. (2012). Plasma aldosterone levels in patients with coronary artery disease without heart failure or myocardial infarction: implications for pathophsiology, prognosis, and therapy. *Eur Heart J*, (2), 162–4.

Poornima, I. G., Parikh, P. and Shannon, R. P. (2006). Diabetic cardiomyopathy: the search for a unifying hypothesis. *Circ Res*, 98(5), 596–605.

Rigatto, C., Foley, R., Jeffery, J., *et al.* (2003). Electrocardiographic left ventricular hypertrophy in renal transplant recipients: prognostic value and impact of blood pressure and anaemia. *J Am Soc Nephrol*, 14(2), 462–8.

Ritz, E. (2009). Left ventricular hypertrophy in renal disease: beyond preload and afterload. *Kidney Int*, 75(8), 771–3.

Roberts, P. R. and Green, D. (2011). Arrhythmias in chronic kidney disease. *Heart*, 2011. 97(9), 766–73.

Rocco, M. V., Lockridge, R. S., Jr., Beck, G. J., *et al.* (2011). The effects of frequent nocturnal home haemodialysis: the Frequent Haemodialysis Network Nocturnal Trial. *Kidney Int*, 80(10), 1080–91.

Roger, S. D., McMahon, L. P., Clarkson, A., *et al.* (2004). Effects of early and late intervention with epoetin alpha on left ventricular mass among patients with chronic kidney disease (stage 3 or 4): results of a randomized clinical trial. *J Am Soc Nephrol*, (1), 148–56.

Sartori, C., Lepori, M., and Scherrer, U. (2005). Interaction between nitric oxide and the cholinergic and sympathetic nervous system in cardiovascular control in humans. *Pharmacol Ther*, 106(2), 209–20.

Selvetella, G., Hirsch, E., Notte, A., *et al.* (2004). Adaptive and maladaptive hypertrophic pathways: points of convergence and divergence. *Cardiovasc Res*, 63(3), 373–80.

Sharma, R., Pellerin, D., Gaze, D. C., *et al.* (2006). Mitral peak Doppler E-wave to peak mitral annulus velocity ratio is an accurate estimate of left ventricular filling pressure and predicts mortality in end-stage renal disease. *J Am Soc Echocardiogr*, 19(3), 266–73.

Shillingford, J. M., Leamon, C. P., Vlahov, I. R., *et al.* (2012). Folate-conjugated rapamycin slows progression of polycystic kidney disease. *J Am Soc Nephrol*, 23(10), 1674–81.

Shimizu, G., Hirota, Y., Kita, Y., *et al.* (1991). Left ventricular midwall mechanics in systemic arterial hypertension. Myocardial function is depressed in pressure-overload hypertrophy. *Circulation*, 83(5), 1676–84.

Shlipak, M. G., Katz, R., Kestenbaum, B., *et al.* (2009). Clinical and subclinical cardiovascular disease and kidney function decline in the elderly. *Atherosclerosis*, 204(1), 298–303.

Siddiqi, L., Prakken, N. H., Velthuis, B. K., *et al.* (2010). Sympathetic activity in chronic kidney disease patients is related to left ventricular mass despite antihypertensive treatment. *Nephrol Dial Transplant*, 25(10), 3272–7.

Siedlecki, A. M., Jin, X., and Muslin, A. J. (2009). Uremic cardiac hypertrophy is reversed by rapamycin but not by lowering of blood pressure. *Kidney Int*, 75(8), 800–8.

Simpson, P. (1983). Norepinephrine-stimulated hypertrophy of cultured rat myocardial cells is an alpha 1 adrenergic response. *J Clin Invest*, 72(2), 732–8.

Spoto, B., Testa, A., Parlongo, R. M., *et al.* (2012). Insulin resistance and left ventricular hypertrophy in end-stage renal disease: association between the ENPP1 gene and left ventricular concentric remodelling. *Nephrol Dial Transplant*, 27(2), 661–6.

Stack, A. G. and Saran, R. (2002). Clinical correlates and mortality impact of left ventricular hypertrophy among new ESRD patients in the United States. *Am J Kidney Dis*, 40(6), 1202–10.

Stack, A. G., Molony, D. A., Rahman, N. S., *et al.* (2003). Impact of dialysis modality on survival of new ESRD patients with congestive heart failure in the United States. *Kidney Int*, 64(3), 1071–9.

Stefenelli, T., Abela, C., Frank, H., *et al.* (1997). Cardiac abnormalities in patients with primary hyperparathyroidism: implications for follow-up. *J Clin Endocrinol Metab*, 82(1), 106–12.

Stella, P., Manunta, P., Mallamaci, F., *et al.* (2008). Endogenous ouabain and cardiomyopathy in dialysis patients. *J Intern Med*, 263(3), 274–80.

Stewart, G. A., Foster, J., Cowan, M., *et al.* (1999). Echocardiography overestimates left ventricular mass in haemodialysis patients relative to magnetic resonance imaging. *Kidney Int*, 56(6), 2248–53.

Stewart, G. A., Gansevoort, R. T., Mark, P. B., *et al.* (2005). Electrocardiographic abnormalities and uremic cardiomyopathy. *Kidney Int*, 67(1), 217–26.

Strozecki, P., Adamowicz, A., Nartowicz, E., *et al.* (2001). Parathormon, calcium, phosphorus, and left ventricular structure and function in normotensive haemodialysis patients. *Ren Fail*, 23(1), 115–26.

Susantitaphong, P., Koulouridis, I., Balk, E. M., *et al.* (2012). Effect of frequent or extended haemodialysis on cardiovascular parameters: a meta-analysis. *Am J Kidney Dis*, 59(5), 689–99.

Taheri, S., Mortazavi, M., Shahidi, S. *et al.* (2009). Spironolactone in chronic haemodialysis patients improves cardiac function. *Saudi J Kidney Dis Transpl*, 20(3), 392–7.

Tenenbaum, A., Fisman, E. Z., Schwammenthal, E., *et al.* (2003). Increased prevalence of left ventricular hypertrophy in hypertensive women with type 2 diabetes mellitus. *Cardiovasc Diabetol*, 2, 14.

Teng, M., Wolf, M., Lowrie, E., *et al.* (2003). Survival of patients undergoing haemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med*, 349(5), 446–56.

Teng, M., Wolf, M., Ofsthun, M. N., *et al.* (2005). Activated injectable vitamin D and haemodialysis survival: a historical cohort study. *J Am Soc Nephrol*, 16(4), 1115–25.

Thadhani, R., Appelbaum, E., Pritchett, Y., *et al.* (2012). Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *JAMA*, 307(7), 674–84.

Toischer, K., Rokita, A. G., Unsöld, B., *et al.* (2010). Differential cardiac remodeling in preload versus afterload. *Circulation*, 122(10), 993–1003.

Trespalacios, F. C., Taylor, A. J., Agodoa, L. Y., *et al.* (2003). Heart failure as a cause for hospitalization in chronic dialysis patients. *Am J Kidney Dis*, 41(6), 1267–77.

Tucker, B., Fabbian, F., Giles, M., *et al.* (1997). Left ventricular hypertrophy and ambulatory blood pressure monitoring in chronic renal failure. *Nephrol Dial Transplant*, 12(4), 724–8.

Wali, R. K., Iyengar, M., Beck, G. J., *et al.* (2011). Efficacy and safety of carvedilol in treatment of heart failure with chronic kidney disease: a meta-analysis of randomized trials. Circ Heart Fail, 4(1), 18–26.

Walker, M. D., Fleischer, J. B., Di Tullio, M. R., *et al.* (2010). Cardiac structure and diastolic function in mild primary hyperparathyroidism. *J Clin Endocrinol Metab*, 95(5), 2172–9.

Wang, A.Y., Fang, F., Chan, J. (2014). Effect of paricalcitol on left ventricular mass and function in CKD-the OPERA trial. *J Am Soc Nephrol*. 25; 175–86.

Wang, T. J., Pencina, M. J., Booth, S. L., *et al.* (2008). Vitamin D deficiency and risk of cardiovascular disease. *Circulation*, 117(4), 503–11.

Xu, X., Hu, X., Lu, Z., *et al.* (2008). Xanthine oxidase inhibition with febuxostat attenuates systolic overload-induced left ventricular hypertrophy and dysfunction in mice. *J Cardiac Fail*, 14(9), 746–53.

Yilmaz, R., Altun, B., Kahraman, S., *et al.* (2010). Impact of amlodipine or ramipril treatment on left ventricular mass and carotid intima-media thickness in nondiabetic haemodialysis patients. *Ren Fail*, 903–12.

Yu, W. C., Lin, Y. P., Lin, I. F., *et al.* (2006). Effect of ramipril on left ventricular mass in normotensive haemodialysis patients. *Am J Kidney Dis*, 47(3), 478–84.

Zamboli, P., De Nicola, L., Minutolo, R., *et al.* (2011). Effect of furosemide on left ventricular mass in non-dialysis chronic kidney disease patients: a randomized controlled trial. *Nephrol Dial Transplant*, 26(5), 1575–83.

Zannad, F., Kessler, M., Lehert, P., *et al.* (2006). Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. *Kidney Int*, 70(7), 1318–24.

Zhou, C., Lu, F., Cao, K., *et al.* (2008). Calcium-independent and 1,25(OH)2D3-dependent regulation of the renin-angiotensin system in 1alpha-hydroxylase knockout mice. *Kidney Int*, 74(2), 170–9.

Zoccali, C. (2008). Cardiovascular risk in patients with chronic kidney disease: not high enough to enter the major league? *Curr Hypertens Rep*, 10(1), 1–2.

Zoccali, C. (2011). Left ventricular mass index as an outcome measure in clinical trials in dialysis patients: a word of caution. *Am J Nephrol*, 33(4), 370–2.

Zoccali, C., Benedetto, F. A., Mallamaci, F., *et al.* (2001). Prognostic impact of the indexation of left ventricular mass in patients undergoing dialysis. *J Am Soc Nephrol*, 12(12), 2768–74.

Zoccali, C., Benedetto, F. A., Mallamaci, F., *et al.* (2004a). Left ventricular mass monitoring in the follow-up of dialysis patients: prognostic value of left ventricular hypertrophy progression. *Kidney Int*, 65(4), 1492–8.

Zoccali, C., Benedetto, F. A., Mallamaci, F., *et al.* (2004b). Prognostic value of echocardiographic indicators of left ventricular systolic function in asymptomatic dialysis patients. *J Am Soc Nephrol*, 15(4), 1029–37.

Zoccali, C., Mallamaci, F., Maas, R., *et al.* (2002a). Left ventricular hypertrophy, cardiac remodeling and asymmetric dimethylarginine (ADMA) in haemodialysis patients. *Kidney Int*, 62(1), 339–45.

Zoccali, C., Mallamaci, F., Tripepi, G., *et al.* (2002b). Norepinephrine and concentric hypertrophy in patients with end-stage renal disease. *Hypertension*, 40(1), 41–6.

CHAPTER 108

Sudden cardiac death in chronic kidney disease

Reza Hajhosseiny, Kaivan Khavandi, and David J. Goldsmith

Cardiorenal syndrome

The function of the kidney and the heart are closely linked, with injury to one organ frequently leading to dysfunction of the other (Schrier et al., 2007; Dar and Cowie, 2008). This bidirectional association was the impetus for coining the term 'cardiorenal syndrome' (CRS). In recent years, Ronco et al. have attempted to formalize the different clinical and mechanistic links which characterize simultaneous cardiac and renal dysfunction (Ronco et al., 2008).

The prevalence of cardiovascular disease (CVD) and incidence of death as a consequence, is high in chronic kidney disease (CKD). This CVD risk begins at an early stage of renal injury—microalbuminuria—and rapidly progresses with advancing kidney damage (Shamseddin and Parfrey et al., 2011). The Hypertension Optimal Treatment (HOT) study (Ruilope et al., 2001), which included 18,790 patients across 26 countries, showed baseline serum creatinine to be highly predictive of adverse cardiovascular outcomes. Individuals with higher baseline serum creatinine levels (> 1.5 mg/dL) had an increased relative risk for cardiovascular mortality of 3.24 (95% confidence interval (CI) 2.13–4.94; $P < 0.001$) when compared to those with a lower serum creatinine (< 1.5mg/dL), after adjusting for blood pressure, age, gender, smoking habits, previous CVD, diabetes, and total serum cholesterol. These findings have been consistently reproduced in other longitudinal, cross-sectional, and randomized studies (Hajhosseiny et al., 2013).

Subjects with CKD stage 3 (around 10% of the population) (Hajhosseiny et al., 2013) are more likely to succumb to CVD than progress to dialysis-requiring renal failure. Cardiovascular outcomes, therefore, should be the priority in patients with CKD, even at the earliest stages of disease.

Sudden cardiac death

The association between cardiac and renal disease has been thoroughly studied, but there is a paucity of studies of the most important (numerically and clinically) complication—that of sudden cardiac death (SCD). The evidence that is available supports the belief that SCD in these populations is different to that seen in the general population, with distinct mechanistic predispositions, working in concert with combinations of traditional cardiovascular insults and risk, leading to premature death.

SCD is defined as death from an unexpected circulatory arrest, usually from a cardiac arrhythmia occurring within 1 hour of the onset of symptoms, and in which medical intervention (such as defibrillation) may potentially reverse the event (Zipes et al., 2006). The incidence of SCD has a wide geographical variation, but in the United States there are thought to be between 300,000–350,000 cases per year (Gillum, 1989; Myerburg et al., 1993; Escobedo and Zack, 1996; Zheng et al., 2001; Cobb et al., 2002; Roger et al., 2011), with similar estimates in Europe (Priori et al., 2001). Using the '1 hour definition', SCD is estimated at approximately 1 death per 1000 subject years, accounting for 6–13% of all deaths in the general population (Priori et al., 2001; Chugh et al., 2004; Zipes et al., 2006). However, using a '24-hour' cut-off, SCD was shown to account for 18.5% of all deaths in a European community dwelling cohort (de Vreede-Swagemakers et al., 1997). Further broadening the definition, Parekh et al. (2008) found that SCD accounted for 22% of all deaths in 'unexpected out of hospital death from an underlying cardiac cause'. Varying definitions of SCD clearly have important implications for aetiology. For example, when using definitions with an extended time course for SCD, arrhythmia will become less of a contributing factor and thromboembolic causes become more prominent.

As already discussed, patients with end-stage renal disease (ESRD) have an extreme susceptibility to cardiovascular mortality, accounting for almost half of all deaths (Levey et al., 1998; United States Renal Data System, 1998). The rate of SCD in ESRD is particularly high, even compared to individuals with less severe renal dysfunction (Pun et al., 2009), with estimates of 60% of deaths in ESRD patients being a result of SCD (Herzog, 2003). In a large retrospective longitudinal study, Pun et al. investigated SCD in 19,440 patients with CKD (Pun et al., 2009). Overall, 522 subjects suffered SCD, with an overall rate of 4.6/1000 patient years. There was a progressive increase in the rate of SCD with increasing stages of CKD. The rate of SCD per 1000 patient years was as follows: estimated glomerular filtration rate (eGFR) 15–59 mL/min, 7.3 (95% CI 2–13); eGFR < 15 not on dialysis, 12.6 (95% CI 5–20); and dialysis, 24.2 (95% CI 14–34). Dialysed patients with ESRD therefore experience almost a three- to fourfold increased risk of SCD compared to those in stages 3–4 (moderate to severe CKD) and 20-fold higher than the general population. In another study, Wang et al. (2010) followed up 230 patients in ESRD for 5 years.

During the follow-up, 115 deaths occurred, 28 (24.3%) of which were attributed to SCD.

In the dialysis population, the incidence of SCD rises with both the time that the patient has been a dialysis patient, as well as the time since the last dialysis session (Karnik et al., 2001; Bleyer et al., 2006). Bleyer et al. (2006) reviewed 228 patients on haemodialysis, reporting a higher than expected mortality (1.7-fold) in the first 12 hours after dialysis. The rate also increased as the time since dialysis exceeded 36 hours, peaking between 60 and 72 hours after dialysis. Additionally, there was a threefold increase in the rate of mortality in the 12-hour period prior to haemodialysis at the end of the weekend interval. The 4D study investigated type 2 diabetic patients on haemodialysis in 178 German dialysis centres with a follow-up period of nearly 4 years (Ritz and Wanner, 2008). More than a quarter of all deaths were SCD, while other non-'sudden' cardiac causes (such as coronary artery disease and heart failure (HF)) accounted for 18% of cases. Table 108.1 is a compilation of all the studies that have investigated the link between CKD and SCD, demonstrating this very strong association.

Mechanisms

Standard cardiovascular risk factors contribute to the high rate of cardiac events in CKD cohorts, as was demonstrated in the Choices for Healthy Outcomes in Caring for ESRD study (Longenecker et al., 2002). The prevalence of coronary artery disease in patients with ESRD starting dialysis has been reported to be 38–40%, but this is likely to be an underestimate. Many patients have atypical symptoms, and an analysis of 67 asymptomatic haemodialysis patients showed 42% had ≥ 50% stenosis of at least one major coronary artery, and 29% had stenosis of a proximal coronary artery (Charytan et al., 2007). The HEMO study confirmed the high prevalence of coronary artery disease in dialysis patients, and showed that ischaemic heart disease accounted for 62% of hospital admissions during 2.8 years of follow-up (Cheung et al., 2004). Furthermore, secondary outcomes are worse in CKD, with in-hospital mortality after acute myocardial infarction (MI) correlating with degree of renal dysfunction: 2% in those with normal renal function, 6% with mild CKD, 21% with severe CKD, and 30% in dialysis-dependant patients (Wright et al., 2002). Similar findings were observed in the data 2–5 years post infarct (Herzog et al., 1998; Herzog, 1999).

The diagnosis and management of coronary artery disease in patients with advanced CKD remains a challenge and is based on limited evidence (Goldsmith and Covic, 2001).

The incidence of SCD is much higher in dialysis patients, than is death directly attributable to obstructive coronary artery disease (Saravanan and Davidson, 2010). Foley et al. (2005) showed that after adjustment for covariates, the odds ratios for patients with eGFR < 60 versus > 60 mL/min/1.73 m^2 were as follows: 1.3 (95% CI 1.0–1.7; P = 0.05) for body mass index > 30 kg/m^2, 40.2 (95% CI 11.1–145.1; P < 0.001) for homocysteine > 11 μmol/L, 3.5 (95% CI 2.8–4.4; P < 0.001) for anaemia, and 10.4 (95% CI 3.9–27.8; P < 0.001) for two or more cardiovascular risk factors. Whilst it is true that patients with CKD are less likely to receive cardiovascular pharmacological interventions (Shlipak et al., 2002), such as β-blockers, aspirin, angiotensin-converting enzyme inhibitors, thrombolytic therapy, and interventional procedures such as primary angioplasty (Fox et al., 2010; Szummer et al., 2011), Pun et al. (2009) showed that the relationship between eGFR and SCD persisted after accounting for medication use and revascularization therapy. Indirect support of non-atherosclerotic mechanisms comes from the poor outcome of dialysis patients following coronary artery bypass surgery. There is still a 7% annual risk of sudden death from arrhythmia after revascularization, comparable to general dialysis populations (Herzog et al., 2008). Furthermore, ischaemic electrocardiogram (ECG) changes observed on ambulatory monitoring in a cohort of dialysis patients were not associated with cardiovascular outcomes over a 2-year follow-up period (Conlon et al., 1998). The relative lack of an effect of systolic failure in predicting SCD in ESRD is remarkable (Mangrum et al., 2006a). This is in contrast to the general population. There must be other distinct mechanisms accounting for SCD in renal patients.

Endothelial dysfunction and microvascular disease

Microalbuminuria is a surrogate marker of early atherosclerosis (Stehouwer and Smulders, 2006), and consequent coronary heart disease (CHD) mortality (Agewall et al., 1995; Bigazzi et al., 1995; Jensen et al., 1995; Kuusisto et al., 1995; Pontremoli et al., 1996; Mykkanen et al., 1997). It has been postulated that microalbuminuria reflects endothelial dysfunction of small and large arteries (Stehouwer, 2004). In diabetes mellitus, microalbuminuria is accompanied by a series of markers of endothelial dysfunction. In type 1 diabetes, it is associated with increased plasma concentrations of von Willebrand factor (vWF), vascular cell adhesion molecule-1, angiotensin-converting enzyme, endothelin, and plasminogen activator inhibitor-1 (PAI-1), high urinary excretion of type IV collagen fragments, and impaired endothelium-dependent, nitric-oxide-mediated vasodilation. In type 2 diabetes, microalbuminuria is associated with elevated plasma vWF, thrombomodulin, tissue-type plasminogen activator (t-PA), PAI-1, and serum type IV collagen (Stehouwer et al., 1997). This relationship has also been shown in non-diabetic populations (Pedrinelli et al., 1994; Kario et al., 1996; Clausen et al., 1999, 2001; Volpe et al., 2003). In a small study of 20 diabetic patients, Kawagishi et al. (1999) examining L-arginine-mediated vasodilation in the brachial, central retinal, and renal interlobar arteries. In all three vascular beds, this marker of endothelial function was significantly impaired in microalbuminuric compared to normoalbuminuric individuals. The link between microalbuminuria and resistant vessel structural and functional changes has been reviewed by Khavandi et al. (2009).

A quarter of ESRD patients experience symptoms of angina in the absence of coronary artery stenosis, explained probably by microvascular disease (Elsner, 2001). Nitric oxide has vasodilator, antiplatelet, antiproliferative, antiadhesive, permeability-decreasing, and anti-inflammatory properties (Stehouwer and Smulders, 2006) and as such, any interruptions in its function or availability will significantly increase the risk of CHD. In a population-based study of 645 subjects, Stehouwer et al. (2004) investigated the relationship between microalbuminuria and endothelial nitric oxide synthesis. Microalbuminuria was defined as urinary albumin-creatinine ratio ≥ 2 mg/mmol. Endothelium-dependent, flow-mediated vasodilation (FMD), a measure of endothelial nitric oxide synthesis, and endothelium-independent, nitroglycerine-induced vasodilation (NID) of the brachial artery were measured ultrasonically. FMD was 0.12 mm in the presence of microalbuminuria, and 0.18 mm in its absence (P = 0.002). After adjustment for age, sex, baseline arterial diameter, and other potential confounders, FMD was

Table 108.1 The main studies that have investigated the association between CKD and SCD

Study	Outcome	Number of participants	Comparison	Adjustment for covariates	Result (95% CI; P value)	Statistically Significant correlation
Deo et al., 2008	Sudden cardiac death	2760	eGFR	> 60 mL/min/1.73 m^2 < 60 vs ≥ 40 mL/min/1.73 m^2 < 40 mL/min/1.73 m^2	3.5% 4.6% 13%	Positive
Deo et al., 2008	Sudden cardiac death	2760	eGFR 40–60 mL/min/1.73 m^2 vs > 60 mL/min/1.73 m^2 eGFR < 40 mL/min/1.73 m^2 vs > 60 mL/min/1.73 m^2	None	HR 1.36 (95% CI 0.91–2.04; P < 0.001) HR 4.65 (95% CI 2.86–7.55; P > 0.001)	Positive
Deo et al., 2008	Sudden cardiac death	2760	eGFR 40–60 mL/min/1.73 m^2 vs > 60 mL/min/1.73 m^2 eGFR < 40 mL/min/1.73 m^2 vs > 60 mL/min/1.73 m^2	Multivariate	HR 1.14 (95% CI 0.76–1.74; P < 0.001) HR 3.16 (95% CI 1.88–5.33; P > 0.001)	Positive
Chonchol et al., 2007	Sudden cardiac death	N/A	eGFR < 75 mL/min/1.73 m^2 vs > 75 mL/min/1.73 m^2	Multivariate	HR 2.00 (95% CI 1.01–4.02)	Positive
Goldenberg et al., 2006	Sudden cardiac death	1232	Every 10 unit reduction in eGFR	Multivariate	HR 1.17 (95% CI 1.01–1.36; P = 0.03)	Positive
Pun et al., 2009	Sudden cardiac death	19,016	eGFR 15–59 mL/min/1.73 m^2 vs > 60 mL/min/1.73 m^2	None	HR 1.88 (95% CI 1.56– 2.28; P < 0.0001)	Positive
Pun et al., 2009	Sudden cardiac death	19,440	Every 10 unit reduction in eGFR	Multivariate	HR 1.11 (95% CI 1.06–1.17; P < 0.001)	Positive
Pun et al., 2009	Sudden cardiac death	19,440	eGFR < 15mL/min/1.73 m^2 vs > 60 mL/min/1.73 m2	None	HR 4.68 (95% CI 3.06–7.17)	Positive
Ritz and Wanner, 2008	Sudden cardiac death	178 dialysis centres	Haemodialysis and SCD	Incidence	26%	Positive
Ganesh et al., 2001	Sudden cardiac death	12,833	Haemodialysis and SCD	Incidence	27%	Positive
Ganesh et al., 2001	Sudden cardiac death	12,833	Serum PO4 > 6.5 mg/dL vs 2.4–6.5 mg/dL	Multivariate	RR 1.20 (P < 0.005)	Positive
Ganesh et al., 2001	Sudden cardiac death	12,833	Per 1 mg/dL increase in serum PO4	Multivariate	RR 1.05 (P < 0.001)	Positive
Saravanan and Davidson, 2010	Sudden cardiac death	Prevalent dialysis patients in the United States, 2005–2007	Dialysis and SCD	Incidence	26.3%	Positive
Genovesi et al., 2009	Sudden cardiac death	476	Dialysis and SCD	Incidence	30%	Positive
Parekh et al., 2008	Sudden cardiac death	1041	Dialysis and SCD	Incidence	22.2%	Positive
Go et al., 2004	Any cardiovascular events	1,120,290	eGFR < 15 mL/min/1.73 m^2 vs > 60 mL/min/1.73 m^2	Multivariate	HR (95% CI 3.1–3.8)	Positive

(*Continued*)

Table 108.1 (Continued)

Study	Outcome	Number of participants	Comparison	Adjustment for covariates	Result (95% CI; P value)	Statistically Significant correlation
Soman et al., 2002	Complete heart block	2254	Long-term dialysis vs corrected-CrCl 81.5 mL/min/72 kg	Multivariate	HR 3.64 (95% CI 1.77–7.48; P = 0.0004)	Positive
Soman et al., 2002	Asystole	2254	Long-term dialysis vs corrected-CrCl 81.5 mL/min/72 kg	Multivariate	HR 2.36 (95% CI 1.00–5.57; P = 0.05)	Positive
Soman et al., 2002	Sustained ventricular tachycardia	2254	Long-term dialysis vs corrected-CrCl 81.5 mL/min/72 kg	Multivariate	HR 2.07 (95% CI 1.02–4.22; P = 0.04)	Positive
Soman et al., 2002	Ventricular fibrillation	2254	Long-term dialysis vs corrected-CrCl 81.5 mL/min/72 kg	Multivariate	HR 2.42 (95% CI 1.13–5.15; P = 0.02)	Positive
Beattie et al., 2001	Ventricular fibrillation	731	Chronic dialysis vs corrected-CrCl 81.5 mL/min/72 kg	None	OR 2.95 (95% CI 0.95–9.22; P = 0.07)	Borderline Positive
Beattie et al., 2001	Complete heart block	731	Chronic dialysis vs corrected-CrCl 81.5 mL/min/72 kg	None	OR 5.88 (95% CI 1.42–24.34; P = 0.03)	Positive
Beattie et al., 2001	Asystole	731	Chronic dialysis vs corrected-CrCl 81.5 mL/min/72 kg	None	OR 11.84 (95% CI 2.32–60.41; P = 0.009)	Positive
Beattie et al., 2001	Acute mitral regurgitation	731	Chronic dialysis vs corrected-CrCl 81.5 mL/min/72 kg	None	OR 7.08 (95% CI 1.64–30.60; P = 0.02)	Positive
Beattie et al., 2001	Cardiogenic shock	731	Chronic dialysis vs corrected-CrCl 81.5 mL/min/72 kg	None	OR 4.09 (95% CI 1.73–9.68; P = 0.003)	Positive

0.038 mm (95% CI 0.001–0.075) lower when microalbuminuria was present (P = 0.04), and decreased linearly across microalbuminuria categories (by 0.027 mm (0.007–0.046) per category increase of microalbuminuria; P = 0.007). NID was similar in individuals with and without microalbuminuria. Results were similar in individuals regardless of diabetes. Accumulation of asymmetric dimethylarginine inhibits nitric oxide synthesis in endothelial cells, causing endothelial injury and vasoconstriction, which combined are pro-atherosclerotic (Ravani et al., 2005).

Dyslipidaemia

Microalbuminuria is also associated with deranged lipid profiles (Chaturvedi et al., 2001). Kahri et al. (1994) compared the lipid concentrations of 52 microalbuminuric patients with 64 normoalbuminuric patients. Median concentration of high density lipoprotein (HDL) and HDL2 cholesterol was 11.6 (P = 0.01) less in microalbuminuric patient compared with normoalbuminuric patients. HDL cholesterol: apoA-I + apoA-II ratio was significantly lower in micro- (19.7 ± 4.2 (± standard deviation (SD)); P < 0.01) than in normoalbuminuric patients (22.1 ± 4.4). Post-heparin plasma lipoprotein lipase: hepatic lipase ratio was lower in microalbuminuric patients compared with normoalbuminuric patients (1.65 vs 1.05 (median), P < 0.01). Plasma cholesteryl ester transfer protein activity was higher in the patients with microalbuminuria than in normoalbuminuric patients (P < 0.05). In a similar study, Jones et al. (1989) observed that patients with microalbuminuria had significantly higher concentrations of low density lipoprotein (LDL) cholesterol (mean 3.33 (standard error (SE) 0.20) vs 2.84 (0.12) mmol/L) and very low-density lipoprotein cholesterol (0.30 (0.05) vs 0.17 (0.03) mmol/L) than controls but significantly lower concentrations of HDL2 subfraction cholesterol (0.32 (0.04) vs 0.54 (0.04) mmol/L). Concentrations of total triglyceride (1.11 (0.14) vs 0.68 (0.08) mmol/L), very LDL triglyceride (0.56 (0.10) vs 0.30 (0.05) mmol/L), apolipoprotein B (0.88 (0.06) vs 0.67 (0.03) g/L), fibrinogen (2.2 (0.1) vs 1.9 (0.1) g/L), and diastolic arterial pressure (80 (2) vs 74 (2) mmHg), were also higher in patients with microalbuminuria. Endothelial dysfunction increases permeability of arteries, giving rise to microalbuminuria, which in turn is damaging to blood vessels, initiating a vicious cycle of endothelial injury. When combined with an atherosclerotic lipid profile, the effect of prerenal disorders on cardiovascular morbidity can be appreciated (Deckert et al., 1989; Heymann et al., 2012; Jenkins and Goldsmith, 2012).

Inflammation

Chronic low-grade inflammation has been linked to CVD when associated with microalbuminuria. Low-grade inflammation is an early marker of many conditions including CVD and is typically assessed by measuring plasma levels of C-reactive protein and cytokines such as interleukin (IL)-6 and tumour necrosis factor alpha (Stehouwer and Smulders, 2006). Several studies looking into these biomarkers have shown that low-grade inflammation is independently associated with microalbuminuria, loss of renal function, and development and progression of CVD (Jager et al., 2002; Stehouwer et al., 2002; Schram et al., 2005). As renal function declines, concentrations of inflammatory cytokines increase. Inflammation has been proposed as a trigger of SCD through premature atherosclerosis and cytokine-induced plaque instability, as well as direct effects on myocardial conduction (Parekh et al., 2008; Shamseddin and Parfrey, 2011). High concentrations of the inflammatory marker homocysteine have been associated with atherothrombotic events and cardiovascular mortality in haemodialysis patients (Ducloux et al., 2000; Mallamaci et al., 2002; Ganji and Kafai, 2003; Heinz et al., 2009; The Renal Association 2010). Hard-endpoint randomized clinical trial interventional studies with folate, and vitamin B_{12} have consistently been negative (Weiner et al., 2012). Other cytokines, including IL-6, may contribute to arrhythmias through ion channel dysfunction (Parekh al., 2008). A number of other biomarkers for coronary ischaemia are in development, for example, ischaemia modified albumin which has been shown to increase sensitivity and specificity for detecting ischaemia and consequent cardiac mortality when used in combination with troponin levels (Sharma et al., 2006). Single-photon emission computed tomography using the iodinated fatty acid analogue iodine-123 methyliodophenyl-pentadecanoic acid and ^{201}thallium chloride, can identify impaired myocardial fatty acid metabolism secondary to ischaemia and has the potential to identifying ESRD patients at risk of SCD (Nishimura et al., 2008).

Electrolyte disturbances

Haemodialysis itself is pro-arrhythmic—reflected by the decline in SCD after renal transplantation (United States Renal Data System, 2006) and conversely the sudden increase in SCD when re-commencing dialysis in failing transplants (Messa et al., 2008). The contribution of dialysis per se to SCD is multifactorial, but the most important mechanism is likely to be the large and sudden shifts in fluid and electrolytes, which provoke arrhythmias (Yetkin et al., 2000; Burton et al., 2008). The incidence of SCD is substantially higher in the 12 hours before and after haemodialysis (Bleyer et al., 2006; Shamseddin and Parfrey, 2011). This could in part be explained by the rapid reduction in electrolyte concentration, in particular potassium during dialysis (Kanbay et al., 2011). Pun et al. (2009) showed the electrolyte composition of the dialysate contributes to rapid fluctuations in plasma electrolytes, which may cause cellular membrane repolarization instability, leading to arrhythmias (Shamseddin and Parfrey, 2011). Even after adjusting for covariates, low potassium and low calcium dialysate remain independent risk factors for SCD (Kovesdy et al., 2007). Cardiac arrests are also more frequent after the 2-day gap from the previous haemodialysis session, supporting the importance of volume status in arrhythmia generation (Santoro et al., 2008).

If arrhythmias in dialysis patients were simply attributable to electrolyte imbalance and shifts, one would expect lower rates of SCD with peritoneal dialysis compared with haemodialysis. Although there is an initial advantage associated with peritoneal dialysis, this is likely to be attributable to the lesser burden of comorbidity in these individuals (Collins et al. 2002) and differences in baseline renal function (Jansen et al., 2002). Indeed, after several years of initiating renal replacement therapy, SCD rates are similar in haemodialysis and peritoneal dialysis (United States Renal Data System, 2006). A number of studies have investigated dialysis dosing (Port et al., 2002), frequency (Marshall et al., 2006), and modality (Cheung et al., 2003) for differences in cardiovascular outcomes. These have largely been inconclusive, although high-flux haemodiafiltration (Cheung et al., 2003) and short daily haemodialysis

seem to be associated with an improved prognosis. Culleton et al. demonstrated regression in left ventricular (LV) mass with frequent nocturnal haemodialysis, whilst conventional regimens were associated with hypertrophy (Culleton et al., 2007).

Calcium, phosphate, and vitamin D

Derangements of plasma calcium, phosphate, parathyroid hormone, and vitamin D concentrations are extremely common in CKD. Hyperphosphataemia is evident from CKD stage 4, and is common in ESRD present in 40–80% of patients undergoing haemodialysis (Block et al., 1998). Hyperphosphataemia is associated with secondary hyperparathyroidism, vascular smooth muscle proliferation, vascular calcification, and coronary atherosclerosis (Schwarz et al., 2000; Shamseddin and Parfrey, 2011) as well as mortality (Block et al., 1998).

Ganesh et al. (2001) showed that patients with serum PO_4 > 2 mmol/L had a 20% higher risk of SCD than those with serum PO_4 < 2 mmol/L (P < 0.005), and with every 0.3 mmol/L increase in serum PO_4, the relative risk of SCD increased by 5% (P < 0.001). There was also an association between parathyroid hormone and SCD. Due to the intricate negative feedback mechanisms involved in mineral bone metabolism, changes in the plasma phosphate influence calcium levels. Given the crucial importance of intracellular calcium in excitation-contraction coupling of the heart, it is conceivable that such variations may interfere with electrical stability, resulting in abnormal conduction and late potential formation (Bozbas et al., 2007; Kanbay et al., 2011). Calcification secondary to hyperphosphataemia may also contribute to microvascular dysfunction (Amann and Ritz, 2000).

Vitamin D has biological effects beyond mineral and bone metabolism. Vitamin D insufficiency or deficiency is very common in the CRS, and the majority of haemodialysis patients have effective vitamin D deficiency (Peterlik and Cross, 2005; Holick, 2007; London et al., 2007; Nibbelink et al., 2007; Wolf et al., 2007; Wang et al., 2008; Barreto et al., 2009; Mehrotra et al., 2009; Pecovnik-Balon et al., 2009; Ravani et al., 2009; Drechsler et al., 2010), predominantly but not exclusively from impaired kidney production of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) (Drechsler et al., 2010). Drechsler et al. (2010) measured 25(OH)D in 1108 diabetic haemodialysis patients who participated in the German Diabetes and Dialysis Study and were followed up for a median of 4 years. Patients with severe vitamin D deficiency (25(OH)D of < 25 nmol/L) had a threefold higher risk of SCD compared with those with sufficient 25(OH)D concentrations > 75 nmol/L (hazard ratio (HR) 2.99; 95% CI 1.39–6.40). Furthermore, cardiovascular events and all-cause mortality were strongly increased (HR 1.78; 95% CI 1.18–2.69, and HR 1.74; 95% CI 1.22–2.47, respectively), all persisting in multivariate models. Recent observational evidence suggests strong links between low vitamin D levels and an impressive range of cardiovascular and renal pathology (Peterlik and Cross, 2005; Holick, 2007; Wang et al., 2008; Drechsler et al., 2010), including stroke, MI, sudden cardiac death, LV mass and function, arterial calcification, hypertension, diabetes, albuminuria, and chronic kidney disease. The potential mechanisms of action vary, with the ubiquitously expressed vitamin D receptor, fibroblast growth factor 23, redox pathways, and the renin–angiotensin–aldosterone system all playing a role (Green et al., 2006; Nibbelink et al., 2007; Chen et al., 2008; Tishkoff et al., 2008; Drechsler et al., 2010). Vitamin D has also been shown to have anti-inflammatory effects by down regulation of prostaglandins and nuclear factor kappa B (McCarty, 2004; Moreno et al., 2005; Krishnan and Feldman, 2010) There is no randomized controlled trial data so guidelines do not recommend supplementation for purposes beyond prevention of CKD-mineral and bone disorders (Covic et al., 2010).

Vascular calcification

Disordered calcium homeostasis results in diffuse myocardial and vascular calcification, resulting in reduced coronary flow during diastole (Shamseddin and Parfrey, 2009). These fibrotic and calcific changes are associated with conduction defects and arrhythmias (Myerburg, 2001). Coronary artery calcification (CAC) represents the atherosclerotic burden for CHD and cardiac mortality (Wexler et al., 1996). In a population-based study, Nakano et al. (2010) investigated 126 patients with CKD for evidence of atherosclerosis and calcification. Adjusted odds ratio for eGFR < 30 versus > 60 mL/min/1.73 m^2 and vascular calcification was 4.71 (95% CI 1.78–12.50, P = 0.002). Di Iorio et al. (2006) investigated cardiac calcification and QT dispersion in 32 haemodialysis and 12 CKD stage 4 patients. A significantly greater number of patients receiving haemodialysis (62.5%) showed cardiac calcification than those with CKD stage 4 (33%; P = 0.01). QT dispersion showed a linear correlation with calcification scores in both groups (r = 0.899 and P < 0.0001 and r = 0.901 and P < 0.0001). In a recent randomized controlled trial, Di Iorio et al. (2012) demonstrated significant regression of CAC in CKD patients who were taking the phosphate binder sevelamer, with an equally significant reduction in all-cause mortality (Di Iorio et al., 2011). In addition to myocardial fibrosis and vascular calcification, disordered mineral bone metabolism can also lead to valvular abnormalities. Studies have shown that up to 40% of ESRD patients have mitral annular calcification, which is in-turn associated with coronary disease and all-cause mortality (Sharma et al., 2007).

Autonomic dysfunction

Renal and CVD is also linked by cardiovascular autonomic dysfunction (C-AD) (Beijers et al., 2009). Microalbuminuria has been shown to be strongly associated with C-AD in several studies (Jermendy et al., 1996; Ritz and Stefanski, 1996; Wirta et al., 1999; Smulders et al., 2000; Moran et al., 2004). C-AD has also been linked to CVD and mortality (Gerritsen et al., 2001; Maser et al., 2003). Various pathophysiological pathways have been proposed including impaired heart rate variability (HRV), resting tachycardia, exercise intolerance, abnormal blood pressure regulation, and orthostatic hypotension (Pop-Busui, 2010). Beijers et al. (2009) investigated the link between microalbuminuria, C-AD, and CVD, by following 490 individuals aged 50–75 years for a median of 13.6 years. Microalbuminuria was defined as an albumin-to-creatinine ratio > 2.0 mg/mmol in an early-morning spot-urine sample. After adjustments for age, sex, glucose tolerance, and other risk factors, C-AD was found to be associated with microalbuminuria (β = 0.16 (95% CI 0.01–0.33)). Both microalbuminuria (relative risk 2.09 (1.07–4.08)) and C-AD (1.74 (1.04–2.89)) were associated with cardiovascular mortality.

Renal injury promotes sympathetic overactivity (Ye et al., 1998) and ESRD is characterized by unopposed sympathetic activity (Converse et al., 1992). Renal norepinephrine release is enhanced by 30% in the cortex of subtotally nephrectomized rats

(Rump et al., 2000) and human studies have shown an association between high circulating levels of norepinephrine in ESRD and SCD (Zoccali et al., 2002). Sympathetic overactivity is particularly pronounced during haemodialysis sessions. Reduced release of the enzyme renalase from injured kidneys has also been implicated in disordered autonomic activity (Xu et al., 2005).

HRV describes the variation in the beat-to-beat interval of the heart rate (Kanbay et al., 2011) and is a surrogate of physiological autonomic regulation—the balance between sympathetic and parasympathetic drive which governs heart rate (Kanbay et al., 2011). A decreased HRV has been shown to be associated with increased risk of ventricular arrhythmias and cardiac death in the general population (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Green et al., 2006; Kanbay et al., 2011). Individuals receiving both haemodialysis and peritoneal dialysis have a reduced HRV (Green et al., 2011). In a small study of 32 haemodialysis patients (Coquet et al., 2005), parasympathetic activity during the non-dialytic period was significantly reduced. In another study of 175 haemodialysis patients with left ventricular hypertrophy (LVH) (Nishimura et al., 2010), HRV was a strong predictor of SCD. SCD-free survival rates at 5 years were 29.4% and 98.1% in patients with low frequency:high frequency ratios of 1.9 (reflecting sympathetic over activity) or more, and below 1.9 (without sympathetic over activity), respectively. In 95 patients on haemodialysis or peritoneal dialysis, or with CKD stages 4–5, Roumelioti et al. (2010) showed that patients with ESRD exhibited disordered autonomic nervous system tone, manifesting as a failure to increase HRV during wakefulness and sleep. Furuland et al. (2008) showed that the autonomic dysregulation and reduced HRV observed in ESRD is also seen in less advanced CKD 4. This study showed that treating anaemia, at least in part, reversed this dysfunction and increased HRV. Two other studies have shown that renal transplantation may improve HRV and restore the autonomic regulation to near normal (Rubinger et al., 2009; Yang et al., 2010). Nishimura et al. (2004, 2010) showed that impaired parasympathetic activity, and the cardiovascular autonomic neuropathy seen in diabetic individuals on haemodialysis closely correlated with LVH. The ratio between low-frequency and high-frequency measures of HRV reflects sympathetic/vagal balance, and has been shown to predict SCD in dialysis populations (Saravanan et al., 2010) and among haemodialysis patients with LVH (Nishimura et al., 2010). Baroreceptor sensitivity and baroreflex effectiveness indices are other measures of autonomic responsiveness and have also been shown to be predictive of SCD in CKD (Johansson et al., 2007).

Electrocardiographic markers and LV structure and function

Myocardial haemodynamics and remodelling

LV mass, composition, and geometry are altered early in renal disease. LVH increases as renal function declines, with 75% of patients starting dialysis having LVH (Foley et al., 1998b) and this progresses while they continue on dialysis treatment (Foley et al., 1998a). Stewart et al. (2005) investigated 296 patients with various degrees of CKD and demonstrated a degree of LVH in all stages of renal disease, progressively worsening as the stage of CKD advanced. Levin et al. (1996) investigated LVH in 175 pre-dialysis patients, demonstrating more prevalent and severe LVH with progressive decline in renal function. 26.7% of patients with creatinine clearance (Ccr) > 50 mL/min; 30.8% of those with Ccr between 25 and 49 mL/min, and 45.2% of patients with severe renal impairment (Ccr < 25 mL/min) had LVH respectively ($P = 0.05$). The mean left ventricular mass index (LVMI) differed significantly between the three groups (97.5 g/m^2 vs 100.8 g/m^2 vs 114.4 g/m^2, respectively; $P < 0.001$). The extent of LVH and fibrosis was more severe still in patients with ESRD (Mark et al., 2006; Kanbay et al., 2011).

LVH is predictive of cardiac death in dialysis patients independent of blood pressure and is associated with a 60% increased risk of SCD in diabetic patients on dialysis (Krane et al., 2009). Regression of LVH confers a survival advantage (London et al., 2001). Uraemia is associated with a number of deleterious redox and pro-inflammatory changes (Roberts and Green, 2011) and in patients with CKD, the term 'uraemic cardiomyopathy' describes the abnormal structural remodelling of the heart, with LVH, fibrosis, and consequent diastolic and systolic dysfunction (Ix et al., 2006; Deo et al., 2008; Pun et al., 2009).

Endomyocardial biopsies in dialysis patients with dilated cardiomyopathy show remodelling with interstitial fibrosis and myocyte hypertrophy (Roberts and Green, 2011). This can be seen as diffuse late gadolinium enhancement on magnetic resonance imaging (Mark et al., 2006). Fibrotic tissue interferes with normal conducting systems in the myocardium, which when combined with the profound electrolyte derangements seen in CKD (Soman et al., 2002), could trigger arrhythmias (Dhoble et al., 2008; Kanbay et al., 2011). Myocardial fibrosis is associated with increased dispersion of repolarization, which is associated with arrhythmias (Tun et al., 1999). Furthermore, as the diameter and length of the myocytes increase in uraemia, the capillary length per unit myocardial volume decreases, so-called vascular rarefaction, resulting in a myocyte/capillary mismatch (Amann et al., 1998; Drueke and Massy, 2010). It is thought that the resultant ischaemia, particularly during high oxygen demand could contribute to increased arrhythmogeneity (Yang et al., 2007; Kanbay et al., 2011). Iron overload is also common in ESRD and has been shown to be prognostic (Besarab, 1999), possibly through causing intercardiomyocytic fibrosis (Wardman and Candeias, 1996) and conduction abnormalities. Indeed, high iron saturation has been shown to correlate with QTc dispersion (Wu et al., 2004).

Patients on regular haemodialysis are subjected to significant haemodynamic insults, with 20–30% of sessions resulting in significant intra-dialytic hypotension (Kanbay et al., 2011). Anaemia and hypovolaemia can have deleterious effects on preload, contributing to aberrant myocardial haemodynamics and consequent arrhythmias. This helps to explain the association between anaemia and the development of LVH (Foley et al., 1996). Although studies targeting anaemia by administration of erythropoiesis-stimulating agents have shown some benefit in cardiovascular parameters (Frank et al., 2004), the optimal haemoglobin levels have not been defined, and correction of anaemia is not recognized as a means to prevent SCD. Nonetheless, anaemia could act synergistically with local ischaemia, leading to regional wall motion abnormalities and ultimately LV systolic dysfunction (McIntyre, 2010; Kanbay et al., 2011). Myocardial stunning (Burton et al., 2009; Kanbay et al., 2011), causing temporary reversible systolic impairment, has been

implicated in the increased incidence of SCD in haemodialysis patients compared to peritoneal dialysis (62.2 vs 42.8 events/1000 patient-years) (Green et al., 2011).

Late potential

A number of ECG markers, including QRS duration, QT interval, and QT dispersion, have been proposed as predictors of arrhythmias in dialysis patients (Stewart et al., 2005). Signal averaged ECG (SAECG) is a high-resolution ECG technique using multiple electric signals, averaged to remove interference and reveal small variations in the terminal deflection of the QRS complex—the late potential (LP) (Goldberger et al., 2008; Saravanan and Davidson, 2010). LPs represent areas of delayed and abnormal ventricular activation, which act as a focus for malign re-entrant arrhythmias (Morales et al., 1998; Twahir et al., 1999; Windhagen-Mahnert et al., 2000; Kanbay et al., 2011).

A common trigger to LPs is scarred and fibrosed myocardium, which result in aberrant conduction. Studies have shown that 20–25% of the dialysis population have evidence of LPs at baseline (Morales et al., 1998), significantly higher than in the general population (0–7%) (Denes et al., 1983; Morales et al., 1998). Premature ventricular complexes correlate with LVH in haemodialysis patients (Sforzini et al., 1992) and severe ventricular ectopy and non-sustained ventricular tachycardia are more common in ESRD patients–the frequency increases before and after the dialysis session (Meier et al., 2001).

QT dispersion

QTc dispersion is defined as the difference between the longest and shortest QT intervals in a 12-lead ECG recording (Kanbay et al., 2011). Patients with chronic renal failure have greater QTc intervals and QTc dispersion compared with those with normal renal function (Yildiz et al., 2001; Kantarci et al., 2002). These are associated with polymorphic ventricular tachycardia (torsade de pointes) and SCD (Patane et al., 2008). Patients with ESRD have significant LVH (Foley et al., 1995) and intercardiomyocytic fibrosis (Stewart et al., 2005), which results in incongruous depolarization and repolarization. Dialysis has been shown to prolong the QTc interval, and this appears to correspond with fluctuations in serum calcium levels (Covic et al., 2002). Moreover, even a single session of haemodialysis increases QT dispersion in both adults and children (Cupisti et al., 1998; Lorincz et al., 1999; Morris et al., 1999; Ozdemir et al., 2005). Dialysis patients with a QTc dispersion > 74 ms have been shown to be at risk of serious ventricular arrhythmias or sudden death (Beaubien et al., 2002; Wang et al., 2002). In a small study of 21 uraemic and 21 non-uraemic patients, Wang et al. (2002) showed that uraemic patients with acute MI had greater QTc dispersion (84 vs 55 ms, $P < 0.001$) and greater 1-year mortality rates (48% vs 18%, $P = 0.003$). They were less likely to receive reperfusion therapies (5/21 vs 17/21 patients, $P = 0.002$) compared with non-uraemic patients with acute MI. A number of other factors have also been implicated in the greater QTc dispersion in haemodialysis patients. These include age, LDL cholesterol, phosphate levels, iron stores, parathyroid hormone, and low dialysate calcium and potassium levels (Wu et al., 2005; Di Iorio et al., 2006; Genovesi et al., 2009). In addition, Di Iorio et al. demonstrated a significant positive association between CAC and QTc interval, suggesting a protective role for agents such sevelamer which oppose CAC progression (Di Iorio et al., 2011).

T-wave alternans

Microvolt T-wave alternans (TWA), or repolarization alternans, is a measure of beat-to-beat variations in the timing, amplitude, or morphology of the T wave in the ECG (Kanbay et al., 2011). Regional or temporal dispersion of repolarization is the mechanism and therefore a measure of abnormal ventricular repolarization, and a surrogate for measuring arrhythmias and SCD (Kanbay et al., 2011). In a pilot study measuring TWA in nine patients before and immediately after an early week haemodialysis session, seven of nine individuals had non-negative (i.e. higher risk) tracings either before or after haemodialysis. Of the four subjects with tracings initially negative, two became non-negative after haemodialysis (Friedman et al., 2007). Secemsky et al. (2011) recorded HRV, heart rate turbulence (HRT), and TWA in 28 haemodialysis patients. Abnormalities were common, with 82%, 75%, and 96% of patients reaching threshold for HRV, HRT, and TWA respectively in at least one 24-hour period. Patel et al. (2011) compared 200 ESRD patients with 30 LVH patients and found that abnormal microvolt TWA were more common in ESRD compared than in patients with LVH (57.5% vs 26.7%, respectively, $P = 0.002$). In ESRD patients, microvolt TWA was significantly associated with uraemic cardiomyopathy, clinical history of atherosclerosis (coronary, cerebral, peripheral) and diabetes mellitus, older age, and haemodialysis therapy.

Prevention of sudden cardiac death in chronic kidney disease

Statins

The use of statins in CKD is generally recommended, as it is shown to reduce the incidence of cardiac events (see Chapters 102, 99). However reductions in mortality have not been evident in several studies, even in ESRD, a group with particularly high mortality is likely to be explained by the significant structural changes to the myocardium, and propensity to arrhythmia at this stage of renal disease (Green et al., 2011).

Beta blockers

Beta blockers are the established standard pharmacotherapy in secondary prevention of ischaemic heart disease, and their benefits are thought to be largely attributable to reducing SCD (de Bie et al., 2009). As a result of the exclusion from clinical trials, there is limited data on the use of antiarrhythmic drugs in advanced stages of CKD. Given the sympathetic overactivity typical of CKD and ESRD, a benefit of beta blockade would be plausible. Foley et al. (2002) demonstrated the significant survival advantage associated with beta-blocker therapy in dialysis patients, and other studies have confirmed this benefit in preventing SCD after aborted cardiac arrests. Cice et al. (2003) randomized 114 patients with dilated cardiomyopathy receiving dialysis to carvedilol or placebo. At 2 years, 51.7% of patients in the carvedilol group died, compared with 73.2% in the placebo group ($P < 0.01$). Furthermore, there were significantly fewer cardiovascular deaths (29.3%) and hospital admissions (34.5%) among patients receiving carvedilol than among those receiving a placebo (67.9% and 58.9%, respectively; $P < 0.00001$). Pun et al. (2007) studied cardiac arrests in 729 dialysis patients between 2002 and 2005 and found that use of beta

blockers was associated with a dose-dependent increase in survival. However, in a post hoc analysis of 4217 CKD patients by Wali et al. (2011), treatment with carvedilol decreased the risks of all-cause mortality (HR 0.76; 95% CI 0.63–0.93; P = 0.007), cardiovascular mortality (HR 0.76; 95% CI 0.62–0.94; P = 0.011), HF mortality (HR 0.68; 95% CI 0.52–0.88; P = 0.003), first hospitalization for HF (HR 0.74; 95% CI 0.61–0.88; P = 0.0009), and the composite of cardiovascular mortality or HF hospitalization (HR 0.75; 95% CI 0.65–0.87; P < 0.001) but there was no significant effect on SCD (HR 0.76; 95% CI 0.56–1.05; P = 0.098). The above data, though not high-level evidence, supports the use of beta blockers in CKD. These agents are, however, under-utilized in ESRD, with reports showing < 30% of haemodialysis patients receiving them (Abbott et al., 2004). There are many reasons for this and some of the rationale for exclusion in these patients is justified (e.g. hypotensive and hyperkalaemic complications), more patients would be likely to

Table 108.2 Summary of studies investigating the link between beta blockers, CKD and SCD

Study	Outcome	Population	Comparison	Hazard ratio (95% CI), P value	Statistically Significant
Cice et al., 2003	All-cause mortality	114 on dialysis	Carvedilol vs placebo	0.51 (0.32–0.82), P < 0.01	Positive
Cice et al., 2003	All cardiovascular mortality	114 on dialysis	Carvedilol vs placebo	0.32 (0.18–0.57), P < 0.0001	Positive
Cice et al., 2003	Sudden deaths	114 on dialysis	Carvedilol vs placebo	0.76 (0.52–1.13), P = 0.12	Negative
Cice et al., 2003	Hospital admission for worsening heart failure	114 on dialysis	Carvedilol vs placebo	0.19 (0.09–0.41), P < 0.00001	Positive
Pun et al., 2007	24-hour mortality following cardiac arrest	729 on dialysis	Beta blocker vs no beta blocker	0.61 (0.44–0.86), P = 0.005	Positive
Pun et al., 2007	6-month mortality following cardiac arrest	729 on dialysis	Beta blocker vs no beta blocker	0.32 (0.17–0.61), P = 0.0006	Positive
Wali et al., 2011	Cardiovascular mortality	2566 CKD patients (eGFR ≤60 mL/min/1.73 m^2)	Carvedilol vs placebo	0.77 (0.62–0.94)	Positive
Wali et al., 2011	First hospitalization for HF	2566 CKD patients (eGFR ≤60 mL/min/1.73 m^2)	Carvedilol vs placebo	0.74 (0.62–0.88)	Positive
Wali et al., 2011	Sudden cardiac death	2566 CKD patients (eGFR ≤60 mL/min/1.73 m^2)	Carvedilol vs placebo	0.76 (0.56–1.05)	Negative
Wali et al., 2011	HF mortality	1450 CKD patients (eGFR ≥45–60 mL/min/1.73 m^2)	Carvedilol vs placebo	0.52 (0.35–0.77)	Positive
Wali et al., 2011	Hospitalization for HF	1450 CKD patients (eGFR ≥45–60 mL/min/1.73 m^2)	Carvedilol vs placebo	0.62 (0.50–0.77)	Positive
Wali et al., 2011	Sudden cardiac death	1450 CKD patients (eGFR ≥45–60 mL/min/1.73 m^2)	Carvedilol vs placebo	0.62 (0.41–0.94)	Positive
Wali et al., 2011	HF mortality	1116 CKD patients (eGFR ≤45 mL/min/1.73 m^2)	Carvedilol vs placebo	0.86 (0.61–1.21)	Negative
Wali et al., 2011	Hospitalization for HF	1116 CKD patients (eGFR ≤45 mL/min/1.73 m^2)	Carvedilol vs placebo	0.92 (0.75–1.13)	Negative
Wali et al., 2011	Sudden cardiac death	1116 CKD patients (eGFR ≤45 mL/min/1.73 m^2)	Carvedilol vs placebo	1.04 (0.64–1.71)	Negative
Tangri et al., 2011	Sudden cardiac death	1747 on haemodialysis	Beta blocker vs no beta blocker	0.87 (0.62–1.22)	Negative
Tangri et al., 2011	Sudden cardiac death	1747 on haemodialysis with IHD	Beta blocker vs no beta blocker	0.65 (0.42–1.01), P = 0.03	Positive
Chonchol et al., 2008	Acute MI/sudden cardiac death	245	Beta blocker	1.03 (0.74–1.42)	Positive
		323	No beta blocker	1.29 (1.01–1.66)	

HF = heart failure; IHD = ischaemic heart disease; MI = myocardial infarction.

benefit from their use (Furgeson and Chonchol, 2008). Table 108.2 summarizes the main studies that have investigated the effectiveness of beta blockers on SCD.

Implantable cardioverter defibrillators

In the general population, use of implantable cardioverter defibrillators (ICDs) has consistently been proven to be superior to medical therapy in the prevention of SCD (de Bie et al., 2009; Green et al., 2011; Kanbay et al., 2011). Unfortunately, patients with CKD have repeatedly been excluded from interventional trials of ICDs (Green et al., 2011; Kanbay et al., 2011; Shamseddin and Parfrey, 2011). This is in part due to the increased frequency of procedural complications in CKD patients, such as pneumothoraces, thrombosis, haematomas, increased defibrillator threshold, and possibly infection (Herzog et al., 2005; Hreybe et al., 2006; Cuculich et al., 2007; Dasgupta et al., 2007; Green et al., 2011). Herzog et al. (2005) analysed 6173 dialysis patients post cardiac arrest using Medicare records. Estimated 1-, 2-, 3-, 4-, and 5-year survivals after 30 days from admission in the ICD group were 71%, 53%, 36%, 25%, and 22%, respectively. In the non-ICD group, there were 49%, 33%, 23%, 16%, and 12% ($P < 0.0001$). ICD implantation was independently associated with a 42% reduction in the risk of death (relative risk 0.58 (95% CI 0.50–0.66)). However, using a decision analysis model on whether ICD should be used in CKD to prevent SCD, Amin et al. (2008) found that the benefit of an ICD for primary prevention of SCD in patients with CKD depends primarily on the patient's age and stage of kidney disease. With CKD stages 1 and 2, ICD implantation reduces mortality. However, in patients with more advanced stages of CKD, the benefit is less significant and age dependent. This is largely attributed to patients with advanced CKD having a higher procedural risk and decreased life expectancy. With average procedural mortality, ICD implantation is favoured at ages < 80 for stage 3, ages < 75 for stage 4, and ages < 65 for stage 5. As procedural mortality rates increase, age thresholds for ICD implantation decrease. This is supported by another study of 6378 patients at different stages of HF and CKD (Alsheikh-Ali et al., 2011), in which 421 arrhythmic and 1188 non-arrhythmic deaths occurred over a median follow-up of 34 months. More severe HF or CKD were associated with increased risk of both arrhythmic and non-arrhythmic death. The increase in the risk of non-arrhythmic death in those with most advanced HF was disproportionately higher than that of arrhythmic death, and this disproportionate effect was more exaggerated in the presence of more advanced CKD. In a similar study, Cheema et al. (2010) showed that mortality rate was higher in those with eGFR < 60 mL/min and those with ESRD on haemodialysis (43% and 54%, respectively) than in patients with eGFR ≥ 60 mL/min (23%, $P < 0.0005$). Although there was a trend towards improved survival in haemodialysis outpatient clinics with on-site automatic external defibrillators compared to those without, this benefit may have been attributed to a higher number of patients on appropriate pharmacotherapy, and after adjusting for these differences survival rates were similar

Table 108.3 Summary of studies investigating the link between implantable cardioverter defibrillators (ICDs), CKD, and SCD

Study	Outcome	Population	Comparison	Hazard ratio (95% CI), P value	Statistically Significant	
Herzog et al., 2005b	All-cause mortality	6173 on dialysis	ICD vs no ICD	0.58 (0.50–0.66), P < 0.0001	Positive	
Herzog et al., 2005b	1-year survival	6173 on dialysis	ICD vs no ICD	71% vs 49%	P < 0.0001	Positive
	2-year survival			53% vs 33%		
	3-year survival			36% vs 23%		
	4-year survival			25% vs 16%		
	5-year survival			22% vs 12%		
Charytan et al., 2011	Overall mortality	11,160 on dialysis	ICD vs no ICD	0.86 (0.81–0.91)	Positive	
Hiremath et al., 2010	All-cause mortality	ESRD	ICD vs no ICD	0.40 (0.19–0.82), P = 0.013	Positive	
Eckart et al., 2006	Overall mortality	741 patients with and without CKD	ICD with CKD vs ICD without CKD	1.69 (1.32–2.17), P < 0.001	Positive	
Levy et al., 2008	Overall mortality	346 CKD patients treated with ICD	eGFR < 45 mL/min/1.73 m^2 vs eGFR > 75 mL/min/1.73 m2	8.82 (3.07–25.4), P < 0.00001	Positive	
Levy et al., 2008	Overall mortality	346 CKD patients treated with ICD	eGFR 45.0–59.9 mL/min/1.73 m^2 vs eGFR > 75 mL/min/1.73 m2	1.70 (0.52–5.52), P = 0.38	Negative	
Levy et al., 2008	Overall mortality	346 CKD patients treated with ICD	eGFR 60.0–74.9 mL/min/1.73 m^2 vs eGFR > 75 mL/min/1.73 m^2	1.76 (0.55–5.66), P = 0.34	Negative	
Sakhuja et al., 2009	Overall mortality	Meta-analysis of 7 studies with 2516 CKD patients receiving ICD	CKD on dialysis vs CKD not on dialysis	2.44 (1.42–4.20), P = 0.001	Positive	

(Herzog et al., 2005; Lehrich et al., 2007). One meta-analysis has also questioned the efficacy of ICD implantation in ESRD (Sakhuja et al., 2009).

These data support the conclusion that younger patients and those with less advanced CKD will benefit from ICD therapy, whilst the elderly and those with ESRD may not. There are, however important caveats and caution should be exercised in accepting these conclusions. LV systolic function is the greatest predictor of SCD in the general population, and hence central to risk stratifying patients for ICDs (Moss et al., 2002). However, in patients with ESRD, only 15% have significant LV systolic dysfunction (Parfrey and Foley, 1999; Mangrum et al., 2006b) and studies have shown that > 70% of ESRD patients dying of SCD did not have severe systolic dysfunction (Mangrum et al., 2006a). One prospective study of mortality in dialysis patients did not find severe LV systolic dysfunction to be an independent predictor of SCD (Genovesi et al., 2009). Dialysis patients have also been shown to receive a greater number of appropriate shocks from ICDs (Robin et al., 2006). Furthermore, the lifetime risk of SCD for dialysis patients with normal LV function is 25% (Mangrum et al., 2006a), which in itself is clear evidence that current risk stratifying tools used for the general population are not appropriate for these patients. Despite this, the main determinant of ICD implantation in ESRD patients is LV systolic function. Taken together with the mechanistic data supporting distinct pathological mechanisms in these patients, the efficacy of ICD implantation in ESRD patients cannot be fairly judged (Saravanan and Davidson, 2010). It is possible to show only 8% of dialysis patients who have survived cardiac arrest receive ICD implants, this represents suboptimal secondary prevention (Herzog et al., 2005). The Implantable Cardioverter Defibrillator in Dialysis patients (ICD2) trial (a first) (de Bie et al., 2008), is a prospective randomized controlled study to evaluate the efficacy and safety of prophylactic ICD therapy in reducing SCD rates in dialysis patients aged 55–80 years with a mean follow-up time of 4 years, and is much needed. This will include a total of 200 patients, using a primary endpoint of sudden cardiac (arrhythmic) death. Table 108.3 summarizes the main studies that have investigated the effectiveness of ICD on SCD.

References

Abbott, K. C., Trespalacios, F. C., Agodoa, L. Y., *et al.* (2004). B-blocker use in long-term dialysis patients: Association with hospitalized heart failure and mortality. *Arch Intern Med*, 164(22), 2465–71.

Agewall, S., Wikstrand, J., Ljungman, S., *et al.* (1995). Does microalbuminuria predict cardiovascular events in nondiabetic men with treated hypertension? Risk Factor Intervention Study Group. *Am J Hypertens*, 8(4 Pt 1), 337–42.

Alsheikh-Ali, A. A., Trikalinos, T. A., Ruthazer, R., *et al.* (2011). Risk of arrhythmic and nonarrhythmic death in patients with heart failure and chronic kidney disease. *Am Heart J*, 161(1), 204–9 e1.

Amann, K., Breitbach, M., Ritz, E., *et al.* (1998). Myocyte/capillary mismatch in the heart of uremic patients. *J Am Soc Nephrol*, 9(6), 1018–22.

Amann, K. and Ritz, E. (2000). Microvascular disease—the Cinderella of uraemic heart disease. *Nephrol Dial Transplant*, 15(10), 1493–503.

Amin, M. S., Fox, A. D., Kalahasty, G., *et al.* (2008). Benefit of primary prevention implantable cardioverter-defibrillators in the setting of chronic kidney disease: a decision model analysis. *J Cardiovasc Electrophysiol*, 19(12), 1275–80.

Barreto, D. V., Barreto, F. C., Liabeuf, S., *et al.* (2009). Vitamin D affects survival independently of vascular calcification in chronic kidney disease. *Clin J Am Soc Nephrol*, 4(6), 1128–35.

Beattie, J. N., Soman, S. S., Sandberg, K. R., *et al.* (2001). Determinants of mortality after myocardial infarction in patients with advanced renal dysfunction. *Am J Kidney Dis*, 37(6), 1191–200.

Beaubien, E. R., Pylypchuk, G. B., Akhtar, J., *et al.* (2002). Value of corrected QT interval dispersion in identifying patients initiating dialysis at increased risk of total and cardiovascular mortality. *Am J Kidney Dis*, 39(4), 834–42.

Beijers, H. J., Ferreira, I., Bravenboer, B., *et al.* (2009). Microalbuminuria and cardiovascular autonomic dysfunction are independently associated with cardiovascular mortality: evidence for distinct pathways: the Hoorn Study. *Diabetes Care*, 32(9), 1698–703.

Besarab, A.(1999). Iron and cardiac disease in the end-stage renal disease setting. *Am J Kidney Dis*, 34(4 Suppl 2), S18–24.

Bigazzi, R., Bianchi, S., Nenci, R., *et al.* (1995). Increased thickness of the carotid artery in patients with essential hypertension and microalbuminuria. *J Hum Hypertens*, 9(10), 827–33.

Bleyer, A. J., Hartman, J., Brannon, P. C., *et al.* (2006). Characteristics of sudden death in hemodialysis patients. *Kidney Int*, 69(12), 2268–73.

Block, G. A., Hulbert-Shearon, T. E., Levin, N. W., *et al.* (1998). Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*, 31(4), 607–17.

Bozbas, H., Atar, I., Yildirir, A., *et al.* (2007). Prevalence and predictors of arrhythmia in end stage renal disease patients on hemodialysis. *Ren Fail*, 29(3), 331–9.

Burton, J. O., Jefferies, H. J., Selby, N. M., *et al.* (2009). Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol*, 4(12), 1925–31.

Burton, J. O., Korsheed, S., Grundy, B. J., *et al.* (2008). Hemodialysis-induced left ventricular dysfunction is associated with an increase in ventricular arrhythmias. *Ren Fail*, 30(7), 701–9.

Charytan, D., Kuntz, R. E., Mauri, L., *et al.* (2007). Distribution of coronary artery disease and relation to mortality in asymptomatic hemodialysis patients. *Am J Kidney Dis*, 49(3), 409–16.

Chaturvedi, N., Fuller, J. H., and Taskinen, M. R. (2001). Differing associations of lipid and lipoprotein disturbances with the macrovascular and microvascular complications of type 1 diabetes. *Diabetes Care*, 24(12), 2071–7.

Cheema, A., Singh, T., Kanwar, M., *et al.* (2010). Chronic kidney disease and mortality in implantable cardioverter-defibrillator recipients. *Cardiol Res Pract*, 2010, 989261

Chen, S., Glenn, D. J., Ni, W., *et al.* (2008). Expression of the Vitamin D receptor is increased in the hypertrophic heart. *Hypertension*, 52(6), 1106–12.

Cheung, A. K., Levin, N. W., Greene, T., *et al.* (2003). Effects of high-flux hemodialysis on clinical outcomes: results of the HEMO study. *J Am Soc Nephrol*, 14(12), 3251–63.

Cheung, A. K., Sarnak, M. J., Yan, G., *et al.* (2004). Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study. *Kidney Int*, 65(6), 2380–9.

Chonchol, M., Goldenberg, I., Moss, A. J., *et al.* (2007). Risk factors for sudden cardiac death in patients with chronic renal insufficiency and left ventricular dysfunction. *Am J Nephrol*, 27(1), 7–14.

Chugh, S. S., Jui, J., Gunson, K., *et al.* (2004). Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. *J Am Coll Cardiol*, 44(6), 1268–75.

Cice, G., Ferrara, L., D'Andrea, A., *et al.* (2003). Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol*, 41(9), 1438–44.

Clausen, P., Feldt-Rasmussen, B., Jensen, G., *et al.* (1999). Endothelial haemostatic factors are associated with progression of urinary albumin excretion in clinically healthy subjects: a 4-year prospective study. *Clin Sci (Lond)*, 97(1), 37–43.

Clausen, P., Jensen, J. S., Jensen, G., *et al.* (2001). Elevated urinary albumin excretion is associated with impaired arterial dilatory capacity in clinically healthy subjects. *Circulation*, 103(14), 1869–74.

Cobb, L. A., Fahrenbruch, C. E., Olsufka, M., *et al.* (2002). Changing incidence of out-of-hospital ventricular fibrillation, 1980-2000. *JAMA*, 288(23), 3008–13.

Collins, A. J., Weinhandl, E., Snyder, J. J., *et al.* (2002). Comparison and survival of hemodialysis and peritoneal dialysis in the elderly. *Semin Dial*, 15(2), 98–102.

Conlon, P. J., Krucoff, M. W., Minda, S., *et al.* (1998). Incidence and long-term significance of transient ST segment deviation in hemodialysis patients. *Clin Nephrol*, 49(4), 236–9.

Converse, R. L., Jacobsen, T. N., Toto, R. D., *et al.* (1992). Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med*, 327(27), 1912–8.

Coquet, I., Mousson, C., Rifle, G., *et al.* (2005). Influence of ischemia on heart-rate variability in chronic hemodialysis patients. *Ren Fail*, 27(1), 7–12.

Covic, A., Diaconita, M., Gusbeth-Tatomir, P., *et al.* (2002). Haemodialysis increases QTc interval but not QTc dispersion in ESRD patients without manifest cardiac disease. *Nephrol Dial Transplant*, 17(12), 2170–7.

Covic, A., Voroneanu, L., and Goldsmith, D. (2010). The effects of vitamin D therapy on left ventricular structure and function—are these the underlying explanations for improved CKD patient survival? *Nephron Clin Pract*, 116(3), 187–95.

Cuculich, P. S., Sanchez, J. M., Kerzner, R., *et al.* (2007). Poor prognosis for patients with chronic kidney disease despite ICD therapy for the primary prevention of sudden death. *Pacing Clin Electrophysiol*, 30(2), 207–13.

Culleton, B. F., Walsh, M., Klarenbach, S. W., *et al.* (2007). Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. *JAMA*, 298(11), 1291–9.

Cupisti, A., Galetta, F., Morelli, E., *et al.* (1998). Effect of hemodialysis on the dispersion of the QTc interval. *Nephron*, 78(4), 429–32.

Dar, O. and Cowie, M. R. (2008). Acute heart failure in the intensive care unit: epidemiology. *Crit Care Med*, 36(1 Suppl), S3–8.

Dasgupta, A., Montalvo, J., Medendorp, S., *et al.* (2007). Increased complication rates of cardiac rhythm management devices in ESRD patients. *Am J Kidney Dis*, 49(5), 656–63.

De Bie, M. K., Lekkerkerker, J. C., van Dam, B., *et al.* (2008). Prevention of sudden cardiac death: rationale and design of the Implantable Cardioverter Defibrillators in Dialysis patients (ICD2) Trial—a prospective pilot study. *Curr Med Res Opin*, 24(8), 2151–7.

De Bie, M. K., van Dam, B., Gaasbeek, A., *et al.* (2009). The current status of interventions aiming at reducing sudden cardiac death in dialysis patients. *Eur Heart J*, 30(13), 1559–64.

De Vreede-Swagemakers, J. J., Gorgels, A. P., Dubois-Arbouw, W. I., *et al.* (1997). Out-of-hospital cardiac arrest in the 1990's: a population-based study in the Maastricht area on incidence, characteristics and survival. *J Am Coll Cardiol*, 30(6), 1500–5.

Deckert, T., Feldt-Rasmussen, B., Borch-Johnsen, K., *et al.* (1989). Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia*, 32(4), 219–26.

Denes, P., Santarelli, P., Hauser, R. G., *et al.* (1983). Quantitative analysis of the high-frequency components of the terminal portion of the body surface QRS in normal subjects and in patients with ventricular tachycardia. *Circulation*, 67(5), 1129–38.

Deo, R., Lin, F., Vittinghoff, E., *et al.* (2008). Kidney dysfunction and sudden cardiac death among women with coronary heart disease. *Hypertension*, 51(6), 1578–82.

Dhoble, A., Punnam, S. R., and Abela, G. S. (2008). Likelihood of ventricular arrhythmias due to myocardial fibrosis in hypertrophic cardiomyopathy as detected by cardiac magnetic resonance imaging. *J Am Coll Cardiol*, 52(11), 969.

Di Iorio, B., Bellasi, A., and Russo, D. (2012). Mortality in kidney disease patients treated with phosphate binders: a randomized study. *Clin J Am Soc Nephrol*, 7(3), 487–93.

Di Iorio, B., Nargi, O., Cucciniello, E., *et al.* (2011). Coronary artery calcification progression is associated with arterial stiffness and cardiac repolarization deterioration in hemodialysis patients. *Kidney Blood Press Res*, 34(3), 180–7.

Di Iorio, B. R., Bortone, S., Piscopo, C., *et al.* (2006). Cardiac vascular calcification and QT interval in ESRD patients: is there a link? *Blood Purif*, 24(5–6), 451–9.

Drechsler, C., Pilz, S., Obermayer-Pietsch, B., *et al.* (2010). Vitamin D deficiency is associated with sudden cardiac death, combined cardiovascular events, and mortality in haemodialysis patients. *Eur Heart J*, 31(18), 2253–61.

Drueke, T. B. and Massy, Z. A. (2010). Atherosclerosis in CKD: differences from the general population. *Nat Rev Nephrol*, 6(12), 723–35.

Ducloux, D., Motte, G., Challier, B., *et al.* (2000). Serum total homocysteine and cardiovascular disease occurrence in chronic, stable renal transplant recipients: a prospective study. *J Am Soc Nephrol*, 11(1), 134–7.

Elsner, D. (2001). How to diagnose and treat coronary artery disease in the uraemic patient: an update. *Nephrol Dial Transplant*, 16(6), 1103–8.

Escobedo, L. G. and Zack, M. M. (1996). Comparison of sudden and nonsudden coronary deaths in the United States. *Circulation*, 93(11), 2033–6.

Fellström, B. C., Jardine, A. G., Schmieder, R. E., *et al.* (2009). Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis. *N Engl J Med*, 360(14), 1395–407.

Foley, R. N., Herzog, C. A., and Collins, A. J. (2002). Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study. *Kidney Int*, 62(5), 1784–90.

Foley, R. N., Parfrey, P. S., Harnett, J. D., *et al.* (1995). The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol*, 5(12), 2024–31.

Foley, R. N., Parfrey, P. S., Harnett, J. D., *et al.* (1996). The impact of anemia on cardiomyopathy, morbidity, and and mortality in end-stage renal disease. *Am J Kidney Dis*, 28(1), 53–61.

Foley, R. N., Parfrey, P. S., Kent, G. M., *et al.* (1998a). Long-term evolution of cardiomyopathy in dialysis patients. *Kidney Int*, 54(5), 1720–5.

Foley, R. N., Parfrey, P. S., and Sarnak, M. J. (1998b). Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis*, 32(5 Suppl 3), S112–9.

Foley, R. N., Wang, C., and Collins, A. J. (2005). Cardiovascular risk factor profiles and kidney function stage in the US general population: the NHANES III study. *Mayo Clin Proc*, 80(10), 1270–7.

Fox, C. S., Muntner, P., Chen, A. Y., *et al.* (2010). Use of evidence-based therapies in short-term outcomes of ST-segment elevation myocardial infarction and non–ST-segment elevation myocardial infarction in patients with chronic kidney disease. *Circulation*, 121(3), 357–65.

Frank, H., Heusser, K., Hoffken, B., *et al.* (2004). Effect of erythropoietin on cardiovascular prognosis parameters in hemodialysis patients. *Kidney Int*, 66(2), 832–40.

Friedman, A. N., Groh, W. J., and Das, M. (2007). A pilot study in hemodialysis of an electrophysiological tool to measure sudden cardiac death risk. *Clin Nephrol*, 68(3), 159–64.

Furgeson, S. B. and Chonchol, M. (2008). Beta-blockade in chronic dialysis patients. *Semin Dial*, 21(1), 43–8.

Furuland, H., Linde, T., Englund, A., *et al.* (2008). Heart rate variability is decreased in chronic kidney disease but may improve with hemoglobin normalization. *J Nephrol*, 21(1), 45–52.

Ganesh, S. K., Stack, A. G., Levin, N. W., *et al.* (2001). Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol*, 12(10), 2131–8.

Ganji, V. and Kafai, M. R. (2003). Demographic, health, lifestyle, and blood vitamin determinants of serum total homocysteine concentrations in the third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr*, 77(4), 826–33.

Genovesi, S., Valsecchi, M. G., Rossi, E., *et al.* (2009). Sudden death and associated factors in a historical cohort of chronic haemodialysis patients. *Nephrol Dial Transplant*, 24(8), 2529–36.

Gerritsen, J., Dekker, J. M., TenVoorde, B. J., *et al.* (2001). Impaired autonomic function is associated with increased mortality, especially

in subjects with diabetes, hypertension, or a history of cardiovascular disease: the Hoorn Study. *Diabetes Care*, 24(10), 1793–8.
Gillum, R. F. (1989). Sudden coronary death in the United States: 1980-1985. *Circulation*, 79(4), 756–65.
Go, A. S., Chertow, G. M., Fan, D., *et al.* (2004). Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*, 351(13), 1296–305.
Goldberger, J. J., Cain, M. E., Hohnloser, S. H., *et al.* (2008). American Heart Association/American College of Cardiology Foundation/*Heart Rhythm* Society Scientific Statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death. *Circulation*, 118(14), 1497–518.
Goldenberg, I., Moss, A. J., McNitt, S., *et al.* (2006). Relations among renal function, risk of sudden cardiac death, and benefit of the implanted cardiac defibrillator in patients with ischemic left ventricular dysfunction. *Am J Cardiol*, 98(4), 485–90.
Goldsmith, D. J. A. and Covic, A. (2001). Coronary artery disease in uremia: Etiology, diagnosis, and therapy. *Kidney Int*, 60(6), 2059–78.
Green, D., Roberts, P. R., New, D. I., *et al.* (2011). Sudden cardiac death in hemodialysis patients: an in-depth review. *Am J Kidney Dis*, 57(6), 921–9.
Green, J. J., Robinson, D. A., Wilson, G. E., *et al.* (2006). Calcitriol modulation of cardiac contractile performance via protein kinase C. *J Mol Cell Cardiol*, 41(2), 350–9.
Hajhosseiny, R., Khavandi, K., and Goldsmith, D. J. (2013). Cardiovascular disease in chronic kidney disease: untying the Gordian knot. *Int J Clin Pract*, 67(1), 14–31.
Heinz, J., Domrose, U., Luley, C., *et al.* (2009). Influence of a supplementation with vitamins on cardiovascular morbidity and mortality in patients with end-stage renal disease: design and baseline data of a randomized clinical trial. *Clin Nephrol*, 71(3), 363–5.
Herzog, C. A. (1999). Acute myocardial infarction in patients with end-stage renal disease. *Kidney Int Suppl*, 71, S130–3.
Herzog, C. A. (2003). Cardiac arrest in dialysis patients: approaches to alter an abysmal outcome. *Kidney Int Suppl*, 84, S197–200.
Herzog, C. A., Li, S. L., Weinhandl, E. D., *et al.* (2005). Survival of dialysis patients after cardiac arrest and the impact of implantable cardioverter defibrillators. *Kidney Int*, 68(2), 818–25.
Herzog, C. A., Ma, J. Z., and Collins, A. J. (1998). Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med*, 339(12), 799–805.
Herzog, C. A., Strief, J. W., Collins, A. J., *et al.* (2008). Cause-specific mortality of dialysis patients after coronary revascularization: why don't dialysis patients have better survival after coronary intervention? *Nephrol Dial Transplant*, 23(8), 2629–33.
Heymann, E. P., Kassimatis, T. I., and Goldsmith, D. J. (2012). Dyslipidemia, statins, and CKD patients' outcomes—review of the evidence in the post-sharp era. *J Nephrol*, 25(4), 460–72.
Holick, M. F. (2007). Vitamin D deficiency. *N Engl J Med*, 357(3), 266–81.
Hreybe, H., Ezzeddine, R., Bedi, M., *et al.* (2006). Renal insufficiency predicts the time to first appropriate defibrillator shock. *Am Heart J*, 151(4), 852–6.
Ix, J. H., Shlipak, M. G., Chertow, G. M., *et al.* (2006). Cystatin C, left ventricular hypertrophy, and diastolic dysfunction: data from the Heart and Soul Study. *J Card Fail*, 12(8), 601–7.
Jager, A., van Hinsbergh, V. W., Kostense, P. J., *et al.* (2002). C-reactive protein and soluble vascular cell adhesion molecule-1 are associated with elevated urinary albumin excretion but do not explain its link with cardiovascular risk. *Arterioscler Thromb Vasc Biol*, 22(4), 593–8.
Jansen, M. A., Hart, A. A., Korevaar, J. C., *et al.* (2002). Predictors of the rate of decline of residual renal function in incident dialysis patients. *Kidney Int*, 62(3), 1046–53.
Jenkins, M. and Goldsmith, D. (2012). Statins and kidney disease: is the study of heart and renal protection at the cutting edge of evidence? *Curr Opin Cardiol*, 27(4), 429–40.
Jensen, J. S., Borch-Johnsen, K., Jensen, G., *et al.* (1995). Microalbuminuria reflects a generalized transvascular albumin leakiness in clinically healthy subjects. *Clin Sci (Lond)*, 88(6), 629–33.
Jermendy, G., Ferenczi, J., Hernandez, E., *et al.* (1996). Day-night blood pressure variation in normotensive and hypertensive NIDDM patients with asymptomatic autonomic neuropathy. *Diabetes Res Clin Pract*, 34(2), 107–14.
Johansson, M., Gao, S. A., Friberg, P., *et al.* (2007). Baroreflex effectiveness index and baroreflex sensitivity predict all-cause mortality and sudden death in hypertensive patients with chronic renal failure. *J Hypertens*, 25(1), 163–8.
Jones, S. L., Close, C. F., Mattock, M. B., *et al.* (1989). Plasma lipid and coagulation factor concentrations in insulin dependent diabetics with microalbuminuria. *BMJ*, 298(6672), 487–90.
Kahri, J., Groop, P. H., Elliott, T., *et al.* (1994). Plasma cholesteryl ester transfer protein and its relationship to plasma lipoproteins and apolipoprotein A-I-containing lipoproteins in IDDM patients with microalbuminuria and clinical nephropathy. *Diabetes Care*, 17(5), 412–9.
Kanbay, M., Solak, Y., Covic, A., *et al.* (2011). Sudden cardiac death in patients with chronic kidney disease: prevention is the sine qua non. *Kidney Blood Press Res*, 34(4), 269–76.
Kantarci, G., Ozener, C., Tokay, S., *et al.* (2002). QT dispersion in hemodialysis and CAPD patients. *Nephron*, 91(4), 739–41.
Kario, K., Matsuo, T., Kobayashi, H., *et al.* (1996). Factor VII hyperactivity and endothelial cell damage are found in elderly hypertensives only when concomitant with microalbuminuria. *Arterioscler Thromb Vasc Biol*, 16(3), 455–61.
Karnik, J. A., Young, B. S., Lew, N. L., *et al.* (2001). Cardiac arrest and sudden death in dialysis units. *Kidney Int*, 60(1), 350–7.
Kawagishi, T., Matsuyoshi, M., Emoto, M., *et al.* (1999). Impaired endothelium-dependent vascular responses of retinal and intrarenal arteries in patients with type 2 diabetes. *Arterioscler Thromb Vasc Biol*, 19(10), 2509–16.
Khavandi, K., Greenstein, A. S., Sonoyama, K., *et al.* (2009). Myogenic tone and small artery remodelling: insight into diabetic nephropathy. *Nephrol Dial Transplant*, 24(2), 361–9.
Kovesdy, C. P., Regidor, D. L., Mehrotra, R., *et al.* (2007). Serum and dialysate potassium concentrations and survival in hemodialysis patients. *Clin J Am Soc Nephrol*, 2(5), 999–1007.
Krane, V., Heinrich, F., Meesmann, M., *et al.* (2009). Electrocardiography and outcome in patients with diabetes mellitus on maintenance hemodialysis. *Clin J Am Soc Nephrol*, 4(2), 394–400.
Krishnan, A. V. and Feldman, D. (2010). Molecular pathways mediating the anti-inflammatory effects of calcitriol: implications for prostate cancer chemoprevention and treatment. *Endocr Relat Cancer*, 17(1), R19–38.
Kuusisto, J., Mykkanen, L., Pyorala, K., *et al.* (1995). Hyperinsulinemic microalbuminuria. A new risk indicator for coronary heart disease. *Circulation*, 91(3), 831–7.
Lehrich, R. W., Pun, P. H., Tanenbaum, N. D., *et al.* (2007). Automated external defibrillators and survival from cardiac arrest in the outpatient hemodialysis clinic. *J Am Soc Nephrol*, 18(1), 312–20.
Levey, A. S., Beto, J. A., Coronado, B. E., *et al.* (1998). Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis*, 32(5), 853–906.
Levin, A., Singer, J., Thompson, C. R., *et al.* (1996). Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. *Am J Kidney Dis*, 27(3), 347–54.
London, G. M., Guerin, A. P., Verbeke, F. H., *et al.* (2007). Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency. *J Am Soc Nephrol*, 18(2), 613–20.
London, G. M., Pannier, B., Guerin, A. P., *et al.* (2001). Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: follow-up of an interventional study. *J Am Soc Nephrol*, 12(12), 2759–67.
Longenecker, J. C., Coresh, J., Powe, N. R., *et al.* (2002). Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. *J Am Soc Nephrol*, 13(7), 1918–27.

Lorincz, I., Matyus, J., Zilahi, Z., *et al.* (1999). QT dispersion in patients with end-stage renal failure and during hemodialysis. *J Am Soc Nephrol*, 10(6), 1297–302.
Mallamaci, F., Zoccali, C., Tripepi, G., *et al.* (2002). Hyperhomocysteinemia predicts cardiovascular outcomes in hemodialysis patients. *Kidney Int*, 61(2), 609–14.
Mangrum, J. M., Lin, D., Dimarco, J. P., *et al.* (2006a). Prognostic value of left ventricular systolic function in renal dialysis patients. *Heart Rhythm*, 3, S154.
Mangrum, A. J., Lin, D., Dimarco, J. P., *et al.* (2006b). Sudden cardiac death and left ventricular function in hemodialysis patients. *Heart Rhythm*, 2, S33.
Mark, P. B., Johnston, N., Groenning, B. A., *et al.* (2006). Redefinition of uremic cardiomyopathy by contrast-enhanced cardiac magnetic resonance imaging. *Kidney Int*, 69(10), 1839–45.
Marshall, M. R., Byrne, B. G., Kerr, P. G., *et al.* (2006). Associations of hemodialysis dose and session length with mortality risk in Australian and New Zealand patients. *Kidney Int*, 69(7), 1229–36.
Maser, R. E., Mitchell, B. D., Vinik, A. I., *et al.* (2003). The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care*, 26(6), 1895–901.
McCarty, M. F. (2004). Targeting multiple signaling pathways as a strategy for managing prostate cancer: multifocal signal modulation therapy. *Integr Cancer Ther*, 3(4), 349–80.
McIntyre, C. W. (2010). Haemodialysis-induced myocardial stunning in chronic kidney disease—a new aspect of cardiovascular disease. *Blood Purif*, 29(2), 105–10.
Mehrotra, R., Kermah, D. A., Salusky, I. B., *et al.* (2009). Chronic kidney disease, hypovitaminosis D, and mortality in the United States. *Kidney Int*, 76(9), 977–83.
Meier, P., Vogt, P., and Blanc, E. (2001). Ventricular arrhythmias and sudden cardiac death in end-stage renal disease patients on chronic hemodialysis. *Nephron*, 87(3), 199–214.
Messa, P., Ponticelli, C., and Berardinelli, L. (2008). Coming back to dialysis after kidney transplant failure. *Nephrol Dial Transplant*, 23(9), 2738–42.
Morales, M. A., Gremigni, C., Dattolo, P., *et al.* (1998). Signal-averaged ECG abnormalities in haemodialysis patients. Role of dialysis. *Nephrol Dial Transplant*, 13(3), 668–73.
Moran, A., Palmas, W., Field, L., *et al.* (2004). Cardiovascular autonomic neuropathy is associated with microalbuminuria in older patients with type 2 diabetes. *Diabetes Care*, 27(4), 972–7.
Moreno, J., Krishnan, A. V., Swami, S., *et al.* (2005). Regulation of prostaglandin metabolism by calcitriol attenuates growth stimulation in prostate cancer cells. *Cancer Res*, 65(17), 7917–25.
Morris, S. T. W., Galiatsou, E., Stewart, G. A., *et al.* (1999). QT dispersion before and after hemodialysis (vol 9, pg 160, 1999). *J Am Soc Nephrol*, 10(7), 1622.
Moss, A. J., Zareba, W., Hall, W. J., *et al.* (2002). Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*, 346(12), 877–83.
Myerburg, R. J. (2001). Sudden cardiac death: exploring the limits of our knowledge. *J Cardiovasc Electrophysiol*, 12, 369–81.
Myerburg, R. J., Kessler, K. M., and Castellanos, A. (1993). Sudden cardiac death: epidemiology, transient risk, and intervention assessment. *Ann Intern Med*, 119(12), 1187–97.
Mykkanen, L., Zaccaro, D. J., O'Leary, D. H., *et al.* (1997). Microalbuminuria and carotid artery intima-media thickness in nondiabetic and NIDDM subjects. The Insulin Resistance Atherosclerosis Study (IRAS). *Stroke*, 28(9), 1710–6.
Nakano, T., Ninomiya, T., Sumiyoshi, S., *et al.* (2010). Association of kidney function with coronary atherosclerosis and calcification in autopsy samples from Japanese elders: the Hisayama study. *Am J Kidney Dis*, 55(1), 21–30.
Nibbelink, K. A., Tishkoff, D. X., Hershey, S. D., *et al.* (2007). 1,25(OH)2-vitamin D3 actions on cell proliferation, size, gene expression, and receptor localization, in the HL-1 cardiac myocyte. *J Steroid Biochem Mol Biol*, 103(3–5), 533–7.
Nishimura, M., Hashimoto, T., Kobayashi, H., *et al.* (2004). Association between cardiovascular autonomic neuropathy and left ventricular hypertrophy in diabetic haemodialysis patients. *Nephrol Dial Transplant*, 19(10), 2532–8.
Nishimura, M., Tokoro, T., Nishida, M., *et al.* (2010). Sympathetic overactivity and sudden cardiac death among hemodialysis patients with left ventricular hypertrophy. *Int J Cardiol*, 142(1), 80–6.
Nishimura, M., Tsukamoto, K., Hasebe, N., *et al.* (2008). Prediction of cardiac death in hemodialysis patients by myocardial fatty acid imaging. *J Am Coll Cardiol*, 51(2), 139–45.
Nishimura, M., Tokoro, T., Nishida, M., *et al.* (2010). Sympathetic over activity and sudden cardiac death among hemodialysis patients with left ventricular hypertrophy. *Int J Cardiol*, 142, 80–6.
Ozdemir, D., Mese, T., Agin, H., *et al.* (2005). Impact of haemodialysis on QTc dispersion in children. *Nephrology (Carlton)*, 10(2), 119–23.
Parekh, R. S., Plantinga, L. C., Kao, W. H., *et al.* (2008). The association of sudden cardiac death with inflammation and other traditional risk factors. *Kidney Int*, 74(10), 1335–42.
Parfrey, P. S. and Foley, R. N. (1999). The clinical epidemiology of cardiac disease in chronic renal failure. *J Am Soc Nephrol*, 10(7), 1606–15.
Patane, S., Marte, F., Di Bella, G., *et al.* (2008). QT interval prolongation, torsade de pointes and renal disease. *Int J Cardiol*, 130(2), e71–3.
Patel, R. K., Mark, P. B., Halliday, C., *et al.* (2011). Microvolt T-wave alternans in end-stage renal disease patients—associations with uremic cardiomyopathy. *Clin J Am Soc Nephrol*, 6(3), 519–27.
Pecovnik-Balon, B., Jakopin, E., Bevc, S., *et al.* (2009). Vitamin D as a novel nontraditional risk factor for mortality in hemodialysis patients. *Ther Apher Dial*, 13(4), 268–72.
Pedrinelli, R., Giampietro, O., Carmassi, F., *et al.* (1994). Microalbuminuria and endothelial dysfunction in essential hypertension. *Lancet*, 344(8914), 14–8.
Peterlik, M. and Cross, H. S. (2005). Vitamin D and calcium deficits predispose for multiple chronic diseases. *Eur J Clin Invest*, 35(5), 290–304.
Pontremoli, R., Sofia, A., Tirotta, A., *et al.* (1996). Microalbuminuria is associated with a worse cardiovascular risk profile and target organ damage in essential hypertension. *Contrib Nephrol*, 119:115–20.
Pop-Busui, R. (2010). Cardiac autonomic neuropathy in diabetes: a clinical perspective. *Diabetes Care*, 33(2), 434–41.
Port, F. K., Ashby, V. B., Dhingra, R. K., *et al.* (2002). Dialysis dose and body mass index are strongly associated with survival in hemodialysis patients. *J Am Soc Nephrol*, 13(4), 1061–6.
Priori, S. G., Aliot, E., Blomstrom-Lundqvist, C., *et al.* (2001). Task Force on Sudden Cardiac Death of the European Society of Cardiology. *Eur Heart J*, 22(16), 1374–450.
Pun, P. H., Lehrich, R. W., Smith, S. R., *et al.* (2007). Predictors of survival after cardiac arrest in outpatient hemodialysis clinics. *Clin J Am Soc Nephrol*, 2(3), 491–500.
Pun, P. H., Smarz, T. R., Honeycutt, E. F., *et al.* (2009). Chronic kidney disease is associated with increased risk of sudden cardiac death among patients with coronary artery disease. *Kidney Int*, 76(6), 652–8.
Ravani, P., Malberti, F., Tripepi, G., *et al.* (2009). Vitamin D levels and patient outcome in chronic kidney disease. *Kidney Int*, 75(1), 88–95.
Ravani, P., Tripepi, G., Malberti, F., *et al.* (2005). Asymmetrical dimethylarginine predicts progression to dialysis and death in patients with chronic kidney disease: a competing risks modeling approach. *J Am Soc Nephrol*, 16(8), 2449–55.
Ritz, E. and Stefanski, A. (1996). Diabetic nephropathy in type II diabetes. *Am J Kidney Dis*, 27(2), 167–94.
Ritz, E. and Wanner, C. (2008). The challenge of sudden death in dialysis patients. Clin *J Am Soc Nephrol*, 3(3), 920–9.
Roberts, P. R. and Green, D. (2011). Arrhythmias in chronic kidney disease. *Heart*, 97(9), 766–73.
Robin, J., Weinberg, K., Tiongson, J., *et al.* (2006). Renal dialysis as a risk factor for appropriate therapies and mortality in implantable cardioverter-defibrillator recipients. *Heart Rhythm*, 3, 1196–201.

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., *et al.* (2011). Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation*, 123(4), e18–209.

Ronco, C., House, A. A., and Haapio, M. (2008). Cardiorenal syndrome: refining the definition of a complex symbiosis gone wrong. *Intensive Care Med*, 34(5), 957–62.

Roumelioti, M. E., Ranpuria, R., Hall, M., *et al.* (2010). Abnormal nocturnal heart rate variability response among chronic kidney disease and dialysis patients during wakefulness and sleep. *Nephrol Dial Transplant*, 25(11), 3733–41.

Rubinger, D., Backenroth, R., and Sapoznikov, D. (2009). Restoration of baroreflex function in patients with end-stage renal disease after renal transplantation. *Nephrol Dial Transplant*, 24(4), 1305–13.

Ruilope, L. M., Salvetti, A., Jamerson, K., *et al.* (2001). Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. *J Am Soc Nephrol*, 12(2), 218–25.

Rump, L. C., Amann, K., Orth, S., *et al.* (2000). Sympathetic overactivity in renal disease: a window to understand progression and cardiovascular complications of uraemia? *Nephrol Dial Transplant*, 15(11), 1735–8.

Sakhuja, R., Keebler, M., Lai, T. S., *et al.* (2009). Meta-analysis of mortality in dialysis patients with an implantable cardioverter defibrillator. *Am J Cardiol*, 103(5), 735–41.

Santoro, A., Mancini, E., London, G., *et al.* (2008). Patients with complex arrhythmias during and after haemodialysis suffer from different regimens of potassium removal. *Nephrol Dial Transplant*, 23(4), 1415–21.

Saravanan, P. and Davidson, N. C. (2010). Risk assessment for sudden cardiac death in dialysis patients. *Circ Arrhythm Electrophysiol*, 3(5), 553–9.

Schram, M. T., Chaturvedi, N., Schalkwijk, C. G., *et al.* (2005). Markers of inflammation are cross-sectionally associated with microvascular complications and cardiovascular disease in type 1 diabetes—the EURODIAB Prospective Complications Study. *Diabetologia*, 48(2), 370–8.

Schrier, R. W. (2007). Cardiorenal versus renocardiac syndrome: is there a difference? Nat *Clin Pract Nephrol*, 3(12), 637.

Schwarz, U., Buzello, M., Ritz, E., *et al.* (2000). Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. *Nephrol Dial Transplant*, 15(2), 218–23.

Secemsky, E. A., Verrier, R. L., Cooke, G., *et al.* (2011). High prevalence of cardiac autonomic dysfunction and T-wave alternans in dialysis patients. *Heart Rhythm*, 8(4), 592–8.

Sforzini, S., Latini, R., Mingardi, G., *et al.* (1992). Ventricular arrhythmias and four-year mortality in haemodialysis patients. Gruppo Emodialisi e Patologie Cardiovascolari. *Lancet*, 339(8787), 212–3.

Shamseddin, M. K. and Parfrey, P. S. (2009). Mechanisms of the cardiorenal syndromes. *Nat Rev Nephrol*, 5(11), 641–9.

Shamseddin, M. K. and Parfrey, P. S. (2011). Sudden cardiac death in chronic kidney disease: epidemiology and prevention. *Nat Rev Nephrol*, 7(3), 145–54.

Sharma, R., Gaze, D. C., Pellerin, D., *et al.* (2006). Ischemia-modified albumin predicts mortality in ESRD. *Am J Kidney Dis*, 47(3), 493–502.

Sharma, R., Pellerin, D., Gaze, D. C., *et al.* (2007). Mitral annular calcification predicts mortality and coronary artery disease in end stage renal disease. *Atherosclerosis*, 191(2), 348–54.

Shlipak, M. G., Heidenreich, P. A., Noguchi, H., *et al.* (2002). Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med*, 137(7), 555–62.

Smulders, Y. M., Jager, A., Gerritsen, J., *et al.* (2000). Cardiovascular autonomic function is associated with (micro-)albuminuria in elderly Caucasian subjects with impaired glucose tolerance or type 2 diabetes: the Hoorn Study. *Diabetes Care*, 23(9), 1369–74.

Soman, S. S., Sandberg, K. R., Borzak, S., *et al.* (2002). The independent association of renal dysfunction and arrhythmias in critically ill patients. *Chest*, 122(2), 669–77.

Stehouwer, C. D. (2004). Endothelial dysfunction in diabetic nephropathy: state of the art and potential significance for non-diabetic renal disease. *Nephrol Dial Transplant*, 19(4), 778–81.

Stehouwer, C. D., Gall, M. A., Twisk, J. W., *et al.* (2002). Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. *Diabetes*, 51(4), 1157–65.

Stehouwer, C. D., Henry, R. M., Dekker, J. M., *et al.* (2004). Microalbuminuria is associated with impaired brachial artery, flow-mediated vasodilation in elderly individuals without and with diabetes: further evidence for a link between microalbuminuria and endothelial dysfunction—the Hoorn Study. *Kidney Int Suppl*, 92, S42–4.

Stehouwer, C. D., Lambert, J., Donker, A. J., *et al.* (1997). Endothelial dysfunction and pathogenesis of diabetic angiopathy. *Cardiovasc Res*, 34(1), 55–68.

Stehouwer, C. D. and Smulders, Y. M. (2006). Microalbuminuria and risk for cardiovascular disease: Analysis of potential mechanisms. *J Am Soc Nephrol*, 17(8), 2106–11.

Stewart, G. A., Gansevoort, R. T., Mark, P. B., *et al.* (2005). Electrocardiographic abnormalities and uremic cardiomyopathy. *Kidney Int*, 67(1), 217–26.

Szummer, K., Lundman, P., Jacobson, S. H., *et al.* (2011). Association between statin treatment and outcome in relation to renal function in survivors of myocardial infarction. *Kidney Int*, 79(9), 997–1004.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation*, 93(5), 1043–65.

Tishkoff, D. X., Nibbelink, K. A., Holmberg, K. H., *et al.* (2008). Functional vitamin D receptor (VDR) in the t-tubules of cardiac myocytes: VDR knockout cardiomyocyte contractility. *Endocrinology*, 149(2), 558–64.

Tun, A., Khan, I. A., Wattanasauwan, N., *et al.* (1999). Increased regional and transmyocardial dispersion of ventricular repolarization in end-stage renal disease. *Can J Cardiol*, 15(1), 53–6.

Twahir, A. C. R., Gill, J., and Goldsmith, D. J. A. (1999). Signal averaged ECG-derived late ventricular potentials in patients with renal disease. Abstract, United Kingdom Renal Association Meeting, Dublin, April.

United States Renal Data System (1998). *USRDS 1998 Annual Data Report*. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases.

United States Renal Data System (2006). *USRDS 2006 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases.

Volpe, M., Cosentino, F., and Ruilope, L. M. (2003). Is it time to measure microalbuminuria in hypertension? *J Hypertens*, 21(7), 1213–20.

Wali, R. K., Iyengar, M., Beck, G. J., *et al.* (2011). Efficacy and safety of carvedilol in treatment of heart failure with chronic kidney disease: a meta-analysis of randomized trials. *Circ Heart Fail*, 4(1), 18–26.

Wang, A. Y., Lam, C. W., Chan, I. H., *et al.* (2010). Sudden cardiac death in end-stage renal disease patients: a 5-year prospective analysis. *Hypertension*, 56(2), 210–16.

Wang, A. Y., Lam, C. W., Sanderson, J. E., *et al.* (2008). Serum 25-hydroxyvitamin D status and cardiovascular outcomes in chronic peritoneal dialysis patients: a 3-y prospective cohort study. *Am J Clin Nutr*, 87(6), 1631–8.

Wang, C. L., Lee, W. L., Wu, M. J., *et al.* (2002). Increased QTc dispersion and mortality in uremic patients with acute myocardial infarction. *Am J Kidney Dis*, 39(3), 539–48.

Wanner, C., Krane, V., Marz, W., *et al.* (2005). Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*, 353(3), 238–48.

Wardman, P. and Candeias, L. P. (1996). Fenton chemistry: an introduction. *Radiat Res*, 145(5), 523–31.

Weiner, D. E., Carpenter, M. A., Levey, A. S., *et al.* (2012). Kidney Function and Risk of Cardiovascular Disease and Mortality in Kidney Transplant Recipients: The FAVORIT Trial. *Am J Transplant*, 12(9), 2437–45.

Wexler, L., Brundage, B., Crouse, J., *et al.* (1996). Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association. Writing Group. *Circulation*, 94(5), 1175–92.

Windhagen-Mahnert, B. and Kadish, A. H. (2000). Application of noninvasive and invasive tests for risk assessment in patients with ventricular arrhythmias. *Cardiol Clin*, 18(2), 243–63, vii.

Wirta, O. R., Pasternack, A. I., Mustonen, J. T., *et al.* (1999). Urinary albumin excretion rate is independently related to autonomic neuropathy in type 2 diabetes mellitus. *J Intern Med*, 245(4), 329–35.

Wolf, M., Shah, A., Gutierrez, O., *et al.* (2007). Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int*, 72(8), 1004–13.

Wright, R. S., Reeder, G. S., Herzog, C. A., *et al.* (2002). Acute myocardial infarction and renal dysfunction: a high-risk combination. *Ann Intern Med*, 137(7), 563–70.

Wu, V. C., Huang, J. W., Wu, M. S., *et al.* (2004). The effect of iron stores on corrected QT dispersion in patients undergoing peritoneal dialysis. *Am J Kidney Dis*, 44(4), 720–8.

Wu, V. C., Lin, L. Y., and Wu, K. D. (2005). QT interval dispersion in dialysis patients. *Nephrology (Carlton)*, 10(2), 109–12.

Xu, J., Li, G., Wang, P., *et al.* (2005). Renalase is a novel, soluble monoamine oxidase that regulates cardiac function and blood pressure. *J Clin Invest*, 115(5), 1275–80.

Yang, Y. W., Wu, C. H., Tsai, M. K., *et al.* (2010). Heart rate variability during hemodialysis and following renal transplantation. *Transplant Proc*, 42(5), 1637–40.

Yang, Z., Zhang, H., Kong, S., *et al.* (2007). Study for relevance of the acute myocardial ischemia to arrhythmia by the optical mapping method. *Physiol Meas*, 28(5), 481–8.

Ye, S., Gamburd, M., Mozayeni, P., *et al.* (1998). A limited renal injury may cause a permanent form of neurogenic hypertension. *Am J Hypertens*, 11(6 Pt 1), 723–8.

Yetkin, E., Ileri, M., Tandogan, I., *et al.* (2000). Increased QT interval dispersion after hemodialysis: role of peridialytic electrolyte gradients. *Angiology*, 51(6), 499–504.

Yildiz, A., Akkaya, V., Sahin, S., *et al.* (2001). QT dispersion and signal-averaged electrocardiogram in hemodialysis and CAPD patients. *Perit Dial Int*, 21(2), 186–92.

Zheng, Z. J., Croft, J. B., Giles, W. H., *et al.* (2001). Sudden cardiac death in the United States, 1989 to 1998. *Circulation*, 104(18), 2158–63.

Zipes, D. P., Camm, A. J., Borggrefe, M., *et al.* (2006). ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European *Heart Rhythm* Association and the *Heart Rhythm* Society. *Circulation*, 114(10), e385–484.

Zoccali, C., Mallamaci, F., Parlongo, S., *et al.* (2002). Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation*, 105(11), 1354–9.

CHAPTER 109

Epidemiology of calcium, phosphate, and parathyroid hormone disturbances in chronic kidney disease

Patrick Biggar, Hansjörg Rothe, and Markus Ketteler

Introduction

The kidneys play a dominant role in the regulation of serum calcium and phosphate balance. Calcium and phosphate concentrations are governed by several powerful hormonal systems, for example, vitamin D, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23). Serum calcium concentrations are maintained within a narrow range. When outside these limits, acute deleterious cardiovascular events can ensue, that is, cardiac arrhythmias. Longer-term hypo- or hypercalcaemia have more protracted effects on the skeleton and vasculature. Although serum phosphate levels are apparently not as closely regulated as calcium and may follow a circadian rhythm, preventing phosphate overload by renal excretion is important to the organism. Large observational studies suggest a close link between disorders of secondary hyperparathyroidism, calcium and phosphate balance, and adverse outcomes in chronic kidney disease (CKD), but definitive prospective and interventional data are scarce. The following chapter attempts to outline current knowledge of CKD-related disturbances in calcium and phosphate handling.

Background

General CKD epidemiology

The prevalence of CKD is estimated to be about 7% in the younger population (≥ 30 years), with a steadily increasing prevalence (23–36%) in older populations (≥ 64 years) (Zhang et al., 2008). In the last 10 years, it has been recognized that CKD is a powerful cardiovascular and all-cause mortality risk predictor. In most studies, it is stronger than key traditional risk factors including hyperlipoproteinaemia, diabetes, or smoking (Levey et al., 2011). A major consequence of the progressive loss of renal function is the development of disturbances in calcium and phosphate homeostasis including secondary hyperparathyroidism. Major cardiovascular events in CKD patients are strongly associated with severe and progressive cardiovascular calcification, linked to disturbances in calcium and phosphate homeostasis. This changed the perception of 'renal osteodystrophy', or the formerly bone-centric view of this problem (Moe et al., 2006). The term CKD-mineral and bone disorders (CKD-MBD) was coined to reflect that MBD is more a 'syndrome' of both the bone and cardiovascular system.

Hyperphosphataemia as a cardiovascular risk factor

In 1998, Block et al. described an association between serum phosphate and mortality in dialysis patients (Block et al., 1998). Since then, the interpretation of elevated phosphate levels in CKD has changed from the perception of supposedly inert hyperphosphataemia towards the recognition that increased phosphate levels in CKD may have detrimental clinical consequences inducing calcification of the vasculature and of soft tissues. This conceptual shift was supported by *in vitro* data demonstrating that in the presence of high extracellular phosphate concentrations, vascular smooth muscle cells (VSMCs) may undergo a procalcifying phenotype switch towards an osteoblast-like cell, induced by an active uptake of phosphate into the cytoplasm (Giachelli, 2009). This process was termed 'osteochondrogenic differentiation' entailing local production of bone proteins (alkaline phosphatase, osteopontin, osteocalcin) and precalcified matrix vesicles, which are shuttled out of the cells and deposited into the vascular wall. Clinical evidence is still weak that active intervention and reduction of phosphate levels, for example, via phosphate binders or targeted dietary phosphate restriction, translates into improvements of prognosis. However, it is an accepted fact that this process occurs in arteries of patients in late stages of CKD, including children on dialysis (Moe et al., 2002; Shroff et al., 2010).

Current knowledge

Epidemiology of deranged phosphate homeostasis in dialysis patients

In 2004, an additional retrospective databank analysis of 40,538 haemodialysis patients in the Fresenius Medical Care (FMC) North America Patient Statistical Profile System showed serum phosphorus concentrations > 5.0 mg/dL are associated with an increased relative risk of death (1.07, 1.25, 1.43, 1.67, and 2.02 for serum

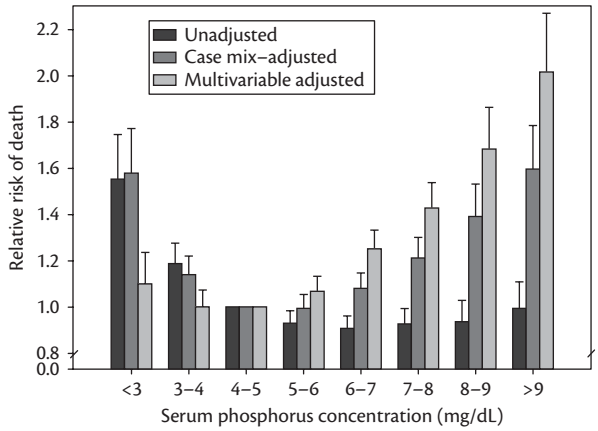

Fig. 109.1 Unadjusted, case mix-adjusted, and multivariable-adjusted relative risks (RRs; of death) and 95% confidence intervals (CIs) for eight categories of serum phosphorus (reference range, 4.0–5.0 mg/dL). For all analyses, case mix adjustment refers to adjustments for age, gender, race or ethnicity, diabetes and vintage. Multivariable adjustment refers to case mix plus body weight, urea reduction rate (URR), serum albumin, creatinine, pre-dialysis BUN, bicarbonate, cholesterol, haemoglobin, ferritin and aluminium. Phosphorus models simultaneously adjusted for calcium and PTH; calcium models simultaneously adjusted for phosphorus and PTH; PTH models simultaneously adjusted for phosphorus and calcium (Block et al., 2004).

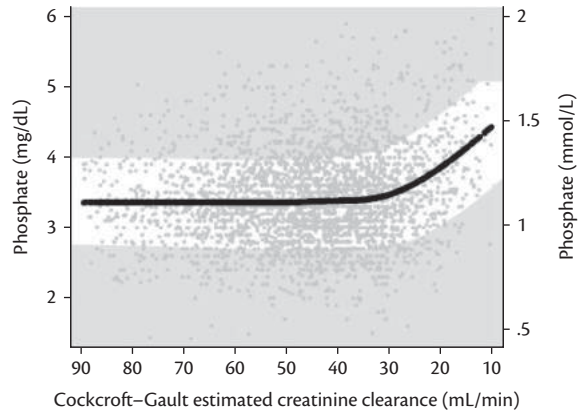

Fig. 109.2 Mean serum phosphate levels as a function of baseline estimated creatinine clearance (CrCl). The black line represents mean serum phosphate plotted against estimated CrCl. Grey shaded areas represent phosphate measurements in the highest and lowest quintiles for estimated CrCl. The white area covers serum phosphate measurements within the three middle quintiles relative to estimated CrCl (Kestenbaum et al., 2005).

phosphorus 5.0–6.0, 6.0–7.0, 7.0–8.0, 8.0–9.0 and ≥ 9.0 mg/dL, respectively) after adjustment for case mix and laboratory variables (Block et al., 2004) (Fig. 109.1).

In the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality Study, approximately 54% of haemodialysis patients in 1993 were hyperphosphataemic (Slinin et al., 2005). Ten years later, the Dialysis Outcomes and Practice Patterns Study (DOPPS) estimated that 47% of patients were hyperphosphataemic (>5.5 mg/dL) in spite of frequent usage of phosphate binders in approximately 80% of patients in this analysis (Tentori et al., 2008). Many additional observational studies have found very similar proportions and associated risk predictions for hyperphosphataemia in dialysis patients, especially when time-averaged serum concentrations, and not just cross-sectional data, were taken into account (Kalantar-Zadeh et al., 2006).

Phosphate in pre-dialysis stages

The clinical sequelae of moderately increased phosphate levels in earlier CKD stages have also been studied. In a study of 439 patients with moderate CKD, higher serum phosphate levels still within the conventional normal range were associated with the degree of vascular calcification (Adeney et al., 2009). Even after adjustment for demographics and estimated glomerular filtration rate (eGFR), each 1 mg/dL increment in serum phosphate concentration was associated with a 21% (P = 0.002), 33% (P = 0.001), 25% (P = 0.16), and 62% (P = 0.007) greater prevalence of coronary artery, thoracic, aortic valve, and mitral valve calcification, respectively. Additional adjustment for traditional risk factors for atherosclerosis, including parathyroid hormone and 1,25-dihydroxyvitamin D levels did not alter these associations. There were similar findings in the prospective analysis of 1203 non-dialysis CKD patients in the Chronic Renal Insufficiency Standards Implementation Study (Eddington et al., 2010).

Surprisingly, analyses of the general population including individuals with normal and only moderate kidney disease also associate comparatively higher phosphate levels, even within the standard normal range, with an impaired prognosis. A cross-sectional study of 1370 individuals, including 440 with a GFR ≤ 60 mL/min/1.73 m^2, demonstrated an association between serum phosphate and progressive arterial stiffness in the peripheral arteries of the lower extremities typical for development of medial arterial calcification as measured by ankle–brachial index (Ix et al., 2009). Additional knowledge has also accrued from major, primarily non CKD studies. In a cholesterol-lowering trial on 4127 participants without known kidney disease, each 1 mg/dL increase in serum phosphate concentration was associated with a 22% greater adjusted risk for all-cause mortality and a 20% greater risk for recurrent myocardial infarction (Tonelli et al., 2005). These results are remarkable given that average serum phosphate concentrations are usually kept stable over a wide range of renal dysfunction. In a study of 3490 US Veterans between 1999 and 2002, Kestenbaum et al. confirmed that normal phosphate levels are maintained until renal function is grossly impaired (Kestenbaum et al., 2005) (Fig. 109.2), probably as a result of regulatory systems counteracting the loss of kidney clearance capacity.

Again, mortality rose within the conventional normal phosphate range, and the association also remained after adjusting for creatinine clearance (Table 109.1).

Serum phosphate levels in different populations

Low socioeconomic status may be involved in the relative increase in serum phosphate. Poverty, which disproportionately affects racial and ethnic minorities, leads to excess intake of relatively inexpensive processed and fast foods enriched with highly absorbable phosphate additives. Natural phosphate is mostly contained in food as organic esters, phosphoproteins, and phospholipids, and bound phosphate is only absorbed at a maximum proportion of between 40% and 60% (Ritz et al., 2012). In contrast, enhanced food items may contain phosphate salts of which 80–100% may be readily absorbed.

Table 109.1 Mortality rates and Cox regression results by phosphate category

Serum phosphate level		No. of patients	Crude mortality rate per 1000 person–years (no. of deaths)	Adjusted hazard ratio (95% CI)[a]
mg/dL	mmol/L			
< 2.5	< 0.81	201	101.7 (54)	0.95 (0.69–1.32)
2.5–2.999	0.81–0.9699	684	102.6 (180)	Reference
3.0–3.499	0.97–1.1299	1098	125.1 (327)	1.15 (0.95–1.39)
3.5–3.999	1.13–1.2899	887	162.7 (309)	1.32 (1.09–1.61)
4.0–4.499	1.29–1.4499	388	192.8 (144)	1.34 (1.05–1.71)
4.5–1.999	1.45–1.6199	141	256.9 (62)	1.83 (1.33–2.51)
≥ 5.0	≥ 1.62	91	304.7 (38)	1.90 (1.30–2.79)

[a] Multiple adjustments, for example, age, race, gender, prevalent diabetes, ischaemic heart disease, serum calcium, etc.

From Kestenbaum et al. (2005).

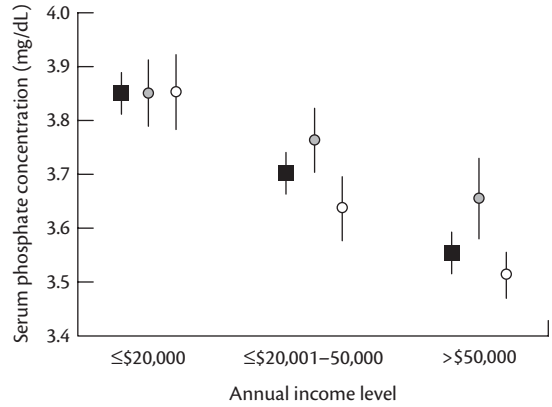

Fig. 109.3 Relationship between race and serum phosphate is modified by income. Black boxes represent mean values for the overall sample within each stratum of income, filled circles represent mean values for black patients, and open circles represent mean values for white patients. Vertical lines represent SD (Gutiérrez et al., 2010).

Race may be another determinant of serum phosphate levels, because despite a similar prevalence of early-stage CKD, black patients are more likely to develop more severe hyperphosphataemia. Gutiérrez et al. showed in a cross-sectional analysis of race, socioeconomic status, and serum phosphate among 2879 participants in the Chronic Renal Insufficiency Cohort (CRIC) study that after adjustment for age, gender, eGFR, diabetes, haemoglobin A1c, PTH, activated vitamin D, phosphate binder use, and dietary phosphate intake, serum phosphate remained 0.10 mg/dL higher in black than in white patients ($p < 0.001$) (Gutiérrez et al., 2010). Division of incomes into tertiles (≤ $20,000, $20,000–50,000, ≥ $50,000 per annum) was the basis for further analysis showing that participants with the lowest incomes or who were unemployed had higher serum phosphate concentrations than participants with the highest incomes or who were employed ($P < 0.001$). Compared with white people with the highest incomes, both black and white people with the lowest incomes had more than twice the likelihood of hyperphosphataemia in multivariable-adjusted analysis. Interestingly, black people had 0.11–0.13 mg/dL higher serum phosphate levels than white people in the highest income groups, whereas there was no difference by race in the lowest income group (Fig. 109.3).

Analyses of serum phosphate concentrations in 14,261 adults participating in the Third National Health and Nutrition Examination Survey (NHANES III) demonstrated that in this cohort the absolute amount of phosphate intake was actually significantly decreased with lower income. However, it confirmed that poverty and adverse health outcomes were associated with increased serum phosphate and twice the odds of hyperphosphataemia (≥ 4.4 mg/dL) in unadjusted and multivariable-adjusted logistic regression models (odds ratio 2.2, 95% confidence interval (CI) 1.5–3.2) (Gutiérrez et al., 2011).

Phosphate binder use and outcomes

Several observational studies have investigated the association of phosphate binder treatment and mortality in CKD populations. The ArMoRR Study was a prospective cohort study of 10,044 incident haemodialysis patients and calculated 1-year mortality stratified for treatment with or without phosphate binders (Isakova et al., 2009). The results showed that phosphorus binder therapy initiated within the first 90 days after start of dialysis was independently associated with decreased mortality compared with no therapy. Patients with phosphate binder treatment initiated before dialysis was started were excluded from the primary analysis. However, an exploratory and not prespecified analysis of this subgroup revealed an even better outcome than those patients who received treatment within the first 3 months of dialysis initiation. Kovesdy et al. observed a cohort of 1188 men with moderate to advanced CKD in a single-centre setting, out of which 344 patients were treated with phosphate binders during a follow-up of 3 years (Kovesdy et al., 2010). Phosphate binder therapy was associated with significantly lower mortality (adjusted hazard ratio, 0.61; 95% CI, 0.45–0.81; $P < 0.001$).

In 2013, the results of a large prospective European observational study on CKD-MBD parameters and treatment (COSMOS) were published demonstrating a 22% reduction in all-cause and a 29% reduction in cardiovascular mortality in patients treated with phosphate binders. The open-cohort study comprised 6797 patients followed prospectively for 3 years in 227 dialysis centres from 20 European countries. Remarkably, a reduction in mortality was also demonstrated in patients administered calcium-based phosphate binders, whilst more marked reductions were noted in patients on phosphate-binder combinations (Cannata-Andía et al., 2013).

Although the epidemiological evidence for an association between serum phosphate levels and morbidity is overwhelming, a recent study by Block et al. underlines the need for additional prospective studies to evaluate whether these parameters are modifiable risk factors (Block et al., 2012). In this prospective, randomized, placebo-controlled pilot study of 148 patients in CKD 3B and 4 assigned to either one of three phosphate binders (sevelamer, lanthanum carbonate, or calcium acetate) with a follow-up of 9 months, patients on placebo unexpectedly showed significantly lower increases in calcification of the coronary arteries (18.1% vs 80.6%; $P = 0.05$) and abdominal aorta (3.4% vs 15.4%; $P = 0.03$). Phosphate and FGF23 were only moderately improved on active phosphate binder medication. Subanalysis of the three different

phosphate binder groups revealed that the majority of the adverse effect was associated with calcium acetate, but the subgroups were too small to allow conclusive interpretations or test mortality associations.

Epidemiology of calcium disturbances

Until the turn of the millennium, serum calcium levels were adjusted to the upper conventional normal range to suppress and control secondary hyperparathyroidism utilizing calcium-containing phosphate binders and the dialysate calcium bath to achieve this. With the introduction of calcium-free phosphate binders, a debate ensued as to whether calcium was actually the cause of the development and progression of vascular calcification or just an innocent bystander. Serum calcium is tightly regulated and, thus, is not reliable as a sole and integrative marker of the whole calcium load. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, published in 2003, suggested maintaining serum calcium levels in the lower normal range, while in 2009 the Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD guidelines returned to recommending levels along the normal range for any CKD stage, due to the weakness of evidence for any recommendation of active treatment beyond these ranges (National Kidney Foundation, 2006; Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009).

In 2007, Levin et al. provided data from a cross-sectional observation (SEEK) of 1814 CKD patients not on dialysis, showing that although PTH increased at early stages of CKD, hypocalcaemia, as defined as serum calcium < 8.4 mg/dL, only developed when renal disease was significantly advanced, that is, at GFR levels of < 20–30 mL/min (Levin et al., 2007). Serum phosphate too increased only when renal function was significantly impaired (Fig. 109.4).

Analysis of The North American Fresenius Medical Care (FMC) dialysis patient database by Block et al. in 2004 showed a modest mortality risk prediction for rising serum calcium levels (Block et al., 2004). Curiously, the lower the calcium levels, the better the life expectancy of this cohort. Floege et al. reported their observational findings in 7970 patients treated in European FMC facilities over a median of 21 months. In addition to confirming increased mortality in CKD 5D, subjects with high and low phosphate levels showed increased all-cause mortality at serum calcium concentrations at both < 2.1 mmol/L and > 2.3 mmol/L (Floege et al., 2011) (Fig. 109.5).

Calcium balance in chronic kidney disease

The kinetics and dynamics of calcium absorption, distribution, and excretion are complex. Serum calcium is an inadequate parameter of calcium load assessment (Byrne et al., 2009) but with sufficient vitamin D ingestion of approximately 1000 mg of calcium daily may compensate for calcium losses (Bushinsky, 2010). In a study comparing normal individuals to patients with CKD stages 3 and 4 on daily diets containing 800 or 2000 mg elemental calcium for 9 days, both normal individuals and CKD patients were in slightly negative to neutral calcium balance on the 800 mg calcium diet (Spiegel and Brady, 2012). On the 2000 mg diet, normal individuals were in modest positive calcium balance, while patients with CKD were in marked positive calcium balance. Although increased calcium intake significantly decreased 1,25-dihydroxy vitamin D and intact PTH levels, serum calcium concentrations remained unaltered. Furthermore, Dhingra et al. were not able to detect an effect of serum calcium concentrations on cardiovascular disease (CVD) risk in their evaluation of 3368 Framingham Offspring study participants (mean age, 44 years; 51% women) initially free of CVD and CKD. They did confirm the association between serum phosphate and CVD risk (Dhingra et al., 2007).

Recently, Hill et al. analysed calcium balance prospectively in patients in CKD stages 3B–4 (Hill et al., 2013). These patients were housed on a metabolic ward for 2 weeks and were given diets containing approximately 1 g of calcium and 1.4 g of phosphate per day. After 1 week, 500 mg calcium carbonate was co-administered to the same diets with each meal. Complete urine and stool sampling was performed for the whole period. The key results were that these patients were in a neutral calcium and phosphate balance at baseline with these diets. However, when calcium carbonate was added, a strongly positive calcium balance was observed, while total phosphate balance remained unaltered (despite calcium carbonate binding phosphate). These results support the calcification results in CKD stage 3B–4 patients associated with the use of calcium acetate described by Block et al. (2012).

Numerous observational studies have indeed shown independent associations between calcium load and vascular calcification

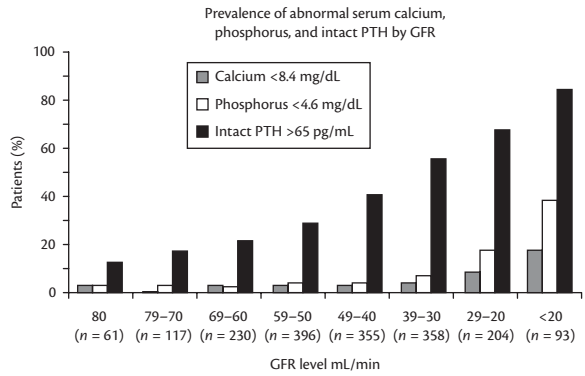

Fig. 109.4 Prevalence of abnormal serum calcium, phosphorus and intact PTH by glomerular filtration rate at 10 mL/min intervals (Levin et al., 2007).

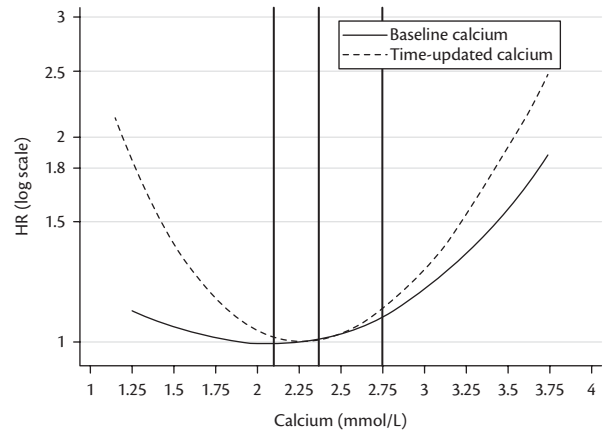

Fig. 109.5 Association between serum calcium and mortality HR in CKD-5D. (Floege et al., 2011).

and morbidity (Goodman et al., 2000; Oh et al., 2002). These association data are now supported by *in vitro* and *in vivo* studies demonstrating that calcium potently and actively induces the process of 'osteochondrogenic differentiation' (Shroff et al., 2010). Managing calcium load is desirable not only in CKD because calcium supplementation may be associated with health risks. In the general population, negative effects of augmenting standard nutritional diets with calcium supplements have been identified as associated with increased morbidity and mortality without any significant benefit of reduction in osteoporotic fractures (Bolland et al., 2010). As a consequence, many osteoporosis societies presently discourage increasing total daily intake of calcium > 1000 mg/day in the general population which—in contrast to the CKD population—should be able to adapt by increasing calcium excretion (Dachverband Osteologie, 2009).

Combined effects of elevated serum calcium and phosphate

Menon et al. failed to demonstrate an independent association between serum phosphorus level and calcium-phosphorus product with all-cause or CVD mortality after adjustment for GFR in their retrospective analysis of data collected in 840 participants for the Modification of Diet in Renal Disease (MDRD) Study. The mean serum phosphorus level was 3.8 mg/dL, the calcium-phosphorus product was 34.7 mg^2/dL^2, the glomerular filtration rate (GFR) was 33 mL/min/1.73 m^2, and all-cause and CVD mortality rates were 25% and 15%, respectively (Menon et al., 2005). Nonetheless, there is rising clinical suspicion that combined derangements of both calcium and phosphate lead to even more extensive vascular and soft tissue calcification (Shroff et al., 2010).

In the Kidney Early Evaluation Program (KEEP) study, as eGFR decreased from 60 mL/min/1.73 m^2 to < 30 mL/min/1.73 m^2, calcium levels decreased from approximately 9.55 to 9.34 mg/dL (P < 0.001), phosphate levels increased from 3.70 to 4.15 mg/dL (P <0.001), and PTH levels increased from 66.3 to 164 pg/mL (P <0.001) (Levin et al., 2007). NHANES 1999–2004 showed comparable trends supporting the importance of including PTH with calcium and phosphate monitoring for individuals with estimated GFR < 60 mL/min/1.73 m^2 (Vassalotti et al., 2008).

Larsson et al. recently evaluated a community-based cohort of 2176 men with a mean age of 50.1 years (Larsson et al., 2010). During follow-up over approximately 29.8 years, 1009 men died and 466 of these deaths were a result of CVD. Both serum phosphate and calcium × phosphate product were independent predictors of total mortality (hazard ratio per standard deviation, 1.06, P = 0.03 and 1.07, P = 0.01, respectively) and cardiovascular mortality (hazard ratio with both parameters 1.10; P = 0.01; P = 0.008). Serum calcium was associated with risk of total mortality (1.08; P = 0.02) and non-cardiovascular mortality (1.10; P = 0.04). The results were unaffected by multivariate adjustments in subsamples of individuals with an estimated GFR > 90 mL/min and low-to-normal serum calcium and phosphate. Larsson et al. concluded that circulating calcium and phosphate levels are associated with risks of total, cardiovascular, and non-cardiovascular mortality in the community and that their conjoint effects are additive (Fig. 109.6).

A meta-analysis of prospective randomized trials by Jamal et al. supports the relevance of a combined approach to a reduction of phosphate and calcium loading in end-stage renal failure by demonstrating a 22% decrease in mortality in patients receiving calcium-free phosphate binders as compared to calcium-based binders (Jamal et al., 2013).

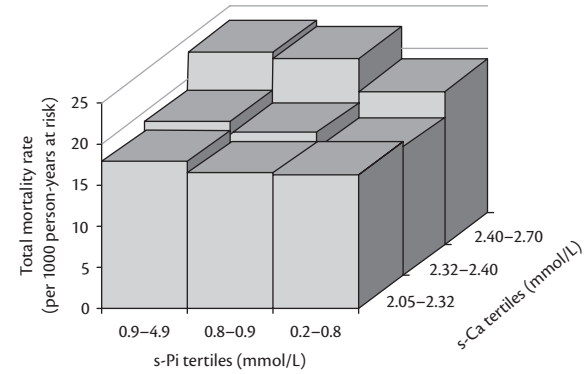

Fig. 109.6 Relation of serum [Ca × Pi] to total mortality. Regression line and 95% confidence limits from a multivariable regression spline model in subsample with serum Ca and Pi in the normal range, adjusting for albumin, eGFR, diabetes, use of antihypertensive medication, systolic and diastolic blood pressures, total cholesterol, triglycerides, body mass index, and smoking. Knot placements at serum [Ca × Pi] are 1.83, 2.06, and 2.35 $mmol^2/L^2$ (Larsson et al., 2010).

Epidemiology of secondary hyperparathyroidism

Secondary hyperparathyroidism (sHPT) develops early in CKD-MBD. A recent analysis of serum PTH levels over different stages of CKD in a large non-dialysis cohort revealed that > 20% of patients at a GFR of < 60 mL/min and > 70% of patients at a GFR of < 30 mL/min had developed sHPT, based on intact parathyroid hormone (iPTH) levels above the normal range (Isakova et al., 2011). In this context, a sufficient vitamin D concentration seems to be of greater importance to prevent sHPT in early CKD than previously anticipated (Ravani et al., 2009). Based on recent data, it appears worthwhile to correct inadequate 25-hydroxy vitamin D at any CKD stage to prevent premature or overwhelming sHPT development, besides any potential pleiotropic effects of additional vitamin D.

Since late-stage CKD and especially dialysis patients are considered to be in a PTH-resistant state, some degree of sHPT seems to be required. The KDOQI 2003 guidelines therefore set a target range of iPTH levels of 150–300 pg/mL as favourable. In 2009, the KDIGO guidelines extended the range to between two- and ninefold elevations above the upper normal range of the employed assay (National Kidney Foundation, 2006; Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009). The reasons for this revision were study results on bone turnover and mortality associated with serum PTH concentrations. While iPTH levels of below approximately 100 pg/mL were strongly associated with biopsy-proven adynamic bone disease and levels above approximately 600 pg/mL with high-turnover bone disease, intermediate iPTH levels were not reliably predictive of the type of renal osteodystrophy (London et al., 2008). Furthermore, mortality risk predictions were only recognizable when PTH levels were very low (< ~ 100 pg/mL) or high (> 600–800 pg/mL) (Block et al., 1998, 2004; Slinin et al., 2005). Compared to the predictive power of hyperphosphataemia, the effect of high iPTH is more modest.

The more recent Analysing Data, Recognising Excellence and Optimising Outcomes (ARO) trial has confirmed the latter associations, while strengthening the previous KDOQI target range showing the most favourable outcome associations (Floege et al., 2011).

Future perspectives

Guidance by phosphatonins

Estimations of phosphate load by measuring phosphatonins and, especially, FGF23 levels may, in the future, deliver more information and explain supposed discrepancies in the present epidemiological observations. In the course of the development of CKD-MBD development, rising FGF23 may indeed be the very first measurable event, long before visible hyperphosphataemia ensues. Early FGF23 upregulation may be an adaptive physiological mechanism protecting the body from developing hyperphosphataemia for as long as possible, and it will probably be crucial in this context to identify the trigger of this FGF23 release and the threshold when rising FGF23 levels may become maladaptive.

In 2011, Gutiérrez et al. published their results associating dietary and non-dietary parameters with plasma FGF23 in 1261 participants of the cross-sectional Health Professionals Follow-up Study (mean age 64 ± 9 years, mean creatinine 0.9 ± 0.2 mg/dL, mean FGF23 64 ± 28 RU/mL) (Gutiérrez et al., 2011). In multivariable-adjusted analyses, each 5-year increase in age was associated with 2.1 RU/mL higher FGF23, each 500 mg increase in phosphate intake was associated with 3.4 RU/mL higher FGF23, and each 0.1 mg/dL increase in creatinine was associated with 3.4 RU/mL higher FGF23. Participants in the highest category of body mass index had 9.5 RU/mL higher FGF23 than those in the lowest, smokers had 17.1 RU/mL higher FGF23 than non-smokers, and participants with hypertension had 6.0 RU/mL higher FGF23 than those without hypertension. Elevated PTH, phosphate, uric acid, and triglyceride levels were all associated independently with higher FGF23 in models adjusted for age, creatinine, and other factors. In a subset of 748 participants with appropriate data, inflammatory biomarkers comprising haemoglobin A1c, adiponectin, interleukin 6 (IL-6), vascular cell adhesion molecule 1, intercellular adhesion molecule 1, and soluble tumour necrosis factor (TNF) receptors 1 and 2 (markers of TNF-α-activity) were associated independently with higher FGF23.

There may be candidates other than FGF23, such as soluble Klotho and intestinal phosphatonins, which may develop into useful co-biomarkers. At present, routine measurements of such factors including FGF23 in clinical practice cannot be recommended. There is no clearly defined clinical consequence of such results. Additionally, assays are not readily available and are expensive.

Phosphate additive restriction

Attention to the role of phosphate additives in the food supply is increasing, especially in CKD patients. Industrially processed food contains much higher phosphate concentrations than natural food, because of enhancement with phosphate salts. The major difference between natural and added phosphates is the intestinal absorption rate. Specifically targeting and restricting food items containing high amounts of readily absorbable phosphate additives may allow diets that do not inherit the risk of protein malnutrition while significantly reducing phosphate exposure (Ritz et al., 2012). A prospective cohort study of dialysis patients was able to provide proof of principle, by achieving a net reduction of 0.6 mg/dL of serum phosphate levels via educational efforts (avoidance of phosphate additive-rich fast foods and supermarket food items) (Sullivan et al., 2009). The key requirement for transferring this approach into a successful general clinical strategy would be transparent and quantitative labelling of all enhanced food items.

Genetic epidemiology

Pharmacogenetic stratifications may in the future play a role in targeting therapies. Genes related to calcium and phosphate metabolism are amongst the most important loci for CKD: *STC1* is one of five genes identified in the first genome-wide association study showing an association with CKD (Sullivan et al., 2009). *STC1* is a human homologue of the calcium maintenance factor stanniocalcin, which plays a major role in calcium-phosphate homoeostasis in fish. A second study revealed 23 further genes and identified the solute carrier *SLC34A1*, which encodes the NaPi-2a cotransporter (Yoshiko et al., 2002). This transporter is expressed in apical sites of the epithelial cells in the small intestine and in the kidney, where it is located in the brush border of renal proximal tubular cells, and mediates reuptake of inorganic phosphate. Mutations in this gene are implicated in hypophosphataemic nephrolithiasis and osteoporosis.

Genetic variation plays a role not only in CKD, but also in normal calcium physiology as serum calcium levels are to a certain degree genetically determined irrespective of comorbidities. In a meta-analysis of four genome-wide association studies (GWAS), 1.26% of variance in serum calcium concentration of European individuals was explained by rs1801725, a missense variant near the calcium-sensing receptor gene locus (Kapur et al., 2010). Polymorphisms of the interleukin 21 receptor and the *PTH* gene were identified in a genome-wide association study of femoral neck bone mineral density (Guo et al., 2010), which is the most important risk phenotype for osteoporosis and significantly correlates with hip fracture rate and mortality. The Notch signalling pathway and especially the *JAG1* gene, which showed an association with bone mineral density and osteoporotic fractures in another GWAS with Asian and European populations (Kung et al., 2010), may also be linked to CKD-MBD, since renal involvement occurs in 40% of *JAG1*-mutation-positive individuals (Kamath et al., 2013).

It has long been held that genetic patterns could play a role in CKD-MBD, since the progression rate of metabolic bone disease in CKD is race dependent. When comparing interethnic differences in the progression of sHPT in patients with chronic kidney disease living in the San Francisco bay area, de Boer et al. found a clear difference in Asian patients with identical degrees of worsening renal function leading to slower progression of sHPT as compared with non-Asians (De Boer et al., 2002). Almost 95% of Chinese and Japanese individuals carry the rs1042636 polymorphism of the calcium-sensing receptor gene which leads to receptor molecules being more sensitive to calcium ions and calcimimetics, while most black people and white people carry the less sensitive allele (Yokoyama et al., 2002; Rothe et al., 2005; Vezzoli et al., 2007).

The CKD-MBD pattern with bone and cardiovascular pathophysiology mutually influencing each other is reflected by several studies suggesting an impact of genetic variation in calcium-, phosphate-, and PTH-related gene loci on cardiovascular mortality: the Ala986Ser polymorphism of the calcium-sensing receptor gene was found to be associated with the incidence of coronary

artery disease (defined by coronary angiography) in a cohort of 3259 German patients (März et al., 2007). Polymorphisms of the vitamin-D receptor gene were found to influence the mortality risk in Spanish haemodialysis patients (Marco et al., 2001).

It is worth remembering that all these genetic associations may serve as risk markers (rather than risk factors) in defined populations, but may not necessarily be reproducible in others due to varying linkage within different haplotype blocks. The question whether a given association is indeed causal and the underlying agent a true risk factor or not, will have to be approached by Mendelian randomization trials based on genetic epidemiology. In a nephrology setting, this was first performed when apolipoprotein (a) phenotypes were found to predict the risk of carotid atherosclerosis in end-stage renal disease patients (Kronenberg et al., 1994). Genetic influence on the course of renal disease is by no means a one-way road as epigenetic phenomena such as DNA methylation altering gene expression and transcription are modified in the uraemic environment (Bochud and Rousson et al., 2010).

References

Adeney, K. L., Siscovick, D. S., Ix, J. H., *et al.* (2009). Association of serum phosphate with vascular and valvular calcification in moderate CKD. *J Am Soc Nephrol*, 20, 381–7.

Block, G. A., Hulbert-Shearon, T. E., Levin, N. W., *et al.* (1998). Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*, 31, 607–17.

Block, G. A., Klassen, P. S., Lazarus, J. M., *et al.* (2004). Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*, 15, 2208–18.

Block, G. A., Wheeler, D. C., Persky, M. S., *et al.* (2012). Effects of phosphate binders in moderate CKD. *J Am Soc Nephrol*, 2012; 23, 1407–15.

Bochud, M. and Rousson, V. (2010). Usefulness of Mendelian randomization in observational epidemiology. *Int J Environ Res Public Health*, 7, 711–28.

Bolland, M. J., Avenell, A., Baron, J. A., *et al.* (2010). Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ*, 341, c3691.

Bushinsky, D. A. (2010). Contribution of intestine, bone, kidney, and dialysis to extracellular fluid calcium content. *Clin J Am Soc Nephrol*, 5, S12–22.

Byrne, F. N., Kinsella, S., Murnaghan, D. J., *et al.* (2009). Lack of correlation between calcium intake and serum calcium levels in stable haemodialysis subjects. *Nephron Clin Pract*, 113(3), c162–8.

Cannata-Andía, J. B., Fernández-Martín, J. L., Locatelli, F., *et al.* (2013). Use of phosphate-binding agents is associated with a lower risk of mortality. *Kidney Int*, 84(5), 998–1008.

Dachverband Osteologie (2009). DVO-Leitlinie 2009 zur Prophylaxe, Diagnostik und Therapie der Osteoporose bei Erwachsenen. *Osteologie*, 18, 304–28.

De Boer, I. H., Gorodetskaya, I., Young, B., *et al.* (2002). The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR-dependent, race-dependent, and associated with cardiovascular disease. *J Am Soc Nephrol*, 13, 2762–9.

Dhingra, R., Sullivan, L. M., Fox, C. S., *et al.* (2007). Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. *Arch Intern Med*, 167, 879–85.

Eddington, H., Hoefield, R., Sinha, S., *et al.* (2010). Serum phosphate and mortality in patients with chronic kidney disease. *Clin J Am Soc Nephrol*, 5, 2251–7.

Floege, J., Kim, J., Ireland, E., *et al.* (2011). Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. *Nephrol Dial Transplant*, 26, 1948–55.

Giachelli, C. M. (2009). The emerging role of phosphate in vascular calcification. *Kidney Int*, 75, 890–7.

Goodman, W. G., Goldin, J., Kuizon, B. D., *et al.* (2000). Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med*, 342, 1478–83.

Guo, Y., Zhang, L. S., Yang, T. L., *et al.* (2010). IL21R and PTH may underlie variation of femoral neck bone mineral density as revealed by a genome-wide association study. *J Bone Miner Res*, 25, 1042–8.

Gutiérrez, O. M., Anderson, C., Isakova, T., *et al.* (2010). Low socioeconomic status associates with higher serum phosphate irrespective of race. *J Am Soc Nephrol*, 21, 1953–60.

Gutiérrez, O. M., Isakova, T., Enfield, G., *et al.* (2011). Impact of poverty on serum phosphate concentrations in the Third National Health and Nutrition Examination Survey. *J Ren Nutr*, 21, 140–8.

Gutiérrez, O. M., Wolf, M., and Taylor, E. N. (2011). Fibroblast growth factor 23, cardiovascular disease risk factors, and phosphorus intake in the Health Professionals Follow-up Study. *Clin J Am Soc Nephrol*, 6, 2871–8.

Hill, K. M., Martin, B. R., Wastney, M. E., *et al.* (2013). Oral calcium carbonate affects calcium but not phosphorus balance in stage 3-4 chronic kidney disease. *Kidney Int*, 83(5), 959–66.

Isakova, T., Gutiérrez, O. M., Chang, Y., *et al.* (2009). Phosphorus binders and survival on hemodialysis. *J Am Soc Nephrol*, 20, 388–96.

Isakova, T., Wahl, P., Vargas, G. S., *et al.* (2011). Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int*, 79, 1370–8.

Ix, J. H., De Boer, I. H., Peralta, C. A., *et al.* (2009). Serum phosphorus concentrations and arterial stiffness among individuals with normal kidney function to moderate kidney disease in MESA. *Clin J Am Soc Nephrol*, 4, 609–15.

Jamal, S. A., Vandermeer, B., Raggi, P., *et al.* (2013). Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. *Lancet*, 382(9900), 1268–77.

Kalantar-Zadeh, K., Kuwae, N., Regidor, D. L., *et al.* (2006). Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int*, 70, 771–80.

Kamath, B. M., Spinner, N. B., and Rosenblum, N. D. (2013). Renal involvement and the role of Notch signalling in Alagille syndrome. *Nat Rev Nephrol*, 7, 409–18.

Kapur, K., Johnson, T., Beckmann, N. D., *et al.* (2010). Genome-wide meta-analysis for serum calcium identifies significantly associated SNPs near the calcium-sensing receptor (CASR) gene. *PLoS Genet*, 6, e1001035.

Kestenbaum, B., Sampson, J. N., Rudser, K. D., *et al.* (2005). Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol*, 16, 520–8.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009). KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*, 76(Suppl 113), S1–130.

Kovesdy, C. P., Kuchmak, O., Lu, J. L., *et al.* (2010). Outcomes associated with phosphorus binders in men with non-dialysis-dependent CKD. *Am J Kidney Dis*, 56, 842–51.

Kronenberg, F., Kathrein, H., König, P., *et al.* (1994). Apolipoprotein(a) phenotypes predict the risk for carotid atherosclerosis in patients with end-stage renal disease. *Arterioscler Thromb*, 14, 1405–11.

Kung, AW, Xiao, SM, Cherny, S, *et al.* (2010). Association of JAG1 with bone mineral density and osteoporotic fractures: a genome-wide association study and follow-up replication studies. *Am J Hum Genet.* 86, 229–39

Larsson, T. E., Olauson, H., Hagström, E., *et al.* (2010). Conjoint effects of serum calcium and phosphate on risk of total, cardiovascular, and noncardiovascular mortality in the community. *Arterioscler Thromb Vasc Biol*, 30, 333–9.

Levey, A. S., de Jong, P. E., Coresh, J., *et al.* (2011). The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*, 80, 17–28.

Levin, A., Bakris, G. L., Molitch, M., *et al.* (2007). Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with

chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int*, 71, 31–8.

London, G. M., Marchais, S. J., Guérin, A. P., *et al.* (2008). Association of bone activity, calcium load, aortic stiffness, and calcifications in ESRD. *J Am Soc Nephrol*, 19, 1827–35.

Marco, M. P., Craver, L., Betriu, A., *et al.* (2001). Influence of vitamin D receptor gene polymorphisms on mortality risk in hemodialysis patients. *Am J Kidney Dis*, 38, 965–74.

März, W., Seelhorst, U., Wellnitz, B., *et al.* (2007). Alanine to serine polymorphism at position 986 of the calcium-sensing receptor associated with coronary heart disease, myocardial infarction, all-cause, and cardiovascular mortality. *J Clin Endocrinol Metab*, 92, 2363–9.

Menon, V., Greene, T., Pereira, A. A., *et al.* (2005). Relationship of phosphorus and calcium-phosphorus product with mortality in CKD. *Am J Kidney Dis*, 46, 455–63.

Moe, S., Drüeke, T., Cunningham, J., *et al.* (2006). Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*, 69, 1945–53.

Moe, S. M., O'Neill, K. D., Duan, D., *et al.* (2002). Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. *Kidney Int*, 61, 638–47.

National Kidney Foundation (2006). KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *Am J Kidney Dis*, 47(Suppl 3), S11–45.

Oh, J., Wunsch, R., Turzer, M., *et al.* (2002). Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. *Circulation*, 106, 100–5.

Prie, D., Huart, V., Bakouh, N., *et al.* (2002). Nephrolithiasis and osteoporosis associated with hypophosphatemia caused by mutations in the type 2a sodium-phosphate cotransporter. *N Engl J Med*, 347, 983–91.

Ravani, P., Malberti, F., Tripepi, G., *et al.* (2009). Vitamin D levels and patient outcome in chronic kidney disease. *Kidney Int*, 75, 88–95.

Ritz, E., Hahn, K., Ketteler, M., *et al.* (2012). Phosphate additives in food—a health risk. *Dtsch Arztebl Int*, 109, 49–55

Rothe, H. M., Shapiro, W. B., Sun, W. Y., *et al.* (2005). Calcium-sensing receptor gene polymorphism Arg990Gly and its possible effect on response to cinacalcet HCl *Pharmacogenet Genomics*, 15, 29–34.

Shroff, R. C., McNair, R., Skepper, J. N., *et al.* (2010). Chronic mineral dysregulation promotes vascular smooth muscle cell adaptation and extracellular matrix calcification. *J Am Soc Nephrol*, 21, 103–12.

Slinin, Y., Foley, R. N., and Collins, A. J. (2005). Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: the USRDS waves 1, 3, and 4 study. *J Am Soc Nephrol*, 16, 1788–93.

Spiegel, D. M. and Brady, K. (2012). Calcium balance in normal individuals and in patients with chronic kidney disease on low- and high-calcium diets. *Kidney Int*, 81, 1116–22.

Sullivan, C., Sayre, S. S., Leon, J. B., *et al.* (2009). Effect of food additives on hyperphosphatemia among patients with end-stage renal disease: a randomized controlled trial. *JAMA*, 301, 629–35.

Tentori, F., Blayney, M. J., Albert, J. M., *et al.* (2008). Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*, 52, 519–30.

Tonelli, M., Isles, C., Craven, T., *et al.* (2005). Effect of pravastatin on rate of kidney function loss in people with or at risk for coronary disease. *Circulation*, 112, 171–8.

Vassalotti, J. A., Uribarri, J., Chen, S. -C., *et al.* (2008). Trends in Mineral Metabolism: Kidney Early Evaluation Program (KEEP) and the National Health and Nutrition Examination Survey (NHANES) 1999–2004. *Am J Kidney Dis*, 51, S56–68.

Vezzoli, G., Terranegra, A., Arcidiacono, T., *et al.* (2007). R990G polymorphism of calcium-sensing receptor does produce a gain-of-function and predispose to primary hypercalciuria. *Kidney Int*, 71, 1155–62.

Yokoyama, K., Shigematsu, T., Tsukada, T., *et al.* (2002). Calcium-sensing receptor gene polymorphism affects the parathyroid response to moderate hypercalcemic suppression in patients with end-stage renal disease. *Clin Nephrol*, 57, 131–5.

Yoshiko, Y., Aubin, J. E., and Maeda, N. (2002). Stanniocalcin 1 (STC1) protein and mRNA are developmentally regulated during embryonic mouse osteogenesis: the potential of stc1 as an autocrine/paracrine factor for osteoblast development and bone formation. *J Histochem Cytochem*, 50, 483–92.

Zhang, Q. L. and Rothenbacher, D. (2008). Prevalence of chronic kidney disease in population-based studies: systematic review. *BMC Public Health*, 8, 117.

CHAPTER 110

The role of inflammation in chronic kidney disease

Juan Jesús Carrero and Peter Stenvinkel

Introduction

For more than a decade, the consequences of systemic inflammation have gained attention in nephrology. In fact, this 'novel' risk factor is nowadays regarded as 'traditional' in the majority of patients with chronic kidney disease (CKD).

Although the release of pro-inflammatory cytokines has acute beneficial effects that are vital for survival, chronic systemic elevation is likely to be detrimental. This is the problem in the uraemic milieu, characterized by a state of persistent low-grade inflammation. Chronic inflammation is typified by the persistent effect of a causative stimulus, which leads to destruction of cells and tissues. In CKD, and especially in end-stage renal disease (ESRD), the systemic concentrations of both pro- and anti-inflammatory cytokines are several-fold higher, due to both decreased renal clearance and increased tissue production. This chapter describes the physiopathology, implications, monitoring, and potential therapeutic management of these complex inflammatory processes.

Pathogenesis of inflammation in chronic kidney disease

Prevalence of inflammation

Based on C-reactive protein (CRP) measurements, inflammation is a common feature in advanced CKD worldwide. The European dialysis patient currently has a mean CRP of 7–8 mg/L and a median of 4–5 mg/L. In the United States, levels are slightly higher and in Asian dialysis patients substantially lower. Findings are similar in patients with CKD at stages 3 to 5 not yet on dialysis. Data from the National Health and Nutrition Examination Survey III (NHANES III) show that about 50% of the patients with a glomerular filtration rate (GFR) of 15–60 mL/min had CRP levels > 2.1 mg/L. In addition, the aged-adjusted probability of having CRP > 2.1 mg/L rose from 44% to 69% at estimated GFR of 60 and 30 mL/min, respectively. One could argue that the 'uraemic inflammation' and disease burden determines the basal level of inflammation and that the dialysis procedure per se has some but not extensive additional impact. However, it is not known whether the inflammatory process would be aggravated if dialysis were not initiated. Thus, although the dialysis procedure per se may provoke inflammation, dialysis treatment could also be a stabilizing factor in a dynamic inflammatory process.

The many causes of inflammation in chronic kidney disease

The many and varied factors, inherent or not to the uraemic milieu, that contribute to systemic inflammation in these patients are outlined in Table 110.1. Of those, intercurrent clinical events are the most important. Infectious agents and microorganisms, such as *Chlamydia pneumoniae* are causative or contributory factors to the inflammatory cascade, being also associated with atherosclerosis progression. Reductions of kidney function per se, and even small changes in residual renal function (RRF) seem to have an impact on the magnitude of 'uraemic inflammation'. It has been hypothesized that retention of circulating cytokines, advanced glycation end products, and pro-oxidants initiate the pro-inflammatory milieu when renal function declines. Additional mechanisms by which failing kidney function may promote inflammation include sympathetic overactivity (and/or blunted vagal nerve activity) or chronic inflammatory process associated to periodontitis. Based on the finding of histological evidence of chronic inflammation in the uraemic gastrointestinal tract (i.e. oesophagitis, gastritis, enteritis, and colitis), it can be speculated that impairment of the intestinal barrier function with increased permeability of large molecules and increased penetration of bacteria may also contribute to uraemic systemic inflammation.

The haemodialysis (HD) procedure per se (Chapter 255) can also contribute to increased systemic inflammation as a result of the interaction of circulating monocytes with non-biocompatible membranes, blood contact with non-sterile dialysate solution, use of impure dialysate, the extent of convective transport, and the frequency and duration of dialysis. However, the dialysis procedure is unlikely to be a major instigator of inflammation because of the high prevalence of elevated inflammation biomarkers in ESRD patients not yet undergoing renal replacement therapy. Overhydration and volume overload may, through bacterial or endotoxin translocation in patients with severe gut oedema, lead to immunoactivation and increased inflammatory cytokine production. Finally, strong interrelations between inflammation, RRF, and left ventricular hypertrophy (Chapter 101) (LVH) have been documented in dialysis patients.

Obesity (Chapter 106), a common finding in CKD patients, may also contribute to enhanced inflammatory activity. Both truncal fat mass or abdominal fat deposition have been associated with increased systemic inflammation in dialysis patients. The reasons for

Table 110.1 Causes of inflammation in chronic kidney disease

Modifiable	Non-modifiable
Reduction of kidney function (toxin retention)	Genetic/racial differences
Intercurrent clinical events (comorbidities, infections)	
Haemodialysis procedure	
Volume overload	
Sympathetic and parasympathetic imbalance	
Obesity/overweight	
Environmental factors (lifestyle, epigenetics?)	
Impaired intestinal barrier function	

Table 110.2 Consequences of inflammation in chronic kidney disease

Protein-energy wasting	Anorexia
	Muscle proteolysis
	Insulin resistance
	Pro-catabolic environment
	Increased energy expenditure
Vascular calcification	Mineralization of vascular cells
	Altered synthesis of bone turnover agents
Endocrine disorders	Resistance to growth hormone/IGF-1 action
	Low thyroid hormone levels
	Testosterone deficiency
Psychosocial disorders	Depression
	Sleep disorders

this association relate to the capacity of adipocytes and fat-infiltrated macrophages to secrete adipokines, interleukin (IL)-6, or tumour necrosis factor (TNF) into systemic circulation. The majority of adipokines (such as leptin and visfatin) seem to have pro-inflammatory effects. Considering the dramatic effect that loss of RRF has on the clearance of adipokines, the systemic effects of adipokine imbalance in CKD patients may be even greater than in the general population. Pro-inflammatory genes have been shown to be upregulated in visceral fat from CKD patients as compared to matched controls.

External and internal environmental stresses may affect the phenotype through changes in the epigenome. Aberrant DNA methylation may, in relation to uraemic dysmetabolism, have complex interactions promoting development of premature cardiovascular disease (CVD). As epigenetic mechanisms regulating the functional properties of the genome are heritable through cell divisions and may be sensitive to an abnormal environment (such as uraemia) they could be potential new targets for interventions. Shortening of telomeres (nucleoprotein complexes protecting the chromosome ends that are involved in chromosome stability and repair) has been associated with an inflammatory phenotype and increased mortality in HD patients. In this context, it is of interest that telomere shortening to a critical length results in loss of histone and DNA methylation at mammalian telomeres, concomitant with increased histone acetylation.

Recent studies suggest that the inflamed uraemic phenotype is also the result of genetic factors. Asian dialysis patients treated in the United States also have a markedly lower adjusted relative risk of mortality than Caucasians. Indeed, a substantial heritability (35–40%) has been found for CRP, and many studies demonstrate a significant impact of genetic variations on the uraemic inflammatory response.

Clinical implications of systemic inflammation

The pleiotropic nature of pro-inflammatory cytokines impinges upon the development of common complications in CKD, briefly outlined in Table 110.2.

Inflammation leading to protein energy wasting

The causes of protein energy wasting (PEW; Chapters 106, 274) include a spectrum of chronic debilitating conditions in which persistent inflammation is a common feature, such as HIV, tuberculosis, congestive heart failure, obstructive pulmonary disease, malignancies, and septicaemia. PEW is associated with anorexia, progressive weight loss, and depletion of both adipose tissue and skeletal muscle, and is present in many ESRD patients. Inflammatory cytokines interact with several pathways in the central nervous system to affect specific brain areas related to appetite regulation. Also, IL-6 per se may stimulate muscle protein breakdown and promote wasting. Increased levels of IL-6 have been related to various markers of wasting in uraemic patients, indicating an important role for this cytokine in the development of PEW and muscle catabolism. As IL-6 also inhibits the secretion of insulin-like growth factor (IGF)-1, decreased IGF-1 signalling may also be involved in the uraemic sarcopenic process. However, signs of PEW are limited to patients with body mass indices (BMIs) < 20 kg/m^2, but also to patients with normal and high BMIs. In each of these BMI categories, CRP and IL-6 concentrations were higher in wasted patients than in non-wasted patients, demonstrating that excess weight does not exclude the occurrence of PEW (i.e. obese sarcopenia). There are several additional mechanisms by which inflammation can lead to muscle wasting in CKD patients: increased insulin resistance, activation of ATP-ubiquitin proteolytic pathway, and increased energy expenditure. It should be stated that to date, there is no solid evidence that normalization of inflammatory markers would lead to differences in nutritional status. In a recent longitudinal study of prevalent HD patients, higher serum IL-6 levels were associated with all-cause mortality without additional changes in clinical and laboratory markers of nutritional status.

Inflammation leading to vascular calcification

There is a wealth of data linking the *vascular calcification* (Chapter 120) process and systemic inflammation. TNF can induce mineralization of calcifying vascular cells *in vitro* and co-culture of these cells with monocyte/macrophages (the source of most cytokines) can accelerate mineralization. Receptor activator of nuclear factor-kappa B ligand (RANKL) is a membrane-bound or soluble cytokine essential for osteoclast differentiation, whereas the decoy receptor osteoprotegerin (OPG) masks RANKL activity. As both seem to influence the inflammatory component of atherosclerosis, it is of interest that OPG upregulates endothelial cell adhesion molecule response to TNF. These findings suggest a mechanism by which OPG may stimulate inflammation in

atheroma and thereby promote the progression and complications of atherosclerosis, which is in accord with the observed detrimental effects on survival of both increased inflammation and OPG levels in HD patients. On the other hand, vascular calcification, as part of the atherosclerotic process, is due to the deposition in the arterial intima of basic calcium phosphate crystals, similar to those that mineralize bone. It was recently shown that these crystals could interact with and activate human monocyte-derived macrophages, inducing a pro-inflammatory state via protein kinase C and MAP kinase pathways. This implies a vicious circle of inflammation and arterial calcification that could explain the associations between inflammation and outcome in CKD. Finally, the most well-studied circulating inhibitor of ossification is fetuin-A. Mice lacking the gene encoding for fetuin-A rapidly develop ectopic soft tissue ossification and die at an early age. In CKD, low levels of circulating fetuin-A are associated with cardiac valvular calcification, increased cardiovascular burden, and elevated mortality risk. Inflammation and PEW may be important causes of a decrease in serum fetuin-A levels in patients with CKD, as it behaves as a negative acute phase reactant (see Chapters 111, 120).

Inflammation, endocrine disorders, and depression

The kidney is a key modulator of *endocrine function* and an important target for hormonal action. As a direct consequence, the uraemic state is associated with abnormalities in the synthesis or action of many hormones. Evidence suggests that this hormonal dysmetabolism may be aggravated by persistent inflammation. Resistance to the anabolic drive by the growth hormone (GH)/IGF-1 axis contributes to the loss of strength and muscle mass in adult CKD patients. The inflammatory response inhibits GH action, and GH forearm perfusion studies demonstrated that a resistance to pharmacologic doses of GH is not related to uraemia per se but rather to an increased inflammatory state. Persistent inflammation may also be an important cause of the 'low triiodothyronine (T_3) syndrome' frequently observed in ESRD. Indeed, a single-dose injection of IL-6 in healthy humans downregulates the peripheral conversion of thyroxine into T_3. Because of this, some authors have hypothesized that subclinical hypothyroidism or the 'low T_3 syndrome' is an intermediate link between inflammation, PEW, and CVD in uraemia. Finally, low-grade persistent inflammation in uraemia may also promote testosterone deficiency, contributing to the overall pro-catabolic state of uraemia.

Depressive symptoms are more frequent with gradual reduction in renal function and relate to poor outcome and mortality in this and other patient groups. Cytokines are thought to be important mediators of brain immune connection and may play an important role in the pathogenesis of depression due to their effect on neurotransmitters and neurohormones. In dialysis patients, depressive symptoms seemed to worsen in the presence of increased IL-6 levels, and 8 weeks of fluoxetine treatment in depressed HD patients decreased serum IL-1β levels. Depression may also link to fatigue and unwillingness to eat, contributing to the vicious cycle of anorexia, physical inactivity, PEW, and worse outcome. All of these have also been attributed, in part, to the effects of systemic inflammation. Sleep disorders have also been linked to systemic inflammation in dialysis patients and it is of interest that the correction of these disorders by cognitive behavioural therapy also reduced CRP levels in a Taiwanese study.

Inflammation as a catalyst of other risk factors

Persistent low-grade inflammation in CKD may, in addition to putative direct pro-atherogenic effects, serve as a catalyst and modulate the effects of other risk factors for PEW and CVD (Fig. 110.1). The concurrent presence of inflammation, CVD, and PEW associates with higher mortality rates than expected from the single effects of these features, illustrating the existence of a real interaction effect that conveys a syndrome where the whole is more than the sum of its parts. Also, persistent inflammation in dialysis patients has supra-additive effects in the prediction of mortality associated to low S-albumin or increased ADMA. Persistent inflammation can also accelerate and/or exacerbate the complications of vascular calcification. For instance, whereas elevated OPG in the context of an inflammatory milieu strongly predicted survival, such effect was not observed in uninflamed dialysis patients. Similarly, ESRD patients with a genetic predisposition to low fetuin-A levels had a higher mortality rate in the presence of inflammation. A significant prognostic value of serum fetuin-A levels in HD patients was only observed in the context of persistent inflammation. Also, the associations between loss of RRF and valvular calcification and LVH in peritoneal dialysis (PD) patients were closely dependent on both the calcium × phosphate product and the inflammatory status. Taken together, an active interplay between vascular calcification and atherosclerosis via inflammation may exist. This seems to catalyse this effect against a background of severe mineral disturbances.

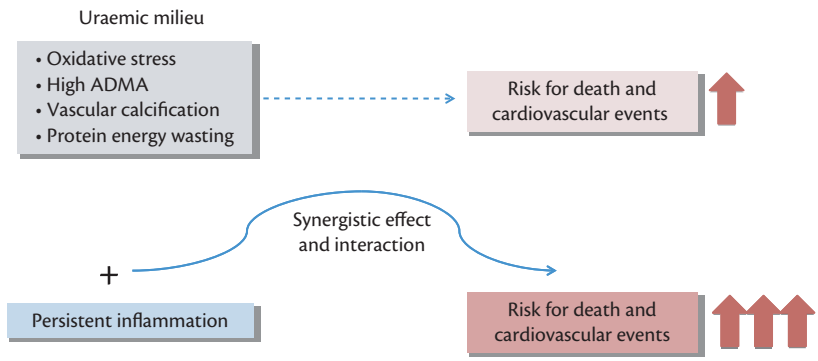

Fig. 110.1 Persistent inflammation as a catalyst for other risk factors in CKD. Certain risk factors in the uraemic milieu are clear and independent predictors of mortality and cardiovascular risk. This risk seems independent of inflammatory status. However, the presence of concurrent inflammation seems to exacerbate the risk associated to these factors over and above that expected from their solo effects. This denotes an additive and in some cases multiplicative interaction, appealing to the hypothesis we propose that persistent inflammation acts as a catalyst and amplifier of other risk factors.

The effects of various interventions should, therefore, always be analysed separately in inflamed and uninflamed CKD patients.

Monitoring inflammation

CRP is the prototypic marker of inflammation because of its reliability, low cost, and availability. When monitoring inflammation in the clinical setting, however, the reasons why CRP needs to be measured and the likelihood that diagnostic and therapeutic strategies might be needed should be considered. Despite a decade of extensive research on the causes and effects of uraemic inflammation, no randomized trials with testing of inflammatory markers as the primary intervention have been performed, nor have cost-effectiveness analyses been completed to assess additional costs or cost savings through the use of such tests. Consequently, the following suggestions about the routine monitoring of inflammatory markers are not evidence based and reflect the authors' opinion.

Inflammation and prediction of mortality

Prospective epidemiological studies in HD, PD, and kidney transplant patients have all shown that a single measurement of inflammatory biomarkers is an independent predictor of poor outcome. There is, nevertheless, biological intra- and interindividual variability for inflammatory mediators in the setting of CKD, even more for the non-specific CRP responses. While decreased renal function, increased number of co-morbidities, PEW, and the uraemic environment affect interindividual inflammatory variability, intraindividual variation may be further exacerbated by intercurrent clinical events, changes in RRF, type of vascular access, membrane bio-incompatibility, dialysate backflow, endotoxaemia, and the intermittent presence of dialysis. Volume status, fluid intake, and RRF are also associated with this phenomenon. Although it is important to understand and to evaluate inflammation in the context of its variability as disease evolves, few studies have addressed the consequences of regular monitoring of inflammatory markers on outcome. Of those, it seems that the average of serial measurements of CRP or IL-6 provides a better survival prediction than single measurements. Patients with a persistent CRP elevation during a specific time period exhibit worse outcome that those with persistent low levels or those increasing their CRP concentration. Although epidemiological research may suggest that regular monitoring of inflammation can be helpful in determining patient prognosis, no solid evidence exists to date demonstrating the advantage of regular CRP monitoring in dialysis units. Whether CRP measurements in uraemic patients add prognostic value beyond that provided by traditional risk factor algorithms (such as the Framingham risk factor score) is not clear. While this has never been addressed in CKD patients, studies at a general population level suggest that CRP measurements provide very limited predictive value for mortality over and above established risk factors, such as hypertension, cholesterol, and smoking. Such a study was acknowledged by the American Heart Association/Centers for Disease Control and Prevention (AHA/CDC) as being indicative that insufficient evidence existed to support the use of CRP as a clinical tool in the prediction of cardiovascular events. CRP levels may, however, help in the clinical decision process by improving the discrimination of subjects that have died and the reclassification of risk prediction by the Framingham scales at a general population levels. Whether this is the case in the CKD population, in whom a considerable proportion of Framingham risk factors are already present, is doubtful.

Why and when should inflammation be monitored?

In dialysis units, monthly CRP estimation could help to monitor the presence of contaminated water or dialysis fluid, and audit vascular access status, especially central line. CRP screening should not be an alternative to screening for major risk factors in determining patient risk, but should complement clinical judgement. Additional reasons for performing CRP measurements could be to motivate individuals with persistently elevated CRP levels to improve their lifestyles (such as smoking cessation, dental care, dietary modification, exercise, and weight loss) or to comply with drug therapies.

At the patient level, regular CRP screening could lead to the discovery of the underlying causes of inflammation and appropriate treatment. During short-term monitoring, the most clinically interesting patients are those presenting a 'smouldering', chronically elevated CRP level in the range of 5–50 mg/L (Table 110.3). Possible causes of these smouldering elevations include access graft-related or catheter-related infections, peripheral arterial disease, silent coronary ischaemia, ulcers, inflammatory bowel disease, malignancies, periodontitis, inflammation in failed transplants, tuberculosis, or hepatitis. According to AHA/CDC recommendations, a second CRP measurement taken 2 weeks after the first might be useful in identifying transient processes excluding biological variation in usual clinical practice. Patients with elevated CRP levels within this smouldering range should undergo an extensive clinical work-up, whether they have clinical symptoms or not. This scenario, in our view, is the most important and justified use for CRP screening at present. Indeed, careful patient monitoring is warranted after infectious processes, as it has been found that during the 30 days following an infection-related hospitalization in dialysis patients, the risk of cardiovascular events increases by 25%. There is a subset of patients undergoing dialysis with CRP elevations for no apparent reason. In patients with rapidly rising CRP levels or levels consistently > 50 mg/L, the clinician should seek overt infection, as well as other conditions associated with elevated CRP levels, such as malignancy or relapse of vasculitis. These diagnoses clearly show dynamic changes in the individual CRP distribution curve over time. The studies addressing longitudinal changes in inflammatory status discussed above could assist clinicians in their interpretation of the outcomes of monitoring of inflammatory status. Clearly, persistent CRP elevations or increases in inflammatory biomarkers identify patients. Strenuous efforts should be made to find the causes to target treatment.

Treatment of inflammation in chronic kidney disease

There are no sufficiently powered randomized controlled trials (RCTs) targeting a decrease in inflammation as a means of improving outcome in CKD patient with underlying co-morbid illnesses, at high risk of death. Current recommendations for treating inflammation in patients with CKD are, therefore, mainly patient specific. Based on the concept that inflammation plays a pivotal role in the development of the uraemic phenotype, circulating inflammatory markers could be primary targets for treatments including not

Table 110.3 Proposed inflammatory ranges in dialysis patients and possible causes of inflammation according to C-reactive protein (CRP) ranges

CRP 5–50 mg/L (smouldering or chronically raised)	CRP > 50 mg/L (acute infection)
Failed kidney transplant *in situ*	Underlying renal diagnosis (infected cysts in autosomal dominant polycystic kidney disease)
Biofilm (grafts, catheters, haemodialysis machine)	Vasculitis relapse, sinusitis, otitis
Silent (encapsulated) infection of arteriovenous or arterial grafts	Discitis, osteomyelitis, endocarditis
Chronic obstructive uropathies	Urinary tract infection/urosepsis, biliary sepsis
Calciphylaxis	Septicaemia, any cause (foreign material)
Cholesterol emboli	
Peripheral arterial disease	
Silent cardiac ischaemia (myocardial ischaemia, stroke)	
Congestive heart failure	
Ischaemic ulcers, neuropathic and venous ulcers	
Chronic chest disease (obstructive pulmonary disease)	
Inflammatory bowel disease	
Periodontal disease	
Arthritis	
Hepatitis	
Surgery	
Malignancy, *de novo* and recurrent	

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only specific anti-inflammatory therapies but also various anti-oxidative and 'antiwasting' approaches. When identifying a patient with elevated inflammatory markers, the clinician first needs to seek complications that may be caused by systemic inflammation. Particular sources of inflammation, such as bowel bacterial overgrowth, non-infected dialysis catheters, and failed kidney transplants should also be considered.

When pre-existing complications (including dialysis-related causes), have been excluded as a cause of persistent inflammation, interventional strategies could be cautiously considered. Although no specific treatment recommendations for uraemic inflammation can be currently recommended, physical, nutritional, and pharmacological approaches have shown beneficial effects on surrogate biomarkers of inflammation in ESRD in small RCTs. We may also expect favourable effects of these approaches on depression, fatigue, and general well-being.

Certain medications have demonstrated non-specific immunomodulatory effects in CKD. For example, in inflamed patients with moderate CKD, rosuvastatin treatment reduced CRP and improved both cardiovascular events and all-cause mortality (Ridker et al., 2010). In contrast, data on the effects of statins on inflammatory biomarkers in ESRD are not as consistent (Krane et al., 2008; Fellstrom et al., 2009). Accumulating evidence reveals an anti-inflammatory potential for cholecalciferol supplementation on circulating inflammatory markers in CKD patients (Matias et al., 2010; Stubbs et al., 2010). Sevelamer, which possesses LPS-binding properties, has also been associated with a reduction in circulating CRP and endotoxin levels in patients with CKD, as well as amelioration of endothelial dysfunction (Caglar et al., 2008; Stinghen et al., 2010). Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers showed suppressive effects on inflammation in various CKD studies (Yilmaz et al., 2009; Yamamoto et al., 2010). Eight-week treatment with aliskiren, a direct renin inhibitor, also lowered CRP levels in patients on dialysis (Morishita et al., 2011). One study showed that allopurinol treatment in patients with moderate CKD resulted in a significant lowering of CRP in addition to a reduction in cardiovascular risk, hospitalization and delay in renal progression (Goicoechea et al., 2010).

Of the currently available anticytokine therapies, etanercept, a TNF-receptor antagonist, was tested in uraemic persistent inflammation in a small number of patients on HD, primarily aiming at an improvement in nutritional profiles. Forty-four weeks of treatment with etanercept showed a positive effect on albumin and pre-albumin levels compared to the placebo group with no adverse events, while the treatment resulted in a non-significant change in CRP and IL-6 (Don et al., 2010). In a recent small prospective controlled trial, 22 HD patients with signs of inflammation were randomized to recombinant human IL-1 receptor antagonist (anakinra) or placebo over 4 weeks (Hung et al., 2011). Those who received IL-1ra treatment showed an impressive 53% reduction in CRP, 40% reduction in IL-6 levels, and 23% increase in mean pre-albumin so further studies are needed.

Further reading

Avesani, C. M., Carrero, J. J., Axelson, J., *et al.* (2006). Inflammation and wasting in chronic kidney disease: partners in crime. *Kidney Int*, 70, S8–13.

Avesani, C. M., Draibe, S. A., Kamimura, M. A., *et al.* (2004). Resting energy expenditure of chronic kidney disease patients: influence of renal function and subclinical inflammation. *Am J Kidney Dis*, 44, 1008–16.

Ayus, J. C., Mizani, M. R., Achinger, S. G., *et al.* (2005). Effects of short daily versus conventional haemodialysis on left ventricular hypertrophy and inflammatory markers: a prospective, controlled study. *J Am Soc Nephrol*, 16, 2778–88.

Bologa, R. M., Levine, D. M., Parker, T. S., *et al.* (1998). Interleukin-6 predicts hypoalbuminemia, hypocholesterolemia, and mortality in haemodialysis patients. *Am J Kidney Dis*, 32, 107–14.

Bossola, M., Sanguinetti, M., Scribano, D., *et al.* (2009). Circulating bacterial-derived DNA fragments and markers of inflammation in chronic haemodialysis patients. *Clin J Am Soc Nephrol*, 4, 379–85.

Carrero, J. J., Chmielewski, M., Axelsson, J., *et al.* (2008a). Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. *Clin Nutr*, 27, 557–64.

Carrero, J. J., Cordeiro, A. C., Lindholm, B., *et al.* (2010). The emerging pleiotrophic role of adipokines in the uraemic phenotype. *Curr Opin Nephrol Hypertens*, 19: 37–42.

Carrero, J. J., Park, S. H., Axelsson, J., *et al.* (2009a). Cytokines, atherogenesis, and hypercatabolism in chronic kidney disease: a dreadful triad. *Semin Dial*, 22, 381–6.

Carrero, J. J., Qureshi, A. R., Axelsson, J., *et al.* (2007). Clinical and biochemical implications of low thyroid hormone levels (total and free forms) in euthyroid patients with chronic kidney disease. *J Intern Med*, 262, 690–701.

Carrero, J. J., Qureshi, A. R., Parini, P., *et al.* (2009b). Low serum testosterone increases mortality risk among male dialysis patients. *J Am Soc Nephrol*, 20, 613–20.

Carrero, J. J. and Stenvinkel, P. (2009). Persistent inflammation as a catalyst for other risk factors in chronic kidney disease: a hypothesis proposal. *Clin J Am Soc Nephrol*, 4 Suppl 1, S49–55.

Carrero, J. J. and Stenvinkel, P. (2010). Inflammation in end-stage renal disease—what have we learned in 10 years? *Semin Dial*, 23(5), 498–509

Carrero, J. J., Stenvinkel, P., Fellstrom, B., *et al.* (2008b). Telomere attrition is associated with inflammation, low fetuin-A levels and high mortality in prevalent haemodialysis patients. *J Intern Med*, 263, 302–12.

Castaneda, C., Gordon, P. L., Parker, R. C., *et al.* (2004). Resistance training to reduce the malnutrition-inflammation complex syndrome of chronic kidney disease. *Am J Kidney Dis*, 43, 607–16.

Chen, H. Y., Cheng, I. C., Pan, Y. J., *et al.* (2011). Cognitive-behavioral therapy for sleep disturbance decreases inflammatory cytokines and oxidative stress in hemodialysis patients. *Kidney Int*, 80(4), 415–22.

Chen, L. P., Chiang, C. K., Chan, C. P., *et al.* (2006). Does periodontitis reflect inflammation and malnutrition status in haemodialysis patients? *Am J Kidney Dis*, 47, 815–22.

Cordeiro, A. C., Qureshi, A. R., Stenvinkel, P., *et al.* (2010). Abdominal fat deposition is associated with increased inflammation, protein-energy wasting and worse outcome in patients undergoing haemodialysis. *Nephrol Dial Transplant*, 25, 562–8.

De Mutsert, R., Grootendorst, D. C., Axelsson, J., *et al.* (2008). Excess mortality due to interaction between protein-energy wasting, inflammation and cardiovascular disease in chronic dialysis patients. *Nephrol Dial Transplant*, 23, 2957–64.

Enia, G., Mallamaci, F., Benedetto, F. A., *et al.* (2001). Long-term CAPD patients are volume expanded and display more severe left ventricular hypertrophy than haemodialysis patients. *Nephrol Dial Transplant*, 16, 1459–64.

Eustace, J. A., Astor, B., Muntner, P. M., *et al.* (2004). Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. *Kidney Int*, 65, 1031–40.

Fanti, P., Asmis, R., Stephenson, T. J., *et al.* (2006). Positive effect of dietary soy in ESRD patients with systemic inflammation—correlation between blood levels of the soy isoflavones and the acute-phase reactants. *Nephrol Dial Transplant*, 21, 2239–46.

Friedman, A. N., Moe, S. M., Perkins, S. M., *et al.* (2006). Fish consumption and omega-3 fatty acid status and determinants in long-term haemodialysis. *Am J Kidney Dis*, 47, 1064–71.

Garibotto, G., Russo, R., Sofia, A., *et al.* (2008). Effects of uraemia and inflammation on growth hormone resistance in patients with chronic kidney diseases. *Kidney Int*, 74, 937–45.

Garibotto, G., Sofia, A., Procopio, V., *et al.* (2006). Peripheral tissue release of interleukin-6 in patients with chronic kidney diseases: effects of end-stage renal disease and microinflammatory state. *Kidney Int*, 70, 384–90.

Goldstein, S. L., Ikizler, T. A., Zappitelli, M., *et al.* (2009). Non-infected haemodialysis catheters are associated with increased inflammation compared to arteriovenous fistulas. *Kidney Int*, 76, 1063–9.

Grootendorst, D. C., de Jager, D. J., Brandenburg, V. M., *et al.* (2007). Excellent agreement between C-reactive protein measurement methods in end-stage renal disease patients—no additional power for mortality prediction with high-sensitivity CRP. *Nephrol Dial Transplant*, 22, 3277–84.

Himmelfarb, J., Phinney, S., Ikizler, T. A., *et al.* (2007). Gamma-tocopherol and docosahexaenoic acid decrease inflammation in dialysis patients. *J Ren Nutr*, 17, 296–304.

Honda, H., Qureshi, A. R., Axelsson, J., *et al.* (2007). Obese sarcopenia in patients with end-stage renal disease is associated with inflammation and increased mortality. *Am J Clin Nutr*, 86, 633–8.

Honda, H., Qureshi, A. R., Heimburger, O., *et al.* (2006). Serum albumin, C-reactive protein, interleukin 6, and fetuin a as predictors of malnutrition, cardiovascular disease, and mortality in patients with ESRD. *Am J Kidney Dis*, 47, 139–48.

Ketteler, M., Bongartz, P., Westenfeld, R., *et al.* (2003). Association of low fetuin-a (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. *Lancet*, 361, 327–33.

Kshirsagar, A. V., Craig, R. G., Moss, K. L., *et al.* (2009). Periodontal disease adversely affects the survival of patients with end-stage renal disease. *Kidney Int*, 75, 746–51.

Liu, Y., Berthier-Schaad, Y., Fallin, M. D., *et al.* (2006). IL-6 haplotypes, inflammation, and risk for cardiovascular disease in a multiethnic dialysis cohort. *J Am Soc Nephrol*, 17, 863–70.

Morena, M., Terrier, N., Jaussent, I., *et al.* (2006). Plasma osteoprotegerin is associated with mortality in haemodialysis patients. *J Am Soc Nephrol*, 17, 262–70.

Muntner, P., Hamm, L. L., Kusek, J. W., *et al.* (2004). Prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. *Ann Intern Med*, 140, 9–17.

Panichi, V., Rizza, G. M., Paoletti, S., *et al.* (2008). Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCAVID study. *Nephrol Dial Transplant*, 23, 2337–43.

Parekh, R. S., Plantinga, L. C., Kao, W. H., *et al.* (2008). The association of sudden cardiac death with inflammation and other traditional risk factors. *Kidney Int*, 74(10), 1335–42.

Qureshi, A. R., Alvestrand, A., Divino-Filho, J. C., *et al.* 92002). Inflammation, malnutrition, and cardiac disease as predictors of mortality in haemodialysis patients. *J Am Soc Nephrol*, 13 Suppl 1, S28–36.

Schiffl, H., Lang, S. M., Stratakis, D., *et al.* (2001). Effects of ultrapure dialysis fluid on nutritional status and inflammatory parameters. *Nephrol Dial Transplant*, 16, 1863–9.

Schindler, R., Beck, W., Deppisch, R., *et al.* (2004). Short bacterial DNA fragments: detection in dialysate and induction of cytokines. *J Am Soc Nephrol*, 15, 3207–14.

Sjoland, J. A., Pedersen, R. S., Jespersen, J., *et al.* (2005). Intraperitoneal heparin ameliorates the systemic inflammatory response in PD patients. *Nephron Clin Pract*, 100, c105–10.

Snaedal, S., Heimburger, O., Qureshi, A. R., *et al.* (2009). Comorbidity and acute clinical events as determinants of C-reactive protein variation in haemodialysis patients: implications for patient survival. *Am J Kidney Dis*, 53, 1024–33.

Sonikian, M., Metaxaki, P., Papavasileiou, D., *et al.* (2010). Effects of interleukin-6 on depression risk in dialysis patients. *Am J Nephrol*, 31, 303–8.

Stenvinkel, P., Carrero, J. J., Axelsson, J., *et al.* (2008). Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uraemic puzzle? *Clin J Am Soc Nephrol*, 3, 505–21.

Stenvinkel, P., Heimburger, O., Paultre, F., *et al.* (1999). Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int*, 55, 1899–911.

Varagunam, M., Finney, H., Trevitt, R., *et al.* (2004). Pretransplantation levels of C-reactive protein predict all-cause and cardiovascular mortality, but not graft outcome, in kidney transplant recipients. *Am J Kidney Dis*, 43, 502–7.

Wanner, C., Krane, V., Marz, W., *et al.* (2005). Atorvastatin in patients with type 2 diabetes mellitus undergoing haemodialysis. *N Engl J Med*, 353, 238–48.

Wong, J. S., Port, F. K., Hulbert-Shearon, T. E., *et al.* (1999). Survival advantage in Asian American end-stage renal disease patients. *Kidney Int*, 55, 2515–23.

Zhang, L., Kao, W. H., Berthier-Schaad, Y., *et al.* (2007). C-Reactive protein haplotype predicts serum C-reactive protein levels but not cardiovascular disease risk in a dialysis cohort. *Am J Kidney Dis*, 49, 118–26.

Zoccali, C., Mallamaci, F., Tripepi, G., *et al.* (2003). Chlamydia pneumoniae, overall and cardiovascular mortality in end-stage renal disease (ESRD). *Kidney Int*, 64, 579–84.

Zoccali, C., Tripepi, G., Cutrupi, S., *et al.* (2005). Low triiodothyronine: a new facet of inflammation in end-stage renal disease. *J Am Soc Nephrol*, 16, 2789–95.

References

Don, B. R., Kim, K., Li, J., *et al.* (2010). The effect of etanercept on suppression of the systemic inflammatory response in chronic hemodialysis patients. *Clin Nephrol*, 73, 431–8.

Caglar, K., Yilmaz, M. I., Saglam, M., *et al.* (2008). Short-term treatment with sevelamer increases serum fetuin-a concentration and improves endothelial dysfunction in chronic kidney disease stage 4 patients. *Clin J Am Soc Nephrol*, 3, 61–8.

Fellstrom, B. C., Jardine, A. G., Schmieder, R. E., *et al.* (2009). Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*, 360, 1395–407.

Goicoechea, M., de Vinuesa, S. G., Verdalles, U., *et al.* (2010). Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clin J Am Soc Nephrol*, 5, 1388–93.

Hung, A. M., Ellis, C. D., Shintani, A., *et al.* (2011). IL-1β receptor antagonist reduces inflammation in hemodialysis patients. *J Am Soc Nephrol*, 22, 437–42.

Krane, V., Winkler, K., Drechsler, C., *et al.* (2008). Effect of atorvastatin on inflammation and outcome in patients with type 2 diabetes mellitus on haemodialysis. *Kidney Int*, 74, 1461–7.

Matias, P. J., Jorge, C., Ferreira, C., *et al.* (2010). Cholecalciferol supplementation in hemodialysis patients: effects on mineral metabolism, inflammation, and cardiac dimension parameters. *Clin J Am Soc Nephrol*, 5, 905–11.

Meuwese, C. L., Stenvinkel, P., Dekker, F. W., *et al.* (2011). Monitoring of inflammation in patients on dialysis: forewarned is forearmed. *Nat Rev Nephrol*, 7(3), 166–76.

Morishita, Y., Hanawa, S., Chinda, J., *et al.* (2011). Effects of Aliskiren on blood pressure and the predictive biomarkers for cardiovascular disease in hemodialysis-dependent chronic kidney disease patients with hypertension. *Hypertens Res*, 34(3), 308–13.

Ridker, P. M., MacFadyen, J., Cressman, M., *et al.* (2010). Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. *J Am Coll Cardiol*, 55, 1266–73.

Stinghen, A. E., Gonçalves, S. M., Bucharles, S., *et al.* (2010). Sevelamer decreases systemic inflammation in parallel to a reduction in endotoxemia. *Blood Purif*, 29, 352–6.

Stubbs, J. R., Idiculla, A., Slusser, J., *et al.* (2010). Cholecalciferol supplementation alters calcitriol-responsive monocyte proteins and decreases inflammatory cytokines in ESRD. *J Am Soc Nephrol*, 21, 353–61.

Yamamoto, D., Takai, S., Hirahara, I., *et al.* (2010). Captopril directly inhibits matrix metalloproteinase-2 activity in continuous ambulatory peritoneal dialysis therapy. *Clin Chim Acta*, 411, 762–4.

Yilmaz, M. I., Axelsson, J., Sonmez, A., *et al.* (2009). Effect of renin angiotensin system blockade on pentraxin 3 levels in type-2 diabetic patients with proteinuria. *Clin J Am Soc Nephrol*, 4, 535–41.

CHAPTER 111

Vascular stiffness in chronic kidney disease: pathophysiology and implications

Jonathan N. Townend and Charles J. Ferro

Introduction: chronic kidney disease and cardiovascular risk

Chronic kidney disease (CKD) is associated with an elevated risk of cardiovascular disease with an inverse graded relationship with glomerular filtration rates (GFRs) < 60 (Go et al., 2004) and probably < 90 mL/min/1.73 m^2 (Van Biesen et al., 2007). Individuals in the general population with early-stage CKD are far more likely to die from cardiovascular disease than progress to end-stage renal disease (ESRD) (Keith et al., 2004). Whilst cardiovascular risk in ESRD is extreme, the burden of cardiovascular disease in the early stages of CKD is much greater in terms of public health. This increased cardiovascular risk cannot be explained by 'traditional' risk factors (Baigent and Landray, 2007).

The development of cardiovascular risk-lowering therapies is however hindered by the fact that although the epidemiological association between CKD and cardiovascular risk is robust, the pathophysiological mechanisms underlying the relationship are not understood (Chue et al., 2010; Moody et al., 2013). Although approximately 50% of all ESRD deaths are due to cardiovascular disease, only 18% of these are attributable to vasculo-occlusive diseases such as myocardial infarction, the remainder being attributed to sudden cardiac death, arrhythmia, or congestive heart failure (Chue et al., 2010). Heart failure is a major cause of morbidity and mortality in CKD with incident rates three to four times higher than in non-CKD subjects (Fig. 111.1; Chapter 98) (Foley et al., 2005; United States Renal Data System, 2012). Powerful evidence suggests that increased arterial stiffness is a major cause of this structural heart disease in CKD.

Vascular pathology in chronic kidney disease

There appear to be two distinct vascular pathologies occurring in CKD patients: atherosclerosis and arteriosclerosis (Edwards et al., 2006; Moody et al., 2013). Atherosclerosis is an intimal disease characterized by fibro-atheromatous plaques which lead to vascular occlusion. In CKD, there are distinct morphological differences compared to patients with normal kidney function, including increased plaque calcification and increased intimal and medial thickness (Schwarz et al., 2000). The other characteristic feature of CKD is thickening and calcification of the medial arterial layer, known as arteriosclerosis. Increased collagen content, calcification, hyperplasia, and hypertrophy of vascular smooth muscle cells (VSMCs) all result in wall hypertrophy, a process strongly associated with arterial stiffness (Edwards et al., 2006). Although associations have also been established between the degree of arterial stiffness and atheromatous plaque burden (van Popele et al., 2001), most studies on the subject have failed to demonstrate a significant influence of traditional atherosclerotic risk factors on the development of arteriosclerosis, suggesting that other mechanisms are driving this process (Cecelja and Chowienczyk, 2009). Whilst endothelial dysfunction and intimal disease are known to contribute to arterial stiffening, the relationship between arteriosclerosis and atheromatous disease remains poorly understood (Moody et al., 2013).

The clinical importance of arterial stiffness

A major function of the aorta and large arteries is to buffer oscillatory changes in blood pressure (BP) that result from intermittent ventricular ejection. The highly distensible arterial system ensures that most tissues receive near steady flow with no exposure to peak systolic pressures. This mechanism is so efficient that there is almost no drop in mean pressure from ascending aorta to peripheral arteries (Avolio et al., 2009). It is hypothesized that loss of arterial distensibility makes the aorta more rigid and less able to accommodate the volume of blood ejected by the left ventricle. This causes a greater pressure augmentation in systole and higher pulse pressures (Davies et al., 2008). An alternative explanation for the elevated systolic pressure that accompanies an increase in arterial stiffness is the more rapid return of reflected waves of ventricular contraction from the distal vasculature (Franklin et al., 1997). Healthy compliant arteries reflect waves returning to the ascending aorta in diastole, thus augmenting diastolic pressure and coronary blood flow, whilst in aged stiffer arteries the reflected waves return earlier in systole, augmenting systolic and pulse pressures and increasing ventricular afterload. Although an attractive idea, there is now abundant evidence showing that reflected waves arrive in systole irrespective of age (Baksi et al., 2009). These data, together with information available from techniques that separate reflected waves from reservoir pressure,

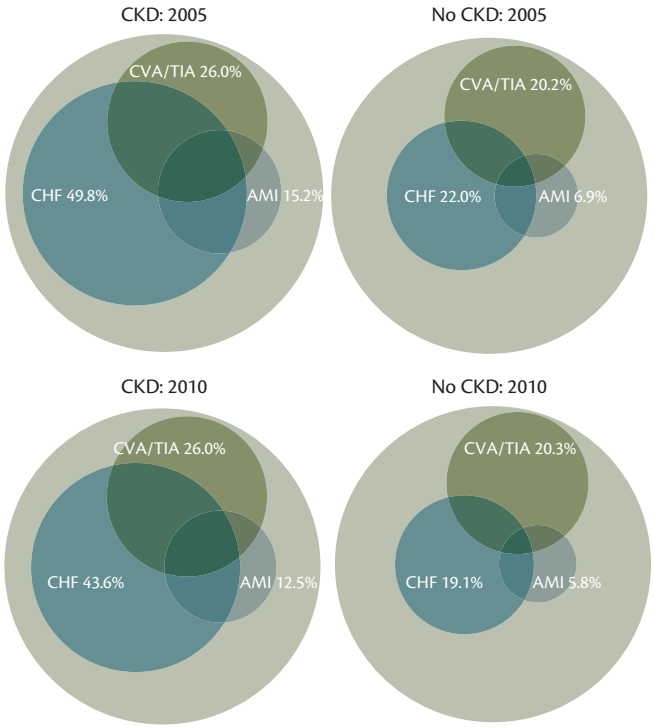

Fig. 111.1 Cardiovascular disease in patients with and without chronic kidney disease. 31 December 2005 and 2010 point prevalent Medicare enrollees, age 66 and older, with fee-for-service coverage for the entire calendar year. AMI, acute myocardial infarction; CHF, congestive heart failure; CKD = chronic kidney disease; CVA = cerebrovascular accident; TIA = transient ischaemic attack.
Adapted from *USRDS 2012 Annual Data Report* (United States Renal Data System, 2012).

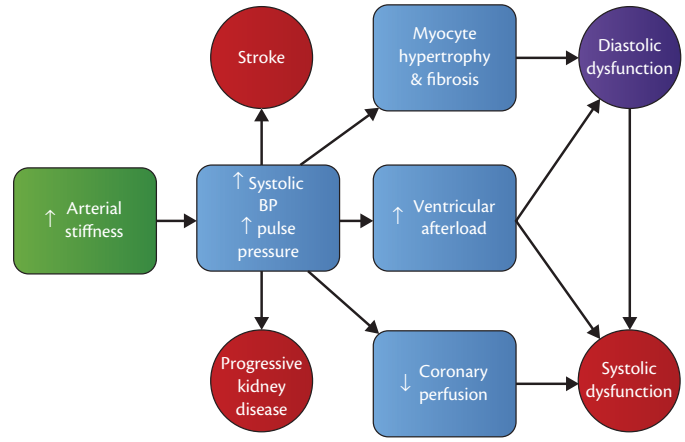

Fig. 111.2 Consequences of increased arterial stiffness in chronic kidney disease. Increased arterial stiffness leads to increases in systolic blood pressure (BP) and pulse pressure causing myocyte hypertrophy, increased ventricular afterload, and reduced coronary perfusion, resulting in diastolic and systolic dysfunction and ultimately congestive heart failure. Raised systolic and pulse pressures also promote further vascular damage increasing the risk of stroke and potentially the further loss of kidney function.
Adapted from Chue et al. (2010).

strongly suggest that the 'cushioning effect' or Windkessel model appears to be the more important physiological explanation (Wang et al., 2003). Regardless of the underlying mechanism, as arterial stiffness increases the myocardium, brain, and kidneys are exposed to higher systolic pressures and greater pressure fluctuations resulting in myocardial, cerebral, and renal microvascular damage and an increased risk of stroke and potentially renal impairment (Fig. 111.2) (O'Rourke and Safar, 2005). Furthermore, the lower diastolic pressure reduces diastolic coronary perfusion and promotes subendocardial ischaemia, myocardial fibrosis, and ventricular stiffening. It also places greater reliance on systolic coronary perfusion, conferring heightened vulnerability of the myocardium to any decline in systolic function (Chue et al., 2010).

Cardiac function is physiologically matched with arterial function through ventricular-arterial coupling to ensure maximum cardiac work and efficiency (Chen et al., 1998). When arterial stiffness increases, the left ventricle generates greater end-systolic pressures that enhance ventricular systolic wall stress and increase ventricular stiffness. These compensatory adaptations maintain cardiac performance with enhanced contractility at rest, but at a price: cardiac reserve is reduced, diastolic function is impaired, and the cardiovascular response to alterations in pressure and volume load is blunted leading to haemodynamic instability (Chen et al., 1998). Myocardial oxygen consumption also increases, promoting subendocardial ischaemia (Watanabe et al., 1993). Increased ventricular stiffening further impairs diastolic coronary perfusion through increased compression of the coronary microvasculature (Davies et al., 2006). Whilst this is a common feature of advanced disease characterized by left ventricular hypertrophy (LVH), it is often present despite normal ventricular wall thickness (Chen et al., 1998). Reduced aortic distensibility also correlates with reduced exercise capacity despite normal or enhanced left ventricular (LV) systolic function (Hundley et al., 2001). Increased arterial stiffness due to underlying CKD may therefore explain heart failure with preserved ejection fraction, otherwise known as diastolic heart failure.

It is known that the rate of deterioration in renal function is a powerful predictor of future cardiovascular events and mortality, with some studies suggesting it is a better predictor than baseline renal function (Matsushita et al., 2009; Shlipak et al., 2009). Both systolic and pulse pressure, independently predict progression of CKD and blood pressure lowering remains the cornerstone of CKD management with the primary aim of slowing decline in GFR (National Kidney Foundation 2002; Madero et al., 2013). Several, although not all (Upadhyay et al., 2009; Chue et al., 2011), studies have found an association between arterial stiffness and the incidence (Madero et al., 2013) or progression of CKD (Takenaka et al., 2005; Taal et al., 2007; Ford et al., 2010) independently of blood pressure. The differences between these studies serve to emphasize the fact that actually very little is known about the natural history of arterial stiffness and CKD and in particular the complex interactions between age, uraemia, blood pressure, and medication in CKD patients (Chue et al., 2013a).

Arterioventricular interaction

Although the higher cardiovascular risk conferred by the presence of LVH is well recognized, the threshold for hypertrophy is arbitrary and it is becoming increasingly accepted that LV mass is a continuous variable and no biological dichotomy exists (Schillaci et al., 2000). Furthermore, > 70% of incident dialysis patients have established LVH, indicating that structural heart disease develops in the earlier stages of CKD (Foley et al., 1995). Abnormalities of LV function associated with early CKD and their relationship to arterial

stiffening have only recently been studied. Compared to controls, patients with stage 2 and 3 CKD had delayed ventricular relaxation, increased LV end diastolic stiffness and pressure, and elevated left atrial volumes (Edwards et al., 2008). Ventricular-arterial coupling was preserved with an increase in both arterial elastance (stiffness) and LV elastance, suggesting that aortic stiffness drives the development of LV stiffness in early CKD (Edwards et al., 2008).

LV systolic dysfunction is also common in ESRD but was considered rare in early CKD. Nevertheless, a study in normotensive patients with stage 2 and 3 CKD has demonstrated evidence of impaired longitudinal tissue deformation despite confirmed normal LV function on conventional echocardiographic criteria (Edwards et al., 2008). These abnormalities are associated with adverse cardiovascular outcomes in late stage CKD (Rakhit et al., 2007).

Measurement of arterial stiffness

Arterial stiffness represents a convenient shorthand term for alterations in the mechanical properties of blood vessels. The term arterial stiffness lacks a precise definition and has no mathematical relationship to the mechanical properties of arteries. As such, arterial stiffness is a purely descriptive term that cannot be directly measured or quantified. Inferences can be made about the mechanical properties of arteries by measuring pulse pressure or by measuring a variety of 'stiffness indices' or surrogates using a number of commercially available devices. Such devices usually measure one of three possible types of arterial stiffness: systemic stiffness (i.e. the entire circulation), regional or segmental stiffness (i.e. measure of the stiffness of a segment of the arterial tree), or local stiffness (i.e. a measure of the stiffness in a small section of one blood vessel) (Hamilton et al., 2007). When reading an article on 'arterial stiffness' it is important to know what is actually being referred to and measured.

Pulse pressure

The measurement of pulse pressure (diastolic subtracted from systolic blood pressure) is the simplest surrogate measure of arterial stiffness. It is determined by cardiac stroke volume and arterial stiffness (Dart and Kingwell, 2001). Pulse pressure indicates the degree of impairment of buffering of larger arteries.

Pulse wave velocity

Carotid-femoral or aortic pulse wave velocity (aPWV) is currently considered the 'gold-standard' measurement of arterial stiffness (Laurent et al., 2006). The principal determinants of PWV are described by the Moens–Korteweg equation (Hamilton et al., 2007). In a given blood vessel filled with blood of fixed density, PWV is proportional to the square root of the Young's modulus of elasticity of that vessel. That is, the stiffer the vessel the faster the PWV. However, the square root relationship between PWV and Young's modulus means that changes in PWV are not a particularly sensitive measure of changes in the mechanical properties of an artery.

PWV is usually obtained by measuring the time taken for a pulse wave to travel a specified distance, the distance being divided by the time to give velocity. Distance is usually estimated using a tape measure over the body surface; timing is performed by measuring the interval between points on a pressure or flow waveform using a proximal and distal sensor (Cohn et al., 2004). There are various devices on the market for measuring PWV (DeLoach and Townsend, 2008; Ferro et al., 2012).

Pulse wave analysis and augmentation index

The characteristics of small blood vessels may be inferred by analysing pulse waveforms obtained in larger, more proximal, feeding vessels. Stiffening of small arteries alters the magnitude and timing of reflected waves that can often be identified visually in late systole or more reliably by computer analysis of the diastolic pressure decay part of the pressure waveform (Ferro et al., 2002). Near the aortic root, the initial rise in pressure following LV ejection is rapidly superimposed with a reflected pressure wave returning from the periphery. The augmentation index (AIx) (Fig. 111.3) is a mathematical expression by which the increment in pressure after the first systolic shoulder to the peak of the aortic pressure is calculated as a percentage of pulse pressure (Ferro et al., 2002). The AIx depends on multiple factors including the shape of the forward wave, which is influenced by LV outflow and the elasticity of the ascending aorta, as well as the timing of the reflected wave, a factor influenced by gender, height, heart rate, reflected wave amplitude, and vessel stiffness. As such it must be interpreted with caution (Williams, 2004).

Central systolic pressure (the pressure representing the precise load to which the left ventricle is subject) can be calculated using validated transfer functions from peripheral arterial waveforms (Fig. 111.3). Although theoretically an attractive concept, doubt persists as to whether these central blood pressure measurements derived from pulse wave analysis provide additional prognostic information compared with brachial blood pressure measurements (Ng et al., 2014).

Local assessment of arterial stiffness

The terms 'compliance' (a change in volume or cross-sectional area for a given change in pressure) and 'distensibility' (a fractional change in volume or cross-sectional area for a given change in blood pressure) are often used interchangeably with stiffness. Changes in arterial diameter for a given distending pressure can be measured using ultrasound or magnetic resonance imaging (Fig. 111.4) (Chue et al., 2012a; Wall et al., 2013). However, measurement of distending pressure is difficult. This is because it is difficult to place a pressure sensor physically next to an ultrasound probe or in a magnetic resonance scanner and invasive pressure catheters can influence local flow and are not suitable for routine use. Thus pressure waveforms taken elsewhere in the circulation are often used and these can introduce pressure errors and phase delay (Meinders and Hoeks, 2004).

Arterial stiffness and mortality

aPWV measured in most reports by applanation tonometry using the carotid and femoral arteries, is the most widely used measure of arterial stiffness and is a powerful independent predictor of all-cause mortality and cardiovascular events in ESRD, hypertensives, the elderly, diabetics and the general population (Laurent et al., 2006; Chue et al., 2010; Moody et al., 2013). Cardiovascular risk and aPWV are both increased with only minor reductions in renal function (Wang et al., 2005). Aortic distensibility measured by cardiac magnetic resonance imaging is reduced compared to controls in stage 2 and 3 non-diabetic CKD (Edwards et al., 2008). An understanding of the potential mechanisms underlying increased arterial stiffness in CKD is important for devising strategies to prevent or reverse this pathophysiology.

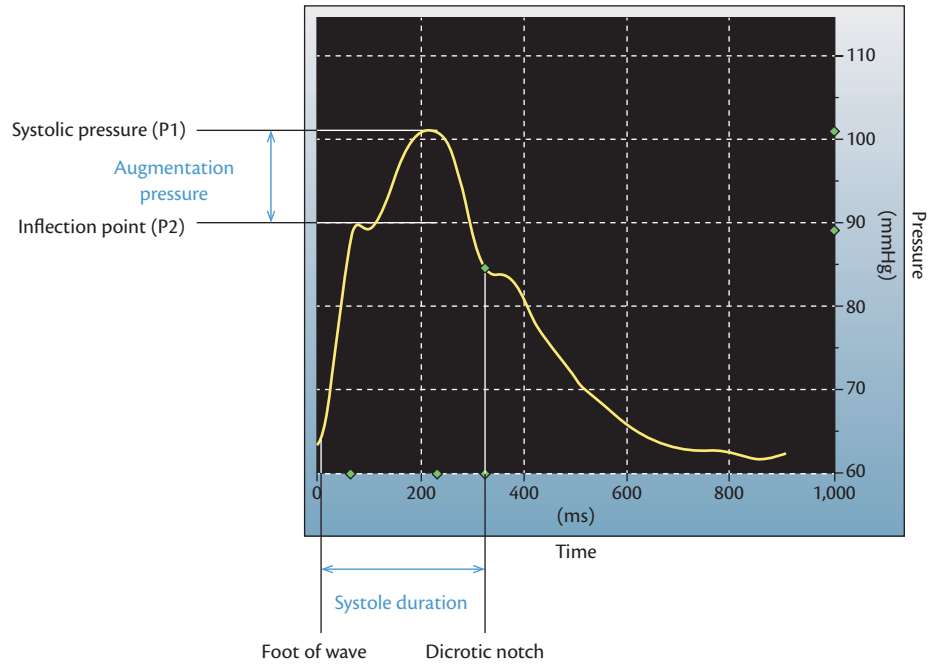

Fig. 111.3 The central proximal aortic waveform generated from pulse wave analysis. Systolic pressure is represented by the peak of the pulse wave (P1). The inflection point (P2) represents the arrival of reflected waves from the periphery. The pressure difference between P1 and P2 is the augmentation pressure. This is expressed as a percentage of pulse pressure to derive the augmentation index.

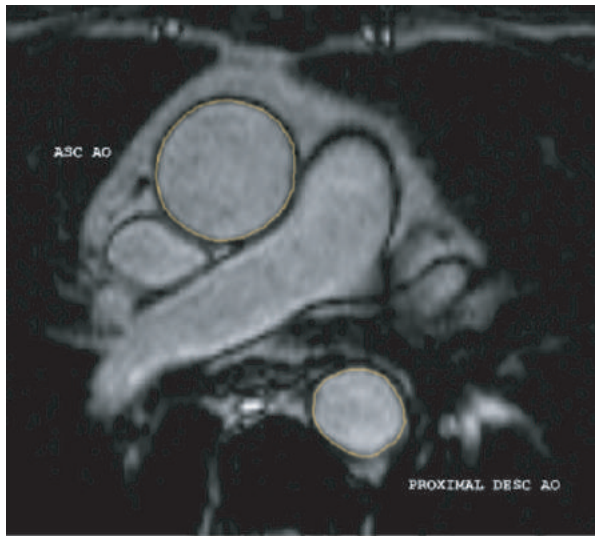

Fig. 111.4 Transverse slice through the aorta at the level of the pulmonary artery using magnetic resonance imaging. Cross-sectional areas for the ascending (ASC AO) and proximal descending aorta (PROXIMAL DESC AO) are determined in systole and diastole to measure regional aortic distensibility.

Mechanisms of increasing arterial stiffness associated with chronic kidney disease

Increasing arterial stiffness with age

Increased arterial stiffness and systolic and pulse pressures are characteristic features of ageing in Western populations and are independent risk factors for mortality (Franklin et al., 2001) and development of heart failure (Haider et al., 2003). Indeed, the detection and treatment of systolic hypertension now dominates clinical practice and isolated systolic hypertension is a well-recognized clinical entity (Dustan, 1989). Furthermore, for any given systolic blood pressure, event rates are inversely related to diastolic blood pressure indicating that increased pulse pressure is an important independent risk factor for cardiovascular disease in older age groups (Amery et al., 1985; Medical Research Council Working Party, 1985; Coope and Warrender, 1986; Dahlof et al., 1991; SHEP Cooperative Research Group, 1991; MRC Working Party, 1992; Staessen et al., 1997; Liu et al., 1998; Franklin et al., 1999; Staessen et al., 2000). Although these findings have been questioned (Lewington et al., 2002), they can potentially be explained by arterial stiffness being the dominant cause of elevated blood pressure and cardiovascular disease with age, and in pathophysiological conditions such as CKD (Franklin et al., 2001; Lewington et al., 2002).

The biomechanical properties of the arteries are largely dependent on the relative quantities of collagen and elastin, the main scaffolding proteins of the extracellular matrix (ECM) (Lee et al., 2012) as well as intrinsic changes in VSMCs (Qiu et al., 2010). Numerous studies have shown that the large arteries stiffen with age with overproduction of abnormal collagen fibres and relative loss of elastin from the ECM (Greenwald, 2007; Lee et al., 2012). The elastin lamellae become sparser with signs of fragmentation and calcification, whilst collagen molecules progressively acquire cross-links. A major unresolved question is whether these changes are truly time dependent or reflect exposure to the risk factors listed below. Similarly, the possible effect of the age-related decline in GFR on arterial stiffness remains unknown. Recent evidence suggests that nitric oxide-donating drugs may reverse the relative loss of elastin and increase in arterial stiffness that occurs with age (Raveaud et al., 2009; Pierce et al., 2012) and improve endothelial

function and cardiac hypertrophy independent of blood pressure (Dovinova et al., 2009). These agents may thus be able to prevent or reverse the increasing arterial stiffness associated with ageing and CKD.

Alterations in the extracellular matrix

Evidence of altered ECM structure in CKD comes from studies of subtotally nephrectomized rats in which aortic wall thickness was significantly greater than in controls (Amann et al., 1997). ECM volume was increased, elastic fibres were smaller, and collagen 'islands' were evident. VSMCs were larger and greater in number with ultrastructural changes suggesting increased secretory activity. No studies have yet examined changes in arterial microstructure in human CKD, but the coronary arteries of CKD patients show increased medial thickness and lower luminal area than those of non-CKD controls (Schwarz et al., 2000).

The mechanisms underlying ECM changes in CKD are currently unknown but matrix metalloproteinases (MMPs) have been implicated (Marson et al., 2012). These endopeptidase enzymes regulate the ECM and are produced by vascular and inflammatory cells. Increased MMP production enhances collagen and elastin turnover through enzymatic cross-link degradation (Jacob 2003) causing unravelling and weakening of the ECM. There are data supporting this mechanism in hypertensive patients (Yasmin et al., 2005) but also accumulating evidence of a role for MMP in the development of arterial stiffness in CKD, including the presence of increased vascular MMP activity in ESRD patients compared to healthy controls (Chung et al., 2009). This highlights a potential target for future therapeutic intervention (Castro et al., 2011; Marson et al., 2012).

Advanced glycation end products

Irreversible covalent cross-linking of collagen and elastin with carbohydrates or carbonyl compounds through non-enzymatic glycation results in the formation of advanced glycation end products (AGEs) (Reiser et al., 1992). Such postsynthetic glycation occurs widely in patients with impaired glucose tolerance and diabetes mellitus and to a lesser extent with ageing, although it is unclear whether or not this is inevitable or a consequence of exposure to factors such as oxidative stress and inflammation (Konova et al., 2004). Affected collagen is stiffer and less susceptible to slow hydrolytic degradation; glycation may also influence arterial stiffening through generation of reactive oxidant species and nitric oxide deactivation, promoting endothelial dysfunction (Bucala et al., 1991).

Levels of circulating AGEs correlate directly with serum creatinine in diabetic and non-diabetic CKD (Makita et al., 1991; Schwedler et al., 2002; Arsov et al., 2014). AGEs accumulate in ESRD as demonstrated by skin autofluorescence and they are independently associated with increased arterial stiffness (Ueno et al., 2008) and mortality (Arsov et al., 2014). Although there is some suggestion that AGEs are implicated in the development of arterial stiffness in CKD, this finding is not universal (Schwedler et al., 2002). Hypertensive subjects and older patients treated with AGE cross-link breakers demonstrate significant reductions in arterial stiffness and endothelial dysfunction (Kass et al., 2001; Zieman et al., 2007). Further studies are required to determine whether dietary AGE restriction or the use of AGE cross-link breakers could be a method of reducing arterial stiffness in CKD (Boutouyrie et al., 2011).

Endothelial dysfunction

The vascular endothelium is recognized as having multiple complex functions which regulate vascular tone, thrombosis, haemostasis, permeability, and cell adhesion (Moody et al., 2012). Although the term 'endothelial dysfunction' was originally coined to describe impaired endothelium-dependent vasodilatation to specific stimuli such as acetylcholine a much wider definition is now accepted encompassing the multiplicity of roles played by the vascular endothelium (Moody et al., 2012). Endothelial dysfunction is strongly associated with increased arterial stiffness in healthy individuals (McEniery et al., 2006).

Endothelial dysfunction (Chpater 113) has been thought to be an early and important feature of CKD (Thambyrajah et al., 2000). This may reflect relatively high levels of oxidative stress and reduced renal clearance of uraemic toxins such as asymmetrical dimethylarginine (ADMA) (Vallance et al., 1992) although this view has recently been challenged as CKD does not appear to be associated with endothelial dysfunction in the absence of other cardiovascular risk factors and hypertension (Lilitkarntakul et al., 2011). ADMA, together with its structural isomer symmetrical dimethylarginine, inhibits nitric oxide synthesis dose-dependently *in vitro* and increases basal vascular tone and BP in humans (Vallance et al., 1992; Bode-Boger et al., 2006). Pro-atherogenic actions of ADMA are evidenced by the association of high plasma ADMA concentrations with increased carotid intima-media thickness in ESRD patients (Zoccali et al., 2002).

Endothelin peptides (Chapter 114) are synthesized by endothelial cells and are powerful vasoconstrictors acting on VSMCs. They are implicated in the pathogenesis of several cardiovascular conditions and the progression of CKD (Dhaun et al., 2006; Chapter 114). Infusion of endothelin-1 in healthy humans to increase plasma levels to those seen in ESRD is associated with significant increases in aPWV, central systolic pressure, and pulse pressure (Vuurmans et al., 2003). Short-term endothelin-A receptor antagonism in non-diabetic CKD reduces proteinuria and arterial stiffness independent of BP lowering (Dhaun et al., 2009). Long-term effects of endothelin antagonism on cardiovascular risk in CKD are yet to be determined, but there is emerging evidence that endothelin antagonists may be of value in treating resistant hypertension, perhaps through direct effects on arterial stiffness (Dhaun et al., 2007, 2009, 2013).

Although it is accepted that endothelial dysfunction promotes arterial stiffening, a study of cultured endothelial cells *in vitro* suggests that stiff arteries themselves further reduce nitric oxide bioavailability through diminished expression of endothelial nitric oxide synthase (Peng et al., 2003). Arterial stiffness may therefore be self-perpetuating. Novel agents such as ghrelin appear to improve endothelial dysfunction (Tesauro et al., 2009) and offer potentially promising avenues for further investigation in CKD (Gunta and Mak, 2013).

Chronic inflammation and infection

Although commonly regarded as a risk factor for atheroma, a clear association between inflammation (Chapter 110) and arterial stiffness also exists. This is demonstrated by studies of conditions of chronic systemic inflammation (Maki-Petaja et al., 2006; Cachofeiro et al., 2008) and by studies of inflammatory markers and arterial stiffness in the healthy population (Yasmin et al., 2004). More specifically, aortic inflammation, as assessed using positron

emission tomography imaging, has recently been shown to influence aortic stiffness (Joly et al., 2009). The long-term use of immunosuppressive agents in inflammatory disorders is associated with a reduction in surrogate markers of cardiovascular risk (Choi et al., 2002) and such agents require further cautious investigation.

Pro-inflammatory cytokines damage endothelial cells by increasing the release of acid sphingomyelinase, which depresses endothelial cell signalling and function. Low glutathione levels further increase activation of sphingomyelinase (Liu and Hannun, 1997). Replenishment of glutathione using *N*-acetylcysteine, a cheap and well-tolerated food supplement, has been shown to improve endothelial function and cardiovascular outcomes in two small studies of patients with ESRD (Tepel et al., 2003; Wittstock et al., 2009) and further assessment of its potential in reducing arterial stiffness is warranted.

Inflammatory degradation of ECM elastin has been shown to accelerate arterial calcification in animal CKD models (Aikawa et al., 2009; New and Aikawa, 2011), prompting potential exploration of the role of immunosuppression and selective inhibition of elastase enzymes as therapeutic interventions in arterial stiffness reduction.

A number of chronic infections, including *Cytomegalovirus* (CMV) have been associated with cardiovascular disease in epidemiological studies although the mechanisms remain largely unknown. Although the evidence linking CMV seropositivity with arterial stiffness in the general population remains weak (Espinola-Klein et al., 2000; Steptoe and Halcox, 2008; Parrinello et al., 2012) there is new evidence linking CMV seropositivity with arterial stiffness in patients with early CKD (Wall et al., 2013). Ultimately, reducing the prevalence of CMV seropositivity might be a potential way of reducing the burden of cardiovascular disease in the general population.

The renin–angiotensin–aldosterone system

Angiotensin II (Chapet 210) is a powerful vasoconstrictor but also promotes inflammation by stimulating VSMCs to generate intracellular superoxides and inflammatory cytokines (Kranzhofer et al., 1999). Furthermore, it induces vascular remodelling through VSMC hypertrophy and proliferation, increased collagen synthesis and increased production of MMP (Takagishi et al., 1995) This ECM remodelling can be controlled by angiotensin-converting enzyme inhibitors (ACEIs) (Ahimastos et al., 2005). ACEIs and angiotensin II receptor blockers (ARBs) also inhibit AGE formation in a dose dependency *in vitro*, possibly by reducing generation of reactive oxygen species and reactive carbonyl compounds (Miyata et al., 2002).

Short- and long-term inhibition of the renin–angiotensin–aldosterone system (RAAS) with ACEIs and ARBs is associated with reductions in arterial stiffness but is almost invariably accompanied by BP reduction (Ahimastos et al., 2005; Mitchell et al., 2007). The relative importance of BP-lowering is difficult to distinguish from the direct tissue effects. In a longitudinal study of haemodialysis patients treated with ACEIs, BP lowering combined with decreased aPWV was associated with reduced all-cause and cardiovascular mortality (Guerin et al., 2001). Such mortality benefits were absent in subjects with unaltered aPWV despite BP reduction, lending some support to the theory that RAAS inhibition reduces risk through a BP-independent mechanism in ESRD.

Aldosterone levels, which frequently remain elevated despite treatment with ACEIs and ARBs, are correlated with arterial stiffness in hypertensive men independently of BP (Blacher et al., 1997). Aldosterone increases arterial stiffness independently of wall stress in subtotally nephrectomized rats given high-salt diets (Lacolley et al., 2002) and these effects are inhibited by the mineralocorticoid receptor (MR) antagonist eplerenone. MR activation is associated with endothelial dysfunction and activation of VSMC genes involved in vascular fibrosis, inflammation and calcification (Brown, 2008). Aldosterone upregulates expression and sensitivity of vascular angiotensin receptors in rats (Ullian et al., 1992). The MR antagonist spironolactone inhibits angiotensin II-mediated VSMC proliferation *in vitro*, reduces aortic and myocardial collagen accumulation (Lacolley et al., 2001) and reduces oxidative stress and endothelial dysfunction (Virdis et al., 2002). In subtotally nephrectomized rats, spironolactone reduces proteinuria, arterial pressure and cardiac hypertrophy (Greene et al., 1996). These studies highlight the importance of aldosterone in the development of cardiovascular and renal injury in animal models of CKD.

There are limited data on the influence of RAAS on arterial stiffness in human CKD. A pilot study of 25 stage 2 and 3 CKD patients demonstrated that ARB treatment improved small artery compliance (Garg et al., 2005). In a randomized placebo-controlled trial, the addition of spironolactone to ACEI/ARB therapy in patients with stage 2 and 3 CKD significantly reduced both arterial stiffness and LV mass, supporting the hypothesis that aldosterone is a major mediator of arterial stiffness and LVH in CKD (Edwards et al., 2009, 2010). There was, however, a significant reduction in BP such that an effect of BP lowering on arterial stiffness could not be excluded. Larger studies are required to determine whether treatment with MR antagonists can lower arterial stiffness safely and blood pressure independently, in patients with CKD and whether this is associated with improved clinical outcomes.

A recent meta-analysis of RAAS blockade with either ACEIs or ARBs in CKD revealed a significant reduction in cardiovascular outcomes and the incidence of heart failure when compared to placebo, although no reduction in cardiovascular, or all-cause mortality, was noted (Balamuthusamy et al., 2008). The mechanism explaining this improvement in cardiovascular outcome arises is unknown, but an assessment of arterial stiffness parameters in such patients may be informative.

Diet

Observational studies highlight the importance of environmental factors such as high-salt diets (Chapter 101) in the development of hypertension and arterial stiffness (Safar et al., 2000). Dietary sodium enhances age-related vascular changes by promoting VSMC hypertrophy and increased VSMC tone. It also increases collagen cross-linking and facilitates aldosterone-induced oxidative stress and inflammation (Safar et al., 2000). In the presence of aldosterone, small increases in plasma sodium concentrations decrease nitric oxide release and increase endothelial cell stiffness *in vitro* (Oberleithner et al., 2007). Restricting dietary sodium in hypertensive subjects effectively reduces arterial stiffness (Gates et al., 2004). The Western diet is relatively rich in dietary oxidants, AGEs, and bioavailable phosphate (Ferro et al., 2009). These substances undergo renal metabolism or excretion and therefore accumulate in CKD. The influence of dietary factors such as sodium, phosphate, and pro-oxidant compounds on arterial structure and function in subjects with and without CKD is poorly understood and is a fertile area for future research.

Vascular calcification and disorders of bone and mineral metabolism

Vascular medial calcification (Chapter 120) is prominent in CKD and plays an important role in the pathogenesis of arterial stiffness (Fig. 111.5). The extent of arterial calcification correlates with severity of arterial stiffness independent of age and BP in ESRD and CKD (Toussaint et al., 2008) and is a strong predictor of all cause and cardiovascular mortality in ESRD (London et al., 2003).

Vascular calcification describes deposition of calcium-phosphate mineral (hydroxyapatite) in cardiovascular tissues. Long thought to be a passive process, there is now strong evidence that arterial calcification is actively regulated, involving direct osteogenic gene activation together with suppression of calcification inhibitors. Exposure of VSMCs to high concentrations of intracellular calcium and phosphate *in vitro* results in their phenotypic switch to an osteogenic cell type with upregulation of genes promoting matrix mineralization and calcium deposition (Jono et al., 2000). Osteogenic differentiation is driven by upregulation of transcription factors such as core-binding factor-alpha-1 (CBFα1) and bone morphogenetic protein (BMP), which control expression of osteogenic proteins such as osteocalcin, osteonectin and alkaline phosphatase.

Upregulation of transcription factors is also induced by hyperphosphataemia, which is common in advanced CKD. A sodium-dependent phosphate co-transporter, Pit-1, facilitates movement of inorganic phosphate into VSMC, which stimulates cbfa1 expression dose dependently (Jono et al., 2000). Osteogenic proteins are also expressed in VSMC following their exposure to uraemic serum *in vitro* (Chen et al., 2002); this occurs independently of phosphate concentration, suggesting that the uraemic milieu, perhaps through oxidative stress, directly induces vascular calcification.

Loss of inhibitors of mineralization such as fetuin A, osteoprotegerin, and matrix G1a protein (MGP) is associated with progressive arterial and ectopic soft tissue calcification. Levels of MGP are inversely correlated with severity of coronary artery calcification (Jono et al., 2004). In a cross-sectional study of ESRD patients, fetuin A levels were lower than in healthy controls and were associated with increased cardiovascular and all-cause mortality (Ketteler et al., 2003). The loss of these inhibitors *in vivo* may allow calcification to occur at relatively low phosphate concentrations, as suggested by the association of modestly elevated serum phosphate (still within the reference range) with greater prevalence of coronary, aortic, and valvular calcification independent of serum vitamin D and parathyroid hormone (PTH) levels in studies of CKD patients (Adeney et al., 2009).

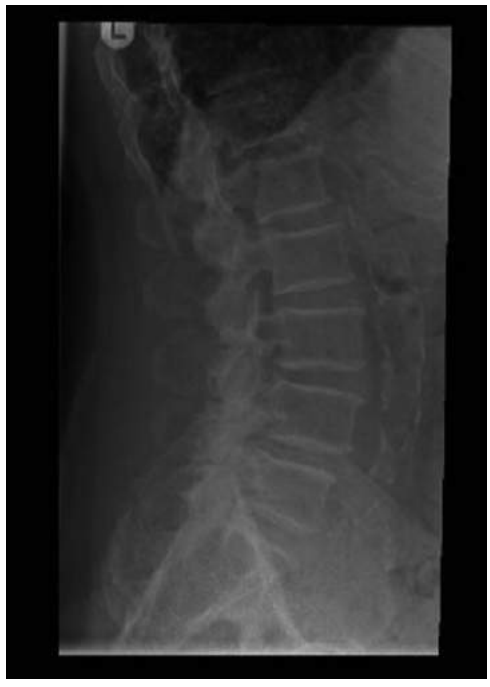

Fig. 111.5 Lateral lumbar spine radiography demonstrating calcification of the anterior and posterior walls of the abdominal aorta.

Calcium-based phosphate binders and vitamin D supplementation used in the treatment of bone and mineral disorders associated with CKD may contribute to hypercalcaemia and subsequent soft tissue calcification. Vitamin D therapy, however, is associated with reduced cardiovascular mortality in observational studies of ESRD (Shoji et al., 2004). This may be partly explained by reduced vascular calcification through suppressed CBFα1 synthesis (Drissi et al., 2002). Hyperparathyroidism, commonly present in advanced CKD, may also contribute to vascular calcification. PTH receptors are present on VSMCs and parathyroidectomy is associated with reduced calcium deposition (Rostand and Drueke, 1999). Hyperparathyroidism is strongly associated with hypertension, increased arterial stiffness, LVH, cardiac fibrosis, impaired cardiac contractility, impaired endothelial function, and cardiovascular mortality (Rostand and Drueke, 1999).

Raised serum phosphate levels even within the reference range, are associated with cardiovascular mortality in the general population and in CKD, renal transplant, and ESRD patients (Connolly et al., 2009; Ferro et al., 2009). In animal models of CKD, high dietary phosphate and hyperphosphataemia induce cardiac fibrosis and arterial wall thickening (Amann et al., 2003). In patients with CKD serum phosphate is independently associated with LV mass (Chue et al., 2012a). The importance of vascular calcification as a determinant of arterial stiffness suggests that treatments that suppress or inhibit this process may be effective in maintaining arterial function. Interestingly, LV mass, bone density, and arterial calcification appear to be very closely inter-related (Chue et al., 2012b). There are a variety of therapeutic targets but powerful phosphate binders are already available. The results of studies determining their influence on markers of vascular calcification and parameters of arterial stiffness will have implications for the management of cardiovascular risk in the CKD population (Block et al., 2012; Di Iorio et al., 2012; Chue et al., 2013b).

Conclusion

This 'modern' paradigm of arterial stiffness providing the link between CKD and cardiovascular disease would not be a surprise to Richard Bright (Fig. 111.6) and other pioneers of renal and cardiovascular medicine in the nineteenth and early twentieth centuries (Ferro et al., 2012). Difficulties in measuring arterial stiffness meant that blood pressure measurement using a sphygmomanometer became the focus of research and treatment throughout most of the twentieth century. Blood pressure control has saved countless lives through the years but the limitations of blood pressure measurements are increasingly recognized. Non-invasive, clinic-based measurements of arterial stiffness are now simple, reliable, and

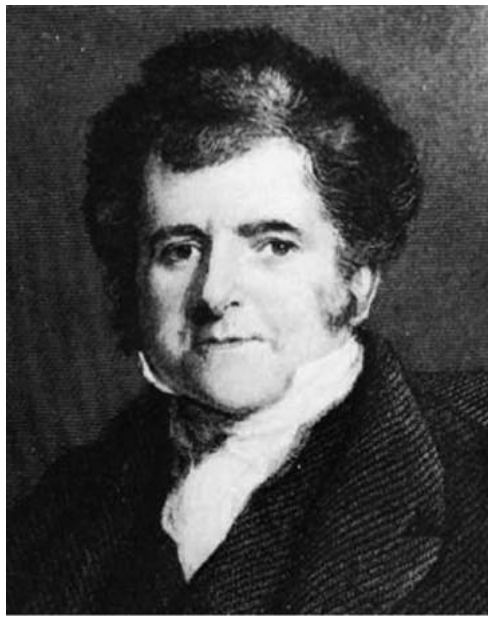

Fig. 111.6 Richard Bright (1789–1858), generally regarded as the 'father of nephrology'.

widely available (DeLoach and Townsend, 2008). Consensus groups have been set up producing guidelines for measurement (Laurent et al., 2006), reference ranges (Reference Values for Arterial Stiffness Collaboration, 2010), and meta-analyses on the predictive value of different parameters of arterial stiffness on cardiovascular outcomes (Reference Values for Arterial Stiffness Collaboration, 2010; Vlachopoulos et al., 2010). Interventions targeting arterial stiffness as a means of reducing the cardiovascular risk of a large and expanding CKD population should now be tested.

References

Adeney, K. L., Siscovick, D. S., Ix, J. H., *et al.* (2009). Association of serum phosphate with vascular and valvular calcification in moderate CKD. *J Am Soc Nephrol*, 20, 381–7.

Ahimastos, A. A., Natoli, A. K., Lawler, A., *et al.* (2005). Ramipril reduces large-artery stiffness in peripheral arterial disease and promotes elastogenic remodeling in cell culture. *Hypertension*, 45, 1194–9.

Aikawa, E., Aikawa, M., Libby, P., *et al.* (2009). Arterial and aortic valve calcification abolished by elastolytic cathepsin S deficiency in chronic renal disease. *Circulation*, 119, 1785–94.

Amann, K., Tornig, J., Kugel, B., *et al.* (2003). Hyperphosphatemia aggravates cardiac fibrosis and microvascular disease in experimental uremia. *Kidney Int*, 63, 1296–301.

Amann, K., Wolf, B., Nichols, C., *et al.* (1997). Aortic changes in experimental renal failure: hyperplasia or hypertrophy of smooth muscle cells? *Hypertension*, 29, 770–5.

Amery, A., Birkenhager, W., Brixko, P., *et al.* (1985). Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. *Lancet*, 1, 1349–54.

Arsov, S., Graaff, R., van Oeveren, W., *et al.* (2014). Advanced glycation end-products and skin autofluorescence in end-stage renal disease: a review. *Clin Chem Lab Med*, 52(1), 11–20.

Avolio, A. P., Van Bortel, L. M., Boutouyrie, P., *et al.* (2009). Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension*, 54, 375–83.

Baigent, C. and Landray, M. (2007). Which cardiovascular risk factors matter in chronic kidney disease? *Nephrol Dial Transplant*, 22, 9–11.

Baksi, A. J., Treibel, T. A., Davies, J. E., *et al.* (2009). A meta-analysis of the mechanism of blood pressure change with aging. *J Am Coll Cardiol*, 54, 2087–92.

Balamuthusamy, S., Srinivasan, L., Verma, M., *et al.* (2008). Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis. *Am Heart J*, 155, 791–805.

Blacher, J., Amah, G., Girerd, X., *et al.* (1997). Association between increased plasma levels of aldosterone and decreased systemic arterial compliance in subjects with essential hypertension. *Am J Hypertens*, 10, 1326–34.

Block, G. A., Wheeler, D. C., Persky, M. S., *et al.* (2012). Effects of phosphate binders in moderate CKD. *J Am Soc Nephrol*, 23, 1407–15.

Bode-Boger, S. M., Scalera, F., Kielstein, J. T., *et al.* (2006). Symmetrical dimethylarginine: a new combined parameter for renal function and extent of coronary artery disease. *J Am Soc Nephrol*, 17, 1128–34.

Boutouyrie, P., Lacolley, P., Briet, M., *et al.* (2011). Pharmacological modulation of arterial stiffness. *Drugs*, 71, 1689–701.

Brown, N. J. (2008). Aldosterone and vascular inflammation. *Hypertension*, 51, 161–7.

Bucala, R., Tracey, K. J., and Cerami, A. (1991). Advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilatation in experimental diabetes. *J Clin Invest*, 87, 432–8.

Cachofeiro, V., Goicochea, M., de Vinuesa, S. G., *et al.* (2008). Oxidative stress and inflammation, a link between chronic kidney disease and cardiovascular disease. *Kidney Int Suppl*, 111, S4–9.

Castro, M. M., Tanus-Santos, J. E., and Gerlach, R. F. (2011). Matrix metalloproteinases: targets for doxycycline to prevent the vascular alterations of hypertension. *Pharmacol Res*, 64, 567–72.

Cecelja, M. and Chowienczyk, P. (2009). Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension. A systematic review. *Hypertension*, 54, 1328–36.

Chen, C. H., Nakayama, M., Nevo, E., *et al.* (1998). Coupled systolic-ventricular and vascular stiffening with age: implications for pressure regulation and cardiac reserve in the elderly. *J Am Coll Cardiol*, 32, 1221–7.

Chen, N. X., O'Neill, K. D., Duan, D., *et al.* (2002). Phosphorus and uremic serum up-regulate osteopontin expression in vascular smooth muscle cells. *Kidney Int*, 62, 1724–31.

Choi, H. K., Hernan, M. A., Seeger, J. D., *et al.* (2002). Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet*, 359, 1173–7.

Chue, C. D., Edwards, N. C., Davis, L. J., *et al.* (2011). Serum phosphate but not pulse wave velocity predicts decline in renal function in patients with early chronic kidney disease. *Nephrol Dial Transplant*, 26, 2576–82.

Chue, C. D., Edwards, N. C., Ferro, C. J., *et al.* (2013a). Effects of age and chronic kidney disease on regional aortic distensibility: a cardiovascular magnetic resonance study. *Int J Cardiol*, 168(4), 4249–54.

Chue, C. D., Edwards, N. C., Moody, W. E., *et al.* (2012a). Serum phosphate is associated with left ventricular mass in patients with chronic kidney disease: a cardiac magnetic resonance study. *Heart*, 98, 219–24.

Chue, C. D., Townend, J. N., Moody, W. E., *et al.* (2013b). Cardiovascular effects of sevelamer in stage 3 CKD. *J Am Soc Nephrol*, 24, 842–52.

Chue, C. D., Townend, J. N., Steeds, R. P., *et al.* (2010). Arterial stiffness in chronic kidney disease: causes and consequences. *Heart*, 96, 817–23.

Chue, C. D., Wall, N. A., Crabtree, N. J., *et al.* (2012b). Aortic calcification and femoral bone density are independently associated with left ventricular mass in patients with chronic kidney disease. *PLoS One*, 7, e39241.

Chung, A. W., Yang, H. H., Kim, J. M., *et al.* (2009). Upregulation of matrix metalloproteinase-2 in the arterial vasculature contributes to stiffening and vasomotor dysfunction in patients with chronic kidney disease. *Circulation*, 120, 792–801.

Cohn, J. N., Quyyumi, A. A., Hollenberg, N. K., *et al.* (2004). Surrogate markers for cardiovascular disease: functional markers. *Circulation*, 109, IV31–46.

Connolly, G. M., Cunningham, R., McNamee, P. T., *et al.* (2009). Elevated serum phosphate predicts mortality in renal transplant recipients. *Transplantation*, 87, 1040–4.

Coope, J. and Warrender, T.S. (1986). Randomised trial of treatment of hypertension in elderly patients in primary care. *Br Med J (Clin Res Ed)*, 293, 1145–51.
Coresh, J., Selvin, E., Stevens, L. A., *et al.* (2007). Prevalence of chronic kidney disease in the United States. *JAMA*, 298, 2038–47.
Dahlof, B., Lindholm, L. H., Hansson, L., *et al.* (1991). Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet*, 338, 1281–5.
Dart, A. M. and Kingwell, B. A. (2001). Pulse pressure—a review of mechanisms and clinical relevance. *J Am Coll Cardiol*, 37, 975–84.
Davies, J. E., Parker, K. H., Francis, D. P., *et al.* (2008). What is the role of the aorta in directing coronary blood flow? *Heart*, 94, 1545–7.
Davies, J. E., Whinnett, Z. I., Francis, D. P., *et al.* (2006). Evidence of a dominant backward-propagating 'suction' wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. *Circulation*, 113, 1768–78.
DeLoach, S. S. and Townsend, R. R. (2008). Vascular stiffness: its measurement and significance for epidemiologic and outcome studies. *Clin J Am Soc Nephrol*, 3, 184–92.
Dhaun, N., Ferro, C. J., Davenport, A. P., *et al.* (2007). Haemodynamic and renal effects of endothelin receptor antagonism in patients with chronic kidney disease. *Nephrol Dial Transplant*, 22, 3228–34.
Dhaun, N., Goddard, J., and Webb, D. J. (2006). The endothelin system and its antagonism in chronic kidney disease. *J Am Soc Nephrol*, 17, 943–55.
Dhaun, N., Macintyre, I. M., Melville, V., *et al.* (2009). Blood pressure-independent reduction in proteinuria and arterial stiffness after acute endothelin-a receptor antagonism in chronic kidney disease. *Hypertension*, 54, 113–19.
Dhaun, N., Melville, V., Blackwell, S., *et al.* (2013). Endothelin-A receptor antagonism modifies cardiovascular risk factors in CKD. *J Am Soc Nephrol*, 24, 31–6.
Di Iorio, B., Bellasi, A., and Russo, D. (2012). Mortality in kidney disease patients treated with phosphate binders: a randomized study. *Clin J Am Soc Nephrol*, 7, 487–93.
Dovinova, I., Cacanyiova, S., Faberova, V., *et al.* (2009). The effect of an NO donor, pentaerythrityl tetranitrate, on biochemical, functional, and morphological attributes of cardiovascular system of spontaneously hypertensive rats. *Gen Physiol Biophys*, 28, 86–93.
Drissi, H., Pouliot, A., Koolloos, C., *et al.* (2002). 1,25-(OH)2-vitamin D3 suppresses the bone-related Runx2/Cbfa1 gene promoter. *Exp Cell Res*, 274, 323–33.
Dustan, H. P. (1989). Isolated systolic hypertension: a long-neglected cause of cardiovascular complications. *Am J Med*, 86, 368–9.
Edwards, N. C., Ferro, C. J., Kirkwood, H., *et al.* (2010). Effect of spironolactone on left ventricular systolic and diastolic function in patients with early stage chronic kidney disease. *Am J Cardiol*, 106, 1505–11.
Edwards, N. C., Ferro, C. J., Townend, J. N., *et al.* (2008). Aortic distensibility and arterial-ventricular coupling in early chronic kidney disease: a pattern resembling heart failure with preserved ejection fraction. *Heart*, 94, 1038–43.
Edwards, N. C., Hirth, A., Ferro, C. J., *et al.* (2008). Subclinical abnormalities of left ventricular myocardial deformation in early-stage chronic kidney disease: the precursor of uremic cardiomyopathy? *J Am Soc Echocardiogr*, 21, 1293–8.
Edwards, N. C., Steeds, R. P., Ferro, C. J., *et al.* (2006). The treatment of coronary artery disease in patients with chronic kidney disease. *QJM*, 99, 723–36.
Edwards, N. C., Steeds, R. P., Stewart, P. M., *et al.* (2009). Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease. A randomized controlled trial. *J Am Coll Cardiol*, 54, 505–12.
Espinola-Klein, C., Rupprecht, H. J., Blankenberg, S., *et al.* (2000). Are morphological or functional changes in the carotid artery wall associated with Chlamydia pneumoniae, Helicobacter pylori, cytomegalovirus, or herpes simplex virus infection? *Stroke*, 31, 2127–33.
Ferro, C. J., Chue, C. D., Steeds, R. P., *et al.* (2009). Is lowering phosphate exposure the key to preventing arterial stiffening with age? *Heart*, 95, 1770–2.
Ferro, C. J., Savage, T., Pinder, S. J., *et al.* (2002). Central aortic pressure augmentation in stable renal transplant recipients. *Kidney Int*, 62, 166–71.
Ferro, C. J., Steeds, R. P., and Townend, J. N. (2012). Hypertension, arterial haemodynamics and left ventricular disease: historical observations. *QJM*, 105(7), 709–16.
Foley, R. N., Murray, A. M., Li, S., *et al.* (2005). Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol*, 16, 489–95.
Foley, R. N., Parfrey, P. S., Harnett, J. D., *et al.* (1995). Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int*, 47, 186–92.
Ford, M. L., Tomlinson, L. A., Chapman, T. P., *et al.* (2010). Aortic stiffness is independently associated with rate of renal function decline in chronic kidney disease stages 3 and 4. *Hypertension*, 55(5), 1110–15.
Franklin, S. S., Jacobs, M. J., Wong, N. D., *et al.* (2001). Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. *Hypertension*, 37, 869–74.
Franklin, S. S., Khan, S. A., Wong, N. D., *et al.* (1999). Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham Heart Study. *Circulation*, 100, 354–60.
Franklin, S. S., Larson, M. G., Khan, S. A., *et al.* (2001). Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation*, 103, 1245–9.
Garg, J. P., Ellis, R., Elliott, W. J., *et al.* (2005). Angiotensin receptor blockade and arterial compliance in chronic kidney disease: a pilot study. *Am J Nephrol*, 25, 393–9.
Gates, P. E., Tanaka, H., Hiatt, W. R., *et al.* (2004). Dietary sodium restriction rapidly improves large elastic artery compliance in older adults with systolic hypertension. *Hypertension*, 44, 35–41.
Go, A. S., Chertow, G. M., Fan, D., *et al.* (2004). Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*, 351, 1296–305.
Greene, E. L., Kren, S., and Hostetter, T. H. (1996). Role of aldosterone in the remnant kidney model in the rat. *J Clin Invest*, 98, 1063–8.
Greenwald, S. E. (2007). Ageing of the conduit arteries. *J Pathol*, 211, 157–72.
Guerin, A. P., Blacher, J., Pannier, B., *et al.* (2001). Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation*, 103, 987–92.
Gunta, S. S. and Mak, R. H. (2013). Ghrelin and leptin pathophysiology in chronic kidney disease. *Pediatr Nephrol*, 28, 611–16.
Haider, A. W., Larson, M. G., Franklin, S. S., *et al.* (2003). Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. *Ann Intern Med*, 138, 10–16.
Hamilton, P. K., Lockhart, C. J., Quinn, C. E., *et al.* (2007). Arterial stiffness: clinical relevance, measurement and treatment. *Clin Sci (Lond)*, 113, 157–70.
Hundley, W. G., Kitzman, D. W., Morgan, T. M., *et al.* (2001). Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol*, 38, 796–802.
Jacob, M. P. (2003). Extracellular matrix remodeling and matrix metalloproteinases in the vascular wall during aging and in pathological conditions. *Biomed Pharmacother*, 57, 195–202.
Joly, L., Djaballah, W., Koehl, G., *et al.* (2009). Aortic inflammation, as assessed by hybrid FDG-PET/CT imaging, is associated with enhanced aortic stiffness in addition to concurrent calcification. *Eur J Nucl Med Mol Imaging*, 36, 979–85.
Jono, S., Ikari, Y., Vermeer, C., *et al.* (2004). Matrix Gla protein is associated with coronary artery calcification as assessed by electron-beam computed tomography. *Thromb Haemost*, 91, 790–4.
Jono, S., McKee, M. D., Murry, C. E., *et al.* (2000). Phosphate regulation of vascular smooth muscle cell calcification. *Circ Res*, 87, E10–17.
Kass, D. A., Shapiro, E. P., Kawaguchi, M., *et al.* (2001). Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. *Circulation*, 104, 1464–70.

Keith, D. S., Nichols, G. A., Gullion, C. M., *et al.* (2004). Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med*, 164, 659–63.

Ketteler, M., Bongartz, P., Westenfeld, R., *et al.* (2003). Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. *Lancet*, 361, 827–33.

Konova, E., Baydanoff, S., Atanasova, M., *et al.* (2004). Age-related changes in the glycation of human aortic elastin. *Exp Gerontol*, 39, 249–54.

Kranzhofer, R., Schmidt, J., Pfeiffer, C.A., *et al.* (1999). Angiotensin induces inflammatory activation of human vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol*, 19, 1623–9.

Lacolley, P., Labat, C., Pujol, A., *et al.* (2002). Increased carotid wall elastic modulus and fibronectin in aldosterone-salt-treated rats: effects of eplerenone. *Circulation*, 106, 2848–53.

Lacolley, P., Safar, M. E., Lucet, B., *et al.* (2001). Prevention of aortic and cardiac fibrosis by spironolactone in old normotensive rats. *J Am Coll Cardiol*, 37, 662–7.

Laurent, S., Cockcroft, J., Van Bortel, L., *et al.* (2006). Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*, 27, 2588–605.

Lee, A. Y., Han, B., Lamm, S. D., *et al.* (2012). Effects of elastin degradation and surrounding matrix support on artery stability. *Am J Physiol Heart Circ Physiol*, 302, H873–84.

Lewington, S., Clarke, R., Qizilbash, N., *et al.* (2002). Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*, 360, 1903–13.

Lilitkarntakul, P., Dhaun, N., Melville, V., *et al.* (2011). Blood pressure and not uraemia is the major determinant of arterial stiffness and endothelial dysfunction in patients with chronic kidney disease and minimal co-morbidity. *Atherosclerosis*, 216, 217–25.

Liu, B. and Hannun, Y. A. (1997). Inhibition of the neutral magnesium-dependent sphingomyelinase by glutathione. *J Biol Chem*, 272, 16281–7.

Liu, L., Wang, J. G., Gong, L., *et al.* (1998). Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic Hypertension in China (Syst-China) Collaborative Group. *J Hypertens*, 16, 1823–9.

London, G. M., Guerin, A. P., Marchais, S. J., *et al.* (2003). Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant*, 18, 1731–40.

Madero, M., Peralta, C., Katz, R., *et al.* (2013). Association of arterial rigidity with incident kidney disease and kidney function decline: the Health ABC study. *Clin J Am Soc Nephrol*, 8, 424–33.

Maki-Petaja, K. M., Hall, F. C., Booth, A. D., *et al.* (2006). Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-alpha therapy. *Circulation*, 114, 1185–92.

Makita, Z., Radoff, S., Rayfield, E. J., *et al.* (1991). Advanced glycosylation end products in patients with diabetic nephropathy. *N Engl J Med*, 325, 836–42.

Marson, B. P., Poli de Figueiredo, C. E., and Tanus-Santos, J. E. (2012). Imbalanced matrix metalloproteinases in cardiovascular complications of end-stage kidney disease: a potential pharmacological target. *Basic Clin Pharmacol Toxicol*, 110, 409–15.

Matsushita, K., Selvin, E., Bash, L. D., *et al.* (2009). Change in estimated GFR associates with coronary heart disease and mortality. *J Am Soc Nephrol*, 20, 2617–24.

McEniery, C. M., Wallace, S., Mackenzie, I. S., *et al.* (2006). Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans. *Hypertension*, 48, 602–8.

Medical Research Council Working Party (1985). MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. *Br Med J (Clin Res Ed)*, 291, 97–104.

Meinders, J. M. and Hoeks, A. P. (2004). Simultaneous assessment of diameter and pressure waveforms in the carotid artery. *Ultrasound Med Biol*, 30, 147–54.

Mitchell, G. F., Dunlap, M. E., Warnica, W., *et al.* (2007). Long-term trandolapril treatment is associated with reduced aortic stiffness: the prevention of events with angiotensin-converting enzyme inhibition hemodynamic substudy. *Hypertension*, 49, 1271–7.

Miyata, T., van Ypersele de Strihou, C., Ueda, Y., *et al.* (2002). Angiotensin II receptor antagonists and angiotensin-converting enzyme inhibitors lower in vitro the formation of advanced glycation end products: biochemical mechanisms. *J Am Soc Nephrol*, 13, 2478–87.

Moody, W. E., Edwards, N. C., Chue, C. D., *et al.* (2013). Arterial disease in chronic kidney disease. *Heart*, 99, 365–72.

Moody, W. E., Edwards, N. C., Madhani, M., *et al.* (2012). Endothelial dysfunction and cardiovascular disease in early-stage chronic kidney disease: cause or association? *Atherosclerosis*, 223(1), 86–94.

MRC Working Party (1992). Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. *BMJ*, 304, 405–12.

National Kidney Foundation (2002). K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kid Dis*, 39 (Suppl. 2), S1–246.

New, S. E. and Aikawa, E. (2011). Molecular imaging insights into early inflammatory stages of arterial and aortic valve calcification. *Circ Res*, 108, 1381–91.

Ng, K., Moody, W., Chue, C., *et al.* (2014). Central pulse pressure in patients with chronic kidney disease and in renal transplant recipients. *J Hum Hypertens*, 28(3), 180–5.

O'Rourke, M. F. and Safar, M. E. (2005). Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension*, 46, 200–4.

Oberleithner, H., Riethmuller, C., Schillers, H., *et al.* (2007). Plasma sodium stiffens vascular endothelium and reduces nitric oxide release. *Proc Natl Acad Sci U S A*, 104, 16281–6.

Parrinello, C. M., Sinclair, E., Landay, A. L., *et al.* (2012). Cytomegalovirus IgG antibody is associated with subclinical carotid artery disease among HIV-infected women. *J Infect Dis*, 205(12), 1788–96.

Peng, X., Haldar, S., Deshpande, S., *et al.* (2003). Wall stiffness suppresses Akt/eNOS and cytoprotection in pulse-perfused endothelium. *Hypertension*, 41, 378–81.

Pierce, G. L., Jablonski, K. L., Walker, A. E., *et al.* (2012). Tetrahydrobiopterin supplementation enhances carotid artery compliance in healthy older men: a pilot study. *Am J Hypertens*, 25, 1050–4.

Qiu, H., Zhu, Y., Sun, Z., *et al.* (2010). Short communication: vascular smooth muscle cell stiffness as a mechanism for increased aortic stiffness with aging. *Circ Res*, 107, 615–19.

Rakhit, D. J., Zhang, X. H., Leano, R., *et al.* (2007). Prognostic role of subclinical left ventricular abnormalities and impact of transplantation in chronic kidney disease. *Am Heart J*, 153, 656–64.

Raveaud, S., Mezin, P., Lavanchy, N., *et al.* (2009). Effects of chronic treatment with a low dose of nicorandil on the function of the rat aorta during ageing. *Clin Exp Pharmacol Physiol*, 36, 988–94.

Reference Values for Arterial Stiffness Collaboration (2010). Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J*, 31, 2338–50.

Reiser, K., McCormick, R. J., and Rucker, R. B. (1992). Enzymatic and nonenzymatic cross-linking of collagen and elastin. *FASEB J*, 6, 2439–49.

Rostand, S. G. and Drueke, T. B. (1999). Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. *Kidney Int*, 56, 383–92.

Safar, M. E., Thuilliez, C., Richard, V., *et al.* (2000). Pressure-independent contribution of sodium to large artery structure and function in hypertension. *Cardiovasc Res*, 46, 269–76.

Schillaci, G., Verdecchia, P., Porcellati, C., *et al.* (2000). Continuous relation between left ventricular mass and cardiovascular risk in essential hypertension. *Hypertension*, 35, 580–6.

Schwarz, U., Buzello, M., Ritz, E., *et al.* (2000). Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. *Nephrol Dial Transplant*, 15, 218–23.

Schwedler, S. B., Metzger, T., Schinzel, R., *et al.* (2002). Advanced glycation end products and mortality in hemodialysis patients. *Kidney Int*, 62, 301–10.

SHEP Cooperative Research Group (1991). Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA*, 265, 3255–64.

Shlipak, M.G., Katz, R., Kestenbaum, B., *et al.* (2009). Rapid decline of kidney function increases cardiovascular risk in the elderly. *J Am Soc Nephrol*, 20, 2625–30.

Shoji, T., Shinohara, K., Kimoto, E., *et al.* (2004). Lower risk for cardiovascular mortality in oral 1alpha-hydroxy vitamin D3 users in a haemodialysis population. *Nephrol Dial Transplant*, 19, 179–84.

Staessen, J. A., Fagard, R., Thijs, L., *et al.* (1997). Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet*, 350, 757–64.

Staessen, J. A., Gasowski, J., Wang, J. G., *et al.* (2000). Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet*, 355, 865–72.

Steptoe, A. and Halcox, J. (2008). Socioeconomic status and cardiovascular disease risk: authors' reply. *Heart*, 94, 1075.

Taal, M. W., Sigrist, M. K., Fakis, A., *et al.* (2007). Markers of arterial stiffness are risk factors for progression to end-stage renal disease among patients with chronic kidney disease stages 4 and 5. *Nephron Clin Pract*, 107, c177–81.

Takagishi, T., Murahashi, N., Azagami, S., *et al.* (1995). Effect of angiotensin II and thromboxane A2 on the production of matrix metalloproteinase by human aortic smooth muscle cells. *Biochem Mol Biol Int*, 35, 265–73.

Takenaka, T., Mimura, T., Kanno, Y., *et al.* (2005). Qualification of arterial stiffness as a risk factor to the progression of chronic kidney diseases. *Am J Nephrol*, 25, 417–24.

Tepel, M., van der Giet, M., Statz, M., *et al.* (2003). The antioxidant acetylcysteine reduces cardiovascular events in patients with end-stage renal failure: a randomized, controlled trial. *Circulation*, 107, 992–5.

Tesauro, M., Schinzari, F., Rovella, V., *et al.* (2009). Ghrelin restores the endothelin 1/nitric oxide balance in patients with obesity-related metabolic syndrome. *Hypertension*, 54, 995–1000.

Thambyrajah, J., Landray, M. J., McGlynn, F. J., *et al.* (2000). Abnormalities of endothelial function in patients with predialysis renal failure. *Heart*, 83, 205–9.

Toussaint, N. D., Lau, K. K., Strauss, B. J., *et al.* (2008). Associations between vascular calcification, arterial stiffness and bone mineral density in chronic kidney disease. *Nephrol Dial Transplant*, 23, 586–93.

United States Renal Data System (2012). *USRDS 2012 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Ueno, H., Koyama, H., Tanaka, S., *et al.* (2008). Skin autofluorescence, a marker for advanced glycation end product accumulation, is associated with arterial stiffness in patients with end-stage renal disease. *Metabolism*, 57, 1452–7.

Ullian, M. E., Schelling, J. R., and Linas, S. L. (1992). Aldosterone enhances angiotensin II receptor binding and inositol phosphate responses. *Hypertension*, 20, 67–73.

Upadhyay, A., Hwang, S. J., Mitchell, G. F., *et al.* (2009). Arterial stiffness in mild-to-moderate CKD. *J Am Soc Nephrol*, 20, 2044–53.

Vallance, P., Leone, A., Calver, A., *et al.* (1992). Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. *Lancet*, 339, 572–5.

Van Biesen, W., De Bacquer, D., Verbeke, F., *et al.* (2007). The glomerular filtration rate in an apparently healthy population and its relation with cardiovascular mortality during 10 years. *Eur Heart J*, 28, 478–83.

Van Popele, N. M., Grobbee, D. E., Bots, M. L., *et al.* (2001). Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke*, 32, 454–60.

Virdis, A., Neves, M. F., Amiri, F., *et al.* (2002). Spironolactone improves angiotensin-induced vascular changes and oxidative stress. *Hypertension*, 40, 504–10.

Vlachopoulos, C., Aznaouridis, K., and Stefanadis, C. (2010). Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*, 55, 1318–27.

Vuurmans, T. J., Boer, P., and Koomans, H. A. (2003). Effects of endothelin-1 and endothelin-1 receptor blockade on cardiac output, aortic pressure, and pulse wave velocity in humans. *Hypertension*, 41, 1253–8.

Wall, N. A., Chue, C. D., Edwards, N. C., *et al.* (2013). Cytomegalovirus seropositivity is associated with increased arterial stiffness in patients with chronic kidney disease. *PLoS One*, 8, e55686.

Wang, J. J., O'Brien, A. B., Shrive, N. G., *et al.* (2003). Time-domain representation of ventricular-arterial coupling as a windkessel and wave system. *Am J Physiol Heart Circ Physiol*, 284, H1358–68.

Wang, M. C., Tsai, W. C., Chen, J. Y., *et al.* (2005). Stepwise increase in arterial stiffness corresponding with the stages of chronic kidney disease. *Am J Kidney Dis*, 45, 494–501.

Watanabe, H., Ohtsuka, S., Kakihana, M., *et al.* (1993). Coronary circulation in dogs with an experimental decrease in aortic compliance. *J Am Coll Cardiol*, 21, 1497–506.

Williams, B. (2004). Pulse wave analysis and hypertension: evangelism versus scepticism. *J Hypertens*, 22, 447–9.

Wittstock, A., Burkert, M., Zidek, W., *et al.* (2009). N-acetylcysteine improves arterial vascular reactivity in patients with chronic kidney disease. *Nephron Clin Pract*, 112, c184–9

Yasmin, McEniery, C. M., Wallace, S., *et al.* (2005). Matrix metalloproteinase-9 (MMP-9), MMP-2, and serum elastase activity are associated with systolic hypertension and arterial stiffness. *Arterioscler Thromb Vasc Biol*, 25, 372

Yasmin, McEniery, C. M., Wallace, S., *et al.* (2004). C-reactive protein is associated with arterial stiffness in apparently healthy individuals. *Arterioscler Thromb Vasc Biol*, 24, 969–74

Zieman, S. J., Melenovsky, V., Clattenburg, L., *et al.* (2007). Advanced glycation endproduct crosslink breaker (alagebrium) improves endothelial function in patients with isolated systolic hypertension. *J Hypertens*, 25, 577–83

Zoccali, C., Benedetto, F. A., Maas, R., *et al.* (2002). Asymmetric dimethylarginine, C-reactive protein, and carotid intima-media thickness in end-stage renal disease. *J Am Soc Nephrol*, 13, 490–6

CHAPTER 112

Oxidative stress and its implications in chronic kidney disease

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Introduction

Chronic kidney disease (CKD) is invariably associated with inflammation in which oxidative stress is likely to be an important mechanism of damage (Himmelfarb et al., 2002; Himmelfarb and Hakim, 2003; Vaziri, 2004a, 2004b; Cachofeiro et al., 2008).

Generation and metabolism of ROS in normal condition

Transformation of molecular oxygen to water in the cell involves its acquisition of four electrons from hydrogen ($O_2 + 4H \rightarrow 2H_2O$). For most of the oxygen processed in the cell conversion to water happens in a single step. However, conversion to water for the remaining 1–4% of oxygen occurs with the transfer of one electron at a time. This leads to production of highly reactive and short-lived intermediary oxygen metabolites, called reactive oxygen species (ROS) (Li et al., 2008; Bartz and Piantadosi, 2010; Gutteridge and Halliwell, 2010). Superoxide anion ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2) which are the primary ROS produced in the body are the by-products of one and two electron reductions of O_2 respectively.

The great majority of ROS produced in the cell are generated in the mitochondria. In addition, small amounts of superoxide anion and hydrogen peroxide are produced in the cytoplasm by various cytosolic enzymes such as oxygenases, oxidases, and peroxidases.

Although uncontained superoxide and hydrogen peroxide can cause oxidative stress and cytotoxicity, under normal condition the body is well equipped to neutralize them. For instance, superoxide anion is normally converted to hydrogen peroxide ($O_2^{\bullet -} + 2H \rightarrow H_2O_2$) by members of the superoxide dismutase (SOD) family which include Mn-SOD (in mitochondria), Cu, Zn-SOD (in cytoplasm), and extracellular SOD (EC-SOD). Hydrogen peroxide is normally converted to water by catalase and glutathione peroxidase. Thus, under normal conditions, superoxide and hydrogen peroxide do not cause oxidative stress or tissue injury. On the contrary, they provide vital functions as signalling molecules or second messengers for various growth factors and hormones (Bartz and Piantadosi, 2010).

Antioxidant defence system

The body's antioxidant system consists of numerous endogenous antioxidant enzymes, phase 2 detoxifying enzymes, and antioxidant molecules, as well as many dietary ROS scavengers and antioxidant nutrients. The individual components of this system work in a coordinated manner to protect against ROS-mediated cytotoxicity and tissue injury. Deficiency of one cannot be compensated by supernormal amounts of the other(s) (Gutteridge and Halliwell, 2010).

Production of various antioxidant and phase 2 detoxifying enzymes and related proteins is regulated by the nuclear factor erythroid-2-related factor 2 (Nrf2) which plays a central role in basal activity and coordinated induction of over 250 genes such as those encoding catalase, SODs, UDP-glucuronosyltransferase, NAD(P)H:quinone oxidoreductase-1 (NQO1), haem oxygenase-1 (HO-1), glutamate cysteine ligase, glutathione S-transferase, glutathione peroxidase, and thioredoxin, among others (Li et al., 2008; Wakabayashi et al., 2010).

Under normal conditions, most of the constitutively produced Nrf2 is held in the cell cytoplasm as an inactive complex and processed for degradation by binding to the repressor molecule, Kelch-like ECH-associated protein 1 (Keap1). Keap1 contains a number of cysteine residues that function as sensors of the cellular redox state. Each Nrf2 molecule is bound by two Keap1 molecules ('hinge and latch' model). Oxidation or covalent modification of the thiols in some of these cysteine residues results in conformational changes in Keap1 molecules which limits their ability to bind Nrf2 and facilitate its proteasomal degradation. This leads to accumulation of the active Nrf2 and its translocation to the nucleus (Kobayashi et al., 2006; Wakabayashi et al., 2010) where it undergoes heterodimerization with other transcription factors such as small Maf. It then binds to the regulatory sequences, called 'antioxidant response elements' (AREs) or 'electrophile response elements' (EpREs), in the promoter regions of its target genes and initiates their transcription. An alternative pathway of activation (nuclear translocation) of Nrf2 is phosphorylation of its threonine or serine residues by upstream kinases, such as protein kinase C, mitogen-activated protein kinases, phosphatidylinositol-3-kinase/Akt, casein kinase-2, and the endoplasmic reticulum enzyme

PERK (Cullinan and Diehl, 2004; Surh et al., 2008; Uruno and Motohashi, 2011).

By regulating the constitutive expression and inductive upregulation of the cellular antioxidant and anti-inflammatory machinery, Nrf2 plays a central role in protection against oxidative stress (Li et al., 2008; Wakabayashi et al., 2010). This assertion is supported by the inability of the Nrf2 deficient mice to mount an antioxidants response to oxidative stress. Moreover, these animals develop a lupus-like autoimmune nephritis and show exacerbation of diabetes-induced oxidative stress, inflammation, and nephropathy (Yoh et al., 2001, 2008).

Diversion of primary ROS to secondary ROS in pathological states

Unlike normal condition where superoxide and hydrogen peroxide are readily contained by the enzymes cited above, under pathological conditions, they become substrates for generation of highly cytotoxic and enzymatically uncontainable products. For instance, in the presence of transition metals such as iron, hydrogen peroxide is converted to hydroxyl radical (•OH) which is the most reactive and cytotoxic ROS ($H_2O_2 + Fe^{2+} \rightarrow {}^{\bullet}OH + OH^- + Fe^{3+}$). Similarly, in the presence of nitric oxide (NO), superoxide is converted to peroxynitrite ($NO + O_2^{\bullet} \rightarrow ONOO^-$), a highly reactive nitrogen species. Finally, in the presence of myeloperoxidase, which is abundantly expressed in granulocytes and macrophages, hydrogen peroxide is converted to hypochlorous acid ($H_2O_2 + Cl^- \rightarrow HOCl$). HOCl which is commonly known as bleach is a highly reactive and cytotoxic reactive halogen species. These extremely cytotoxic secondary reactive products are responsible for many of the pathological lesions found in a variety of degenerative and progressive diseases (Halliwell, 2007).

Oxidative stress in chronic kidney disease

ROS produced in the course of metabolism and signal transduction processes are normally contained by the natural antioxidant defence system. Oxidative stress occurs as a result of either increased production of ROS, depressed capacity of the antioxidant system, or both (Halliwell, 2007). In the presence of oxidative stress, the uncontained or uncontainable ROS attack, denature, and modify structural and functional molecules and activate redox-sensitive transcription factors and signal transduction pathways. These events lead to tissue damage and dysfunction by promoting necrosis, apoptosis, inflammation, fibrosis, and other disorders. As outlined below, oxidative stress in CKD is due to a combination of increased production of ROS and impaired antioxidant capacity.

Increased production of ROS in chronic kidney disease

ROS production is markedly increased in the diseased kidney, as well as vascular and various other tissues. This is primarily driven by mitochondrial dysfunction, activation, or upregulation of the ROS-producing enzymes, for example, NAD(P)H oxidase (NOX) isoforms, cyclooxygenase-2, lipoxygenase, and uncoupled nitric oxide synthase (NOS) as well as endoplasmic reticulum stress (Vaziri et al., 2004a; Cachofeiro et al., 2008; Aminzadeh et al., 2012).

Increased ROS production in the diseased kidney is, in part, also driven by upregulation of the intrarenal angiotensin system which is marked by significant increases in expression the angiotensin II receptors (AT_1 and AT_2) and the number of angiotensin II-producing cells. Interestingly, macrophages constitute a large segment of the angiotensin II-producing cells and represent an ectopic source of this hormone in the diseased kidney (Vaziri et al., 2007). Moreover the kidney contains angiotensinogen, angiotensin-converting enzyme, and renin (Vio and Jeanneret, 2003; Kobori et al., 2007). Thus the kidney serves as both a source and the target of angiotensin II. Interestingly, liver appears to be the source of the angiotensinogen found in the kidney (Matsusaka et al., 2012).

Binding of angiotensin II to the AT_1 receptor results in production of superoxide by NAD(P)H oxidase which is consistently upregulated in the kidney and vascular tissue of animals with CKD (Vaziri et al., 2003; Kim et al., 2011). Thus upregulation of the intrarenal angiotensin system plays an important part in the pathogenesis oxidative stress in the diseased kidney (Shah et al., 2007).

Oxidative stress in CKD is invariably coupled with the activation of nuclear factor kappa B (NF-κB) and inflammatory cell infiltration in the diseased kidney (Fujihara et al., 2007; Kim et al., 2011). In fact, rats with CKD induced by subtotal nephrectomy as well as Imai rats with spontaneous focal segmental glomerulosclerosis exhibit oxidative stress and upregulation of ROS-producing enzymes which are accompanied by activation of NF-κB and infiltration of immune cell in the kidney (Fujihara et al., 2007; Cho et al., 2009; Kim et al., 2011).

In many forms of immune complex-induced and complement-mediated glomerulonephritis, such as antiglomerular basement membrane antibody-mediated glomerulonephritis and membranoproliferative glomerulonephritis, both the infiltrating leucocytes and the resident cells contribute to oxidative stress by producing ROS (Boyce et al., 1989; Poelstra et al., 1990; Oberle et al., 1992; Gaertner et al., 2002).

Although, when present, infiltrating leucocytes play a major part in production of ROS in the diseased kidneys, oxidative stress is present in leucocyte-independent nephropathies such as puromycin aminonucleoside-induced nephrotic syndrome (a commonly used model of minimal change disease) (Kawaguchi et al., 1992) and in passive Heymann nephritis (a widely used model of membranous nephropathy) (Shah, 1988; Neale et al., 1993). These observations point to the native renal cells as the sole source of excess ROS production in these conditions.

Contribution of underlying diabetes to oxidative stress in CKD

Mesangial cells cultured in media with high glucose concentration to simulated hyperglycaemia show increased ROS generation (Ha et al., 1999, 2002), and isolated glomeruli from diabetic rats produce large amounts of superoxide and hydrogen peroxide (Chen et al., 2000; Koya et al., 2003).

In addition, diabetes results in accumulation of advanced glycation end products (AGEs) in the kidney and various other tissues. The AGEs have been shown to increase intracellular generation of ROS by binding to their receptors on macrophages and mesangial cells (Yan et al., 1994; Scivittaro et al., 2000). The primary sources of increased ROS production in diabetic nephropathy include NOX4 (Gorin et al., 2005), uncoupled NOS (Satoh et al., 2005),

and mitochondria (Nishikawa et al., 2000; Brownlee, 2001; Lee et al., 2003).

Contribution of hypertension to oxidative stress in CKD

Production of ROS in kidney and arterial tissues is increased in all forms of hereditary and acquired hypertension (Rodríguez-Iturbe et al., 2004; Wilcox et al., 2005; Vaziri and Rodríguez-Iturbe, 2006). Oxidative stress in the renal and vascular tissues raises arterial pressure by increasing systemic vascular resistance and promoting sodium retention by several mechanisms.

- via ROS-mediated inactivation of NO, depletion of tetrahydrobiopterin (the NOS cofactor), and accumulation of the NOS inhibitor (asymmetrical dimethylarginine), oxidative stress lowers bioavailability of NO which is a potent vasodilator and natriuretic factor.
- via oxidation of arachidonic acid ROS promote formation of F2 isoprostane which causes vasoconstriction and sodium retention (Rodríguez-Iturbe et al., 2004; Wilcox et al., 2005; Vaziri and Rodríguez-Iturbe, 2006).
- via activation of NF-κB, oxidative stress results in intrarenal inflammation which promotes sodium retention (Rodríguez-Iturbe et al., 2012). Thus by raising systemic vascular resistance and renal sodium retention, oxidative stress increases arterial pressure.

Conversely, hypertension can raise ROS production and promote oxidative stress in the arterial wall as shown in the animal model of aorta coarctation. These animals show severe oxidative stress, upregulation of NAD(P)H oxidase, and ROS-mediated NO inactivation in the hypertensive zone (proximal to coarctation) but not in the normotensive (distal to coarctation) zone of the arterial tree (Barton et al., 2001; Sindhu et al., 2005; Vaziri and Ni, 2005).

Thus, CKD-associated oxidative stress can contribute to the pathogenesis of hypertension and hypertension can contribute to the CKD-associated oxidative stress.

Contribution of inflammation to oxidative stress in CKD

Inflammation is a common feature of CKD (see Chapter 110). Together, systemic inflammation and oxidative stress contribute to the development and progression of atherosclerosis, cardiovascular disease, cachexia, anaemia, and many other morbidities in the CKD patients (Kaysen, 2004; Carrero and Stenvinkel, 2010). Inflammation in CKD is due to the activation of the innate immune system, including monocytes, macrophages, granulocytes and resident cells. In fact end-stage renal disease (ESRD) patients exhibit:

- increased number of circulating monocytes expressing markers of activation and spontaneous production of cytokine and ROS (Yoon et al., 2007; Gollapudi et al., 2010)
- spontaneous activation, degranulation, and increased basal ROS production of polymorphonuclear leucocytes (Yoon et al., 2007)
- reduced number and impaired activity of regulatory T cells (Treg) which normally suppress the inflammatory response (Hendrikx et al., 2009; Meier et al., 2009)
- elevated chemokine expression and upregulation of ROS producing pathways in various tissues, denoting participation of non-immune cells in the CKD-induced inflammation (Vaziri, 2004a).

Several factors contribute to the activation of the innate immune system in CKD. These include:

- accumulation of pro-inflammatory oxidized low-density lipoprotein (LDL) and remnant lipoproteins coupled with the reduction of anti-inflammatory and antioxidant properties of high-density lipoprotein (HDL) (Vaziri et al., 2010; Vaziri and Norris, 2011)
- impaired Nrf2 activity leading to reduced production of endogenous antioxidant and anti-inflammatory enzymes and related proteins (Kim and Vaziri, 2010; Ruiz et al., 2013; Aminzadehet al., 2013)
- comorbid conditions such as autoimmune disorders and diabetes
- accumulation of pro-oxidant and pro-inflammatory uraemic toxins, such as indoxyl sulphate and p-cresol sulphate which are by-products of colonic microbial flora (Aronov et al., 2011; Vaziri, 2012a)
- blood exposure to dialyser membrane and extracorporeal circuits and influx of dialysate impurities in the systemic circulation
- hypervolemia and hypertension
- episodes of intradialytic and post-dialytic hypotension leading to bowel ischaemia and leakage of endotoxin in the systemic circulation
- infections such as infected blood access, hepatitis, and peritonitis which commonly occur in haemodialysis and peritoneal dialysis patients
- alteration of the intestinal microbiome (Vaziri et al., 2013a) which can contribute to systemic inflammation via loss of the protective and symbiotic properties of the normal microbial flora, and finally
- uraemia-induced impairment of the intestinal epithelial barrier structure and function which causes systemic inflammation by enabling the influx of endotoxin and other noxious luminal contents into the systemic circulation (Vaziri et al., 2012c). Recent *in vitro* studies have identified urea and its hydrolysis to ammonia by microbial urease as the main culprit in the breakdown of the intestinal epithelial tight junction in uraemia (Vaziri et al., 2012a, 2012b, 2013b).

Role of dyslipidaemia in amplification and dissemination of oxidative stress in CKD

CKD results in deficiency and impaired antioxidant and anti-inflammatory properties of HDL, accumulation of small dense LDL, intermediate density lipoprotein (IDL), and chylomicron remnants (Vaziri et al., 2010) (see Chapter 102). Small dense LDL, chylomicron remnants, and IDL are highly prone to oxidation are readily oxidized in CKD patients. This process is accelerated by CKD-associated systemic oxidative stress and HDL deficiency and dysfunction. Plasma oxidized LDL and lipid peroxidation products are consistently elevated in CKD patients (Vaziri, 2006, 2010). Formation and accumulation of the oxidized forms of LDL, IDL, and chylomicron remnants play an important part in amplification of systemic inflammation and oxidative stress in this population.

Via binding to oxidized LDL receptor-1 (LOX-1), scavenger receptor A-1 (SRA-1), and oxidized phospholipid receptors on monocytes and macrophages, these oxidized lipoproteins cause release of pro-inflammatory cytokines and chemokines (Li and Mehta, 2000; Glass and Witztum, 2001) and thereby promote inflammation and oxidative stress. In addition by virtue of their presence in the circulation, these pro-inflammatory particles serve as vehicles to readily disseminate inflammation throughout the body. Moreover, via lipid peroxidation chain reaction, these circulating oxidized particles facilitate the dissemination of oxidative stress in the CKD patients. Thus the CKD-associated alteration of lipid metabolism contributes to systemic inflammation and oxidative stress and hence cardiovascular disease, CKD progression, anaemia, cachexia, and wasting among other morbidities (Vaziri, 2014).

Role of iron overload and intravenous iron in CKD-associated oxidative stress

IV administration of iron (see Chapter 126) bypasses biological safeguards designed to prevent iron overload and iron-mediated oxidative stress and inflammation. IV iron compounds are usually given as bolus injections of 100–1000 mg which when compared to the intestinal absorption of 1–2 mg/day represents a massive quantity. The rapid and direct delivery of massive amounts of iron in the circulation overwhelms the available pool of free transferrin, stresses the reticuloendothelial system (RES), and leads to the rise in plasma and tissue pools of poorly liganded and catalytically active iron.

When bound by transferrin in the plasma, or by ferritin or metalloproteins in the intracellular compartment, iron is safely maintained in a catalytically inactive state. Poorly liganded ferrous iron reacts with H_2O_2 which is abundantly produced by the mitochondria and inflammatory cells. This leads to conversion of ferrous to ferric iron and formation of hydroxyl radical which is a highly reactive and cytotoxic free radical ($H_2O_2 + Fe^{2+} \rightarrow {}^{\bullet}OH + OH^- + Fe^{3+}$; Fenton reaction). Ferric iron is then readily converted back to ferrous iron by superoxide which is widely generated by mitochondria and cytoplasmic mono-oxygenases ($Fe^{3+} + O_2^{\bullet-} \rightarrow Fe^{2+} + O_2$; Haber Weise reaction), or by reducing molecules such as ascorbic acid. Through these reactions, poorly liganded iron leads to production of $^{\bullet}OH$ and intensification of oxidative stress. $^{\bullet}OH$ causes cytotoxicity and tissue damage by attacking and denaturing DNA, lipids, proteins, and other molecules. In fact plasma concentration and urinary excretion of 8-hydroxy-20 deoxyguanosine (8-OHdG) which is the by-product of DNA damage by $^{\bullet}OH$ is strongly associated with body iron stores and serum ferritin level (Kuo et al., 2008).

IV iron compounds consist of a ferric hydroxide core which is encased in a 'carbohydrate shell' to prevent rapid release of iron (Danielson, 2004) and enable their uptake by the RES. Administration of these products results in saturation of transferrin and the rise in catalytically active non-transferrin bound iron (NTBI) (Van Wyck et al., 2004; Van Campenhout et al., 2008). In fact, trials of IV iron products in ESRD patients have revealed a significant rise in the by-products of lipid, protein, and DNA oxidation and of inflammatory mediators (Parkkinen et al., 2000; Kuo et al., 2008; Garcia-Fernandez et al., 2010). In addition, at pharmacologically relevant concentrations IV iron products have been shown to cause endothelial damage and dysfunction (Limet al., 2004; Kamanna et al., 2011), impair immune system (Ichii et al., 2012; Vaziri, 2013), and increase the incidence and severity of microbial infections (Ellis et al., 2013).

Inflammation and iron overload independently raise hepcidin and ferritin production which work in concert to inhibit intestinal absorption and block release of iron from the storage sites (see Chapter 123). In addition to its effects on oxidative stress, it may be important that it can deprive invading pathogens from access to iron. Thus administration of IV iron in ESRD patients with elevated ferritin (> 350 micrograms/L) and systemic inflammation or chronic infection can intensify oxidative stress and inflammation and compromise their defence against microbial infections.

Impaired antioxidant defence system in chronic kidney disease

Oxidative stress in CKD fails to elicit an appropriate antioxidant defence response (Ruiz et al., 2013). In fact, oxidative stress in rats with CKD induced by 5/6 nephrectomy or adenine-induced chronic interstitial nephropathy and in the Imai rats with spontaneous focal segmental glomerulosclerosis is paradoxically associated with a marked and time-dependent decline in Nrf2 activity (see above) and a marked elevation of the Nrf2 repressor molecule, Keap1, in the remnant kidney (Kim and Vaziri, 2010; Kim et al., 2011; Aminzadeh et al., 2012, 2013; Ruiz et al., 2013). The decline in the Nrf2 activity in these animals is accompanied by a steady fall in expression of Nrf2 target gene products, including antioxidant enzymes (i.e. SOD isoforms, catalase, glutathione peroxidase, and HO-1), the key enzymes responsible for glutathione synthesis (i.e. glutamate-cysteine ligase catalytic and modifier subunits), and the major detoxifying enzyme, NQO1. In addition to rendering the diseased kidney more susceptible to oxidative stress, impaired Nrf2 function leads to amplification of intrarenal inflammation via ROS-mediated activation of NF-κB.

A number of studies have demonstrated the anti-inflammatory function of Nrf2 (Morimitsu et al., 2002; Surh et al., 2005; Chen et al., 2006; Li et al., 2008). *Nrf2* gene ablation intensifies diabetes-induced oxidative stress, inflammation, and renal injury (Yoh et al., 2008; Zheng et al., 2011). Moreover ischaemic and nephrotoxic insults lead to more severe acute kidney injury and dysfunction and higher mortality in Nrf2-deficient compared to the wild-type mice (Liu et al., 2009).

Consequences of oxidative stress in chronic kidney disease

Oxidative stress causes cytotoxicity and tissue damage or dysfunction directly via ROS-mediated oxidation of the various molecules or indirectly by activating the redox-sensitive transcription factors and signal transduction pathways. Some of the CKD-associated disorders in which oxidative stress is involved are briefly mentioned below:

Role of oxidative stress in CKD progression

Diseased kidneys in various models of CKD show accumulation of markers of oxidative stress, upregulation of ROS-producing enzymes, and impaired activation of the antioxidant pathway (Ruiz et al., 2013). The causal role of oxidative stress in CKD progression is evidenced by experiments which have shown the salutary effects of the therapeutic interventions which can fortify the endogenous antioxidant system (e.g. natural Nrf2 activators) (Sahin et al., 2010; Molina-Jijon et al., 2011; Peng et al., 2011; Tsai et al., 2011) or

reduce ROS production (e.g. AT_1 receptor blockers and ACE inhibitors) (Ruggenenti et al., 2012).

Role of oxidative stress in CKD-associated cardiovascular complications

Via ROS-mediated NO inactivation, reduced NO production, and LDL oxidation, oxidative stress causes endothelial dysfunction and atherosclerosis. Studies in animal models of CKD have revealed marked downregulation of NO synthase expression, ROS-mediated NO inactivation, endothelial dysfunction, and lipid accumulation in the artery wall (Vaziri et al., 1998a, 1998b, 2002).

Role of oxidative stress in CKD-associated anaemia

By depleting the erythrocytes' antioxidant reservoirs and oxidizing their phospholipid membranes CKD-associated oxidative stress shortens the erythrocyte lifespan (Cruz et al., 2008; Babitt and Lin, 2012). In addition, by promoting inflammation, oxidative stress causes erythropoietin resistance and raises hepcidin production which limits intestinal iron absorption and iron release from storage sites, thereby limiting haemoglobin production.

Role of oxidative stress in CKD-associated systemic inflammation

As noted above via ROS-mediated activation of NF-kB and formation of pro-inflammatory oxidized lipoproteins, advanced protein and glycation end products, oxidative stress triggers the release of inflammatory cytokines and chemokines and activation of immune cells. Activated leucocytes and resident cells, in turn, generate ROS and reactive halogen and nitrogen species which help to amplify and perpetuate oxidative stress in CKD.

Role of oxidative/nitrosative stress in CKD-associated neurological disorders

Via oxidation of the polyunsaturated fatty acids which are highly prone to oxidation and are heavily abundant in neuronal tissues, oxidative stress can cause neurological damage and dysfunction. In addition, oxidative stress can cause neuronal injury by triggering excitotoxicity which is marked by elevation of intracellular ionized calcium, activation of neuronal NOS, formation of peroxynitrite, nitration of proteins, and mitochondrial damage. In fact, Deng et al. have demonstrated heavy accumulation of nitrotyrosine (a biomarker of oxidative and nitrosative stress) in the cerebral cortex of the CKD animals (Deng et al., 2001). This finding is of particular interest with regard to the cognitive dysfunction in CKD since formation of nitrotyrosine and lipid peroxidation products is a critical step in the pathogenesis and progression of Alzheimer disease (Butterfield et al., 2011).

Potential strategies to attenuate chronic kidney disease-associated oxidative stress

Hypertension, hypotension and fluid volume control

AT_1 receptor blockers and ACE inhibitors are likely to reduce oxidative stress as the intrarenal angiotensin system is markedly upregulated and is a major source of ROS production and inflammation in the diseased kidney tissue (Vaziri and Rodríguez-Itrube, 2006).

Hypervolemia is a common consequence of advanced CKD and when severe may contribute to systemic inflammation and oxidative stress. This is, in part, due to the impairment of intestinal epithelial barrier structure and function in the heavily oedematous bowels.

Rapid removal of fluid during haemodialysis frequently results in hypotension which can cause bowel ischaemia and epithelial barrier dysfunction enabling influx of endotoxin in the systemic circulation. This will amplify systemic inflammation and oxidative stress. Lower weight gains, longer and more frequent dialysis can minimize intra- and post-dialytic hypotension and its adverse consequences.

Prevention, detection, and treatment of infection

Infections cause inflammation which is a major cause of oxidative stress. Thus prevention, detection, and treatment can attenuate oxidative stress.

Adequate uraemia control

Urea hydrolysis to ammonia by microbial urease leads to formation of ammonium hydroxide in the intestinal lumen. This leads to the breakdown of the intestinal epithelial tight junction which causes systemic inflammation and oxidative stress by enabling the influx of endotoxin and other noxious luminal contents into the internal milieu (Vaziri et al., 2012a, 2012b, 2012c, 2013b). Consequently, strategies aimed at improving uraemia control such as reduction of dietary protein and longer and more frequent dialysis can help to attenuate oxidative stress and inflammation.

Adequate glycemia control in diabetics

By promoting mitochondrial dysfunction and formation of glycated proteins which serve as ligands for catalytically active iron, poor glycemia control causes oxidative stress. In addition it leads to formation of AGEs which promote inflammation and thereby oxidative stress.

Avoidance of iron overload

The potential hazards of iron treatment were mentioned above (Vaziri, 2012b, 2013). Studies currently under way aim to test the safety and efficacy of different iron management regimens.

Potential strategies to enhance antioxidant capacity

Endogenous antioxidant capacity is suppressed in CKD (Kim et al., 2010; Aminzadehet al., 2013; Ruiz et al., 2013; Vaziri et al., 2013a). Dietary restriction of fruits and vegetables prescribed to limit potassium intake could contribute to this. This is because fresh fruits and vegetables contain numerous precious micronutrients including antioxidant compounds and serve as substrates for the generation of other nutrients by gut microbial flora (Ruiz et al., 2013).

Dialysis results in not only the intended removal of the excess fluid, electrolytes, and uraemic retention products but also many small-sized molecules including antioxidant compounds. It is possible that this contributes to the pro-oxidant state.

Finally, recent demonstration of uraemia-induced changes in the structure and function of the gut microbiome (Vaziri et al., 2013a) which is a major source of important micronutrients can potentially contribute to the impaired antioxidant system in advanced CKD.

Future studies are needed to address the ideal composition of the diet and the potential benefit of prebiotics in CKD/ESRD populations. In addition, future studies are needed to identify strategies

aimed at restoring production of the endogenous antioxidant and phase 2 detoxifying enzymes and related molecules in these populations. However, studies in experimental animals have demonstrated the salutary effects of natural Nrf2 activators. For example, sulphoraphane, an organosulphur compound found in cruciferous vegetables, has been shown to ameliorate nephropathy in animals with streptozotocin-induced diabetes (Zheng et al., 2011). Likewise, epigallocatechin-3-gallate (the bioactive polyphenol in green tea) has been shown to improve renal lesions in animal models of systemic lupus erythematosus (Tsai et al., 2011), in mice with anti-glomerular basement membrane glomerulonephritis (Peng et al., 2011), and in animals with cisplatin-induced nephrotoxicty (Sahin et al., 2010). Similarly, curcumin, a polyphenolic compound extracted from turmeric, has been shown to confer protection in an animal model of chromium-induced nephrotoxicity (Molina-Jijon et al., 2011). These observations support the role of Nrf2 deficiency in the pathogenesis of oxidative stress, inflammation, and progression of CKD. Future studies are needed to explore the potential utility of Nrf2 agonists in patients with CKD.

References

Aminzadeh, M. A., Nicholas, S. B., Norris, K. C., *et al.* (2013). Role of impaired Nrf2 activation in the pathogenesis of oxidative stress and inflammation in chronic tubulo-interstitial nephropathy. *Nephrol Dial Transplant*, 28(8), 2038–45.

Aminzadeh, M. A., Sato, T., and Vaziri, N. D. (2012). Participation of endoplasmic reticulum stress in the pathogenesis of spontaneous glomerulosclerosis. Role of intra-renal angiotensin system. *Transl Res*, 160(4), 309–18.

Aronov, P. A., Luo, F. J., Plummer, N. S., *et al.* (2011). Colonic contribution to uremic solutes. *J Am Soc Nephrol*, 22(9), 1769–76.

Babitt, J. L. and Lin, H. Y. (2012). Mechanisms of anemia in CKD. *J Am Soc Nephrol*, 23(10), 1631–4.

Barton, C. H., Ni, Z., and Vaziri, N. D. (2001). Enhanced nitric oxide inactivation in aortic coarctation-induced hypertension. *Kidney Int*, 60(3), 1083–7.

Bartz, R. R, Piantadosi, C. A. (2010). Clinical review: oxygen as a signaling molecule. *Crit Care*, 14(5), 234.

Boyce, N. W., Tipping, P. G., and Holdsworth, S. R. (1989). Glomerular macrophages produce reactive oxygen species in experimental glomerulonephritis. *Kidney Int*, 35(3), 778–82.

Brownlee, M. (2001). Biochemistry and molecular cell biology of diabetic complications. *Nature*, 414(6865), 813–20.

Butterfield, D. A., Reed, T., and Sultana, R. (2011). Roles of 3-nitrotyrosine- and 4-hydroxynonenal-modified brain proteins in the progression and pathogenesis of Alzheimer's disease. *Free Radic Res*, 45(1), 59–72.

Cachofeiro, V., Goicochea, M., de Vinuesa, S. G., *et al.* (2008). Oxidative stress and inflammation, a link between chronic kidney disease and cardiovascular disease. *Kidney Int Suppl*, 111, S4–9.

Carrero, J. J. and Stenvinkel, P. (2010). Inflammation in end-stage renal disease—what have we learned in 10 years? *Semin Dial*, 23(5), 498–509.

Chen, H. C., Guh, J. Y., Shin, S. J., *et al.* (2000). Reactive oxygen species enhances endothelin-1 production of diabetic rat glomeruli in vitro and in vivo. *J Lab Clin Med*, 135(4), 309–15.

Chen, X. L., Dodd, G., Thomas, S., *et al.* (2006). Activation of Nrf2/ARE pathway protects endothelial cells from oxidant injury and inhibits inflammatory gene expression. *Am J Physiol Heart Circ Physiol*, 290(5), H1862–70.

Cho, K. H., Kim, H. J., Rodríguez-Iturbe, B., *et al.* (2009). Niacin ameliorates oxidative stress, inflammation, proteinuria, and hypertension in rats with chronic renal failure. *Am J Physiol Renal Physiol*, 297(1), F106–13.

Cruz, D. N., de Cal, M., and Ronco, C. (2008). Oxidative stress and anemia in chronic hemodialysis: the promise of bioreactive membranes. *Contrib Nephrol*, 161, 89–98.

Cullinan, S. B. and Diehl, J. A. (2004). PERK-dependent activation of Nrf2 contributes to redox homeostasis and cell survival following endoplasmic reticulum stress. *J Biol Chem*, 279(19), 20108–17.

Danielson, B. G. (2004). Structure, chemistry, and pharmacokinetics of intravenous iron agents. *J Am Soc Nephrol*, 15, S93–8.

Deng, G., Vaziri, N. D., Jabbari, B., *et al.* (2001). Increased tyrosine nitration of the brain in chronic renal insufficiency: reversal by antioxidant therapy. *J Am Soc Nephrol*, 12, 1892–8.

Ellis, A. R., Wang, L., Winkelmayer, W. C., *et al.* (2013). Infection risk with bolus versus maintenance iron supplementation in hemodialysis patients. *J Am Soc Nephrol*, 24, 24(7), 1151–8.

Fujihara, C. K., Antunes, G. R., Mattar, A. L., *et al.* (2007). Chronic inhibition of nuclear factor-kappaB attenuates renal injury in the 5/6 renal ablation model. *Am J Physiol Renal Physiol*, 292(1), F92–9.

Gaertner, S. A., Janssen, U., Ostendorf, T., *et al.* (2002). Glomerular oxidative and antioxidative systems in experimental mesangioproliferative glomerulonephritis. *J Am Soc Neph*rol, 13(12), 2930–7.

Garcia-Fernandez, N., Echeverria, A., Sanchez-Ibarrola, A., *et al.* (2010). Randomized clinical trial on acute effects of i.v. iron sucrose during haemodialysis. *Nephrology (Carlton)*, 15(2), 178–83.

Glass, C. K. and Witztum, J. L. (2001). Atherosclerosis: the road ahead. *Cell*, 104, 503–16.

Gollapudi, P., Yoon, J. W., Gollapudi, S., *et al.* (2010). Leukocyte toll-like receptor expression in end-stage kidney disease. *Am J Nephrol*, 31(3), 247–54.

Gorin, Y., Block, K., Hernandez, J., *et al.* (2005). Nox4 NAD(P)H oxidase mediates hypertrophy and fibronectin expression in the diabetic kidney. *J Biol Chem*, 280(47), 39616–26.

Gutteridge, J. M. C. and Halliwell, B. (2010). Antioxidants: molecules, medicines, and myths. *Biochem Biophys Res Comm*, 393, 561–4.

Ha, H., Yu, M. R., Choi, Y. J., *et al.* (2002). Role of high glucose-induced nuclear factor-kappaB activation in monocyte chemoattractant protein-1 expression by mesangial cells. *J Am Soc Nephrol*, 13(4), 894–902.

Ha, H. and Kim, K. H. (1999). Pathogenesis of diabetic nephropathy: the role of oxidative stress and protein kinase C. *Diabetes Res Clin Pract*, 45(2–3), 147–51.

Halliwell, B. (2007). Biochemistry of oxidative stress. *Biochem Soc Trans*, 35(Pt 5), 1147–50.

Hendrikx, T. K., van Gurp, E. A., Mol, W. M., *et al.* (2009). End-stage renal failure and regulatory activities of CD4+CD25bright+FoxP3+ T-cells. *Nephrol Dial Transplant*, 24(6), 1969–78.

Himmelfarb, J. and Hakim, R. M. (2003). Oxidative stress in uremia. *Curr Opin Nephrol Hypertens*, 12(6), 593–8.

Himmelfarb, J., Stenvinkel, P., Ikizler, T. A., *et al.* (2002). The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int*, 62(5), 1524–38.

Ichii, H., Masuda, Y., Hassanzadeh, T., *et al.* (2012). Iron sucrose impairs phagocytic function and promotes apoptosis in polymorphonuclear leukocytes. *Am J Nephrol*, 36(1), 50–7.

Kamanna, V. S., Ganji, S. H., Shelkovnikov, S., *et al.* (2011). Iron sucrose promotes endothelial injury and dysfunction and monocyte adhesion/infiltration. *Am J Nephrol*, 35(2), 114–19.

Kawaguchi, M., Yamada, M., Wada, H., *et al.* (1992). Roles of active oxygen species in glomerular epithelial cell injury in vitro caused by puromycin aminonucleoside. *Toxicology*, 72(3), 329–40.

Kaysen, G. A. (2004). Inflammation: cause of vascular disease and malnutrition in dialysis patients. *Seminar Nephrol*, 24(5), 431–6.

Kim, H. J., Sato, T., Rodríguez-Iturbe, B., *et al.* (2011). Role of intrarenal angiotensin system activation, oxidative stress, inflammation, and impaired nuclear factor-erythroid-2-related factor 2 activity in the progression of focal glomerulosclerosis. *J Pharmacol Exp Ther*, 337(3), 583–90.

Kim, H. J. and Vaziri, N. D. (2010). Contribution of impaired Nrf2-Keap1 pathway to oxidative stress and inflammation in chronic renal failure. *Am J Physiol Renal Physiol*, 298(3), F662–71.

Kobayashi, A., Kang, M. I., Watai, Y., *et al.* (2006). Oxidative and electrophilic stresses activate Nrf2 through inhibition of ubiquitination activity of Keap1. *Mol Cell Biol*, 26(1), 221–9.

Kobori, H., Nangaku, M., Navar, L. G., *et al.* (2007). The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. *Pharmacol Rev*, 59(3), 251–87.

Koya, D., Hayashi, K., Kitada, M., *et al.* (2003). Effects of antioxidants in diabetes-induced oxidative stress in the glomeruli of diabetic rats. *J Am Soc Nephrol*, 14(8 Suppl 3), S250–3.

Kuo, K. L., Hung, S. C., Wei, Y. H., *et al.* (2008). Intravenous iron exacerbates oxidative DNA damage in peripheral blood lymphocytes in chronic hemodialysis patients. *J Am Soc Nephrol*, 19(9), 1817–26.

Lee, H. B., Yu, M. R., Yang, Y., *et al.* (2003). Reactive oxygen species-regulated signaling pathways in diabetic nephropathy. *J Am Soc Nephrol*, 14(8 Suppl 3), S241–5.

Li, D. and Mehta, J. L. (2000). Antisense to LOX-1 inhibits oxidized LDL-mediated upregulation of monocyte chemoattractant protein-1 and monocyte adhesion to human coronary artery endothelial cells. *Circulation* 101, 2889–95.

Li, W., Khor, T. O., Xu, C., *et al.* (2008). Activation of Nrf2-antioxidant signaling attenuates NFkappaB-inflammatory response and elicits apoptosis. *Biochem Pharmacol*, 76(11), 1485–9.

Lim, C. S. and Vaziri, N. D. (2004). The effects of iron dextran on the oxidative stress in cardiovascular tissues of rats with chronic renal failure. *Kidney Int*, 65, 1802–9.

Liu, M., Grigoryev, D. N., Crow, M. T., *et al.* (2009). Transcription factor Nrf2 is protective during ischemic and nephrotoxic acute kidney injury in mice. *Kidney Int*, 76(3), 277–85.

Matsusaka, T., Niimura, F., Shimizu, A., *et al.* (2012). Liver angiotensinogen is the primary source of renal angiotensin II. *J Am Soc Nephrol*, 23(7), 1181–9.

Meier, P., Golshayan, D., Blanc, E., *et al.* (2009). Oxidized LDL modulates apoptosis of regulatory T cells in patients with ESRD. *J Am Soc Nephrol*, 20, 1368–84.

Miyamoto, T., Carrero, J. J., and Stenvinkel, P. (2011). Inflammation as a risk factor and target for therapy in chronic kidney disease. *Curr Opin Nephrol Hypertens*, 20(6), 662–8.

Molina-Jijon, E., Tapia, E., Zazueta, C., *et al.* (2011). Curcumin prevents Cr(VI)-induced renal oxidant damage by a mitochondrial pathway. *Free Radic Biol Med*, 51(8), 1543–57.

Morimitsu, Y., Nakagawa, Y., Hayashi, K., *et al.* (2002). A sulforaphane analogue that potently activates the Nrf2-dependent detoxification pathway. *J Biol Chem*, 277(5), 3456–63.

Neale, T. J., Ullrich, R., Ojha, P., *et al.* (1993). Reactive oxygen species and neutrophil respiratory burst cytochrome b558 are produced by kidney glomerular cells in passive Heymann nephritis. *Proc Natl Acad Sci U S A*, 90, 3645–9.

Nishikawa, T., Edelstein, D., Du, X. L., *et al.* (2000). Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature*, 404(6779), 787–90.

Oberle, G. P., Niemeyer, J., Thaiss, F., *et al.* (1992). Increased oxygen radical and eicosanoid formation in immune-mediated mesangial cell injury. *Kidney Int*, 42(1), 69–74.

Parkkinen, J., von Bonsdorff, L., Peltonen, S., *et al.* (2000). Catalytically active iron and bacterial growth in serum of haemodialysis patients after IV iron-saccharate administration. *Nephrol Dial Transplant*, 15, 1827–34.

Peng, A., Ye, T., Rakheja, D., *et al.* (2011). The green tea polyphenol (-)-epigallocatechin-3-gallate ameliorates experimental immune-mediated glomerulonephritis. *Kidney Int*, 80(6), 601–11.

Poelstra, K., Hardonk, M. J., Koudstaal, J., *et al.* (1990). Intraglomerular platelet aggregation and experimental glomerulonephritis. *Kidney Int*, 37(6), 1500–8.

Rodríguez-Iturbe, B., Franco, M., Tapia, E., *et al.* (2012). Renal inflammation, autoimmunity and salt-sensitive hypertension. *Clin Exp Pharmacol Physiol*, 39(1), 96–103.

Rodríguez-Iturbe, B., Vaziri, N. D., Herrera-Acosta, J., *et al.* (2004). Oxidative stress, renal infiltration of immune cells, and salt-sensitive hypertension: all for one and one for all. *Am J Physiol Renal Physiol*, 286(4), F606–16.

Ruggenenti, P., Cravedi, P., and Remuzzi, G. (2012). Mechanisms and treatment of CKD. *J Am Soc Nephrol*, 23(12), 1917–28.

Ruiz, S., Pergola, P. E., Zager, R. A., *et al.* (2013). Targeting Nrf2 activation to ameliorate oxidative stress and inflammation in chronic kidney disease. *Kidney Int*, 83(6), 1029–41.

Sahin, K., Tuzcu, M., Gencoglu, H., *et al.* (2010). Epigallocatechin-3-gallate activates Nrf2/HO-1 signaling pathway in cisplatin-induced nephrotoxicity in rats. *Life Sci*, 87(7–8), 240–5.

Satoh, M., Fujimoto, S., Haruna, Y., *et al.* (2005). NAD(P)H oxidase and uncoupled nitric oxide synthase are major sources of glomerular superoxide in rats with experimental diabetic nephropathy. *Am J Physiol Renal Physiol*, 288(6), F1144–52.

Scivittaro, V., Ganz, M. B., and Weiss, M. F. (2000). AGEs induce oxidative stress and activate protein kinase C-beta(II) in neonatal mesangial cells. *Am J Physiol Renal Physiol*, 278(4), F676–83.

Shah, S. V. (1988). Evidence suggesting a role for hydroxyl radical in passive Heymann nephritis in rats. *Am J Physiol*, 254(3 Pt 2), F337–44.

Shah, S. V., Baliga, R., Rajapurkar, M., *et al.* (2007). Oxidants in chronic kidney disease. *J Am Soc Nephrol*, 18(1), 16–28.

Sindhu, R. K., Roberts, C. K., Ehdaie, A., *et al.* (2005). Effects of aortic coarctation on aortic antioxidant enzymes and NADPH oxidase protein expression. *Life Sci*, 76(8), 945–53.

Surh, Y. J., Kundu, J. K., Na, H. K., *et al.* (2005). Redox-sensitive transcription factors as prime targets for chemoprevention with anti-inflammatory and antioxidative phytochemicals. *J Nutr*, 135(12 Suppl), 2993S–3001S.

Surh, Y. J., Kundu, J. K., and Na, H. K. (2008). Nrf2 as a master redox switch in turning on the cellular signaling involved in the induction of cytoprotective genes by some chemopreventive phytochemicals. *Planta Med*, 74(13), 1526–39.

Tsai, P. Y., Ka, S. M., Chang, J. M., *et al.* (2011). Epigallocatechin-3-gallate prevents lupus nephritis development in mice via enhancing the Nrf2 antioxidant pathway and inhibiting NLRP3 inflammasome activation. *Free Radic Biol Med*, 51(3), 744–54.

Uruno, A. and Motohashi, H. (2011). The Keap1-Nrf2 system as an in vivo sensor for electrophiles. *Nitric Oxide*, 25(2), 153–60.

Van Campenhout, A., Van Campenhout, C., Lagrou, A., *et al.* (2008). Iron-induced oxidative stress in hemodialysis patients: a pilot study on the impact of diabetes. *Biometals*, 21, 159–70.

Van Wyck, D., Anderson, J., and Johnson, K. (2004). Labile iron in parenteral iron formulations: a quantitative and comparative study. *Nephrol Dial Transplant*, 19(3), 561–5.

Vaziri, N. D. (2004a). Oxidative stress in uremia: nature, mechanisms, and potential consequences. *Semin Nephrol*, 24(5), 469–73.

Vaziri, N. D. (2004b). Roles of oxidative stress and antioxidant therapy in chronic kidney disease and hypertension. *Curr Opin Nephrol Hypertens*, 13(1), 93–9.

Vaziri, N. D. (2006). Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences. *Am J Physiol Renal Physiol*, 290(2), F262–72.

Vaziri, N. D. (2010). Lipotoxicity and impaired high density lipoprotein-mediated reverse cholesterol transport in chronic kidney disease. *J Ren Nutr*, 20(5 Suppl), S35–43.

Vaziri, N. D. (2012a). CKD impairs barrier function and alters microbial flora of the intestine—A major link to inflammation and uremic toxicity. *Curr Opin Nephrol Hypertens*, 21(6), 587–92.

Vaziri, N. D. (2012b). Epidemic of iron overload in dialysis population caused by intravenous iron products: a plea for moderation. *Am J Med*, 125(10), 951–2.

Vaziri, N. D. (2013). Understanding iron: promoting its safe use in patients with chronic kidney failure treated by hemodialysis. *Am J Kidney Dis*, 61(6), 992–1000.

Vaziri, N. D. (2014). Contribution of dyslipidemia to impairment of energy metabolism, oxidative stress, inflammation, and CVD in CKD. *Clin Exp Nephrol*, 18(2), 265–8.

Vaziri, N. D., Bai, Y., Ni, Z., *et al.* (2007). Intra-renal angiotensin II/AT1 receptor, oxidative stress, inflammation, and progressive injury in renal mass reduction. *J Pharmacol Exp Ther*, 323(1), 85–93.

Vaziri, N. D., Dicus, M., Ho, N. D., *et al.* (2003). Oxidative stress and dysregulation of superoxide dismutase and NADPH oxidase in renal insufficiency. *Kidney Int*, 63(1), 179–85.

Vaziri, N. D., Goshtasby, N., Yuan, J., *et al.* (2012a). Uremic human plasma degrades intestinal epithelial barrier structure and function. *Am J Nephrol*, 36(5), 438–43.

Vaziri, N. D., Navab, M., and Fogelman, A. M. (2010). HDL metabolism and activity in chronic kidney disease. *Nat Rev Nephrol*, 6(5), 287–96.

Vaziri, N. D., Ni, Z., Oveisi, F., *et al.* (2002). Enhanced nitric oxide inactivation and protein nitration by reactive oxygen species in chronic renal insufficiency. *Hypertension*, 39, 135–41.

Vaziri, N. D. and Ni, Z. (2005). Expression of NOX-I, gp91phox, p47phox and P67phox in the aorta segments above and below coarctation. *Biochim Biophys Acta*, 1723(1–3), 321–7.

Vaziri, N. D., Ni, Z., Wang, X. Q., *et al.* (1998a). Downregulation of nitric oxide synthase in chronic renal insufficiency: role of excess PTH. *Am J Physiol Renal Physiol*, 274, 642–9.

Vaziri, N. D. and Norris, K. (2011). Lipid disorders and their relevance to outcomes in chronic kidney disease. *Blood Purif*, 31, 189–96.

Vaziri, N. D., Oveisi, F., and Ding, Y. (1998b). Role of increased oxygen free radical activity in the pathogenesis of uremic hypertension. *Kidney Int*, 53, 1748–54.

Vaziri, N. D. and Rodríguez-Iturbe, B. (2006). Mechanisms of disease: oxidative stress and inflammation in the pathogenesis of hypertension. *Nat Clin Pract Nephrol*, 2(10), 582–93.

Vaziri, N. D., Wong, J., Pahl, M. V., *et al.* (2013a).Chronic kidney disease alters the composition of intestinal microbial flora. *Kidney Int*, 83(2), 308–15.

Vaziri, N. D., Yuan, J., Khazaeli, M., *et al.* (2013b). Oral activated charcoal adsorbent (AST-120) ameliorates CKD-induced intestinal epithelial barrier disruption and systemic inflammation. *Am J Nephrol*, 37, 518–25.

Vaziri, N. D., Yuan, J., and Norris, K. (2012b). Role of urea in intestinal barrier dysfunction and disruption of epithelial tight junction in CKD. *Am J Nephrol,* 37(1), 1–6.

Vaziri, N. D., Yuan, J., Rahimi, A., *et al.* (2012c). Disintegration of colonic epithelial tight junction in uremia: a likely cause of CKD-associated inflammation. *Nephrol Dial Transplant*, 27(7), 2686–93.

Vio, C. P. and Jeanneret, V. A. (2003). Local induction of angiotensin-converting enzyme in the kidney as a mechanism of progressive renal diseases. *Kidney Int Suppl*, 86, S57–63.

Wakabayashi, N., Slocum, S. L., Skoko, J. J., *et al.* (2010). When NRF2 talks, who's listening? *Antioxid Redox Signal*, 13(11), 1649–63.

Wilcox, C. S. (2005). Oxidative stress and nitric oxide deficiency in the kidney: a critical link to hypertension? *Am J Physiol Regul Integr Comp Physiol*, 289(4), R913–35.

Yan, S. D., Schmidt, A. M., Anderson, G. M., *et al.* (1994). Enhanced cellular oxidant stress by the interaction of advanced glycation end products with their receptors/binding proteins. *J Biol Chem*, 269(13), 9889–97.

Yoh, K., Hirayama, A., Ishizaki, K., *et al.* (2008). Hyperglycemia induces oxidative and nitrosative stress and increases renal functional impairment in Nrf2-deficient mice. *Genes Cells*, 13(11), 1159–70.

Yoh, K., Itoh, K., Enomoto, A., *et al.* (2001). Nrf2-deficient female mice develop lupus-like autoimmune nephritis. *Kidney Int*, 60(4), 1343–53.

Yoon, J. W., Pahl, M. V., and Vaziri, N. D. (2007). Spontaneous leukocyte activation and oxygen-free radical generation in end-stage renal disease. *Kidney Int*, 71(2), 167–72.

Zheng, H., Whitman, S. A., Wu, W., *et al.* (2011). Therapeutic potential of Nrf2 activators in streptozotocin-induced diabetic nephropathy. *Diabetes*, 60(11), 3055–66.

CHAPTER 113

Abnormal endothelial vasomotor and secretory function

Thimoteus Speer and Danilo Fliser

Endothelial function

The endothelium is the largest organ of the human body consisting of approximately 10^{13} cells with a total surface of roughly 1000 m^2. Endothelial cells cover the vasculature as a barrier between the bloodstream and the vessel wall. However, the endothelium is more a complex control centre than a simple physical barrier. Endothelial cells are key regulators of the vascular homeostasis: they control vascular tone, modulate inflammation of the vessel wall, and equilibrate platelet activation and haemostasis, thereby interacting with other cell types of the vessel wall (e.g. vascular smooth muscle cells, macrophages) and circulating blood cells (e.g. mononuclear cells, platelets) (Fleming and Busse, 2003; Rao et al., 2007; Munzel et al., 2008). To regulate vascular function and structure, endothelial cells produce a broad variety of anti-atherosclerotic substances (Table 113.1), of which nitric oxide (NO) is the best characterized and most studied. Generated by endothelial NO synthase (eNOS), NO induces relaxation of vascular smooth muscle cells, prevents expression of vascular cell adhesion molecules and adhesion of leucocytes, and inhibits platelet activation (Feletou et al., 2012). Deterioration of these beneficial endothelial effects (endothelial dysfunction) is thought to be the first critical step in the pathogenesis of atherosclerosis (Ross, 1999).

Endothelial dysfunction

A widely used definition of endothelial dysfunction refers to an imbalance between the production of vasodilatory and vasoconstrictive substances by the endothelium. However, endothelial dysfunction may include deterioration of more endothelial properties than dysregulation of the vascular tone. Accordingly, endothelial dysfunction can generally be defined as an impairment of endothelial functional properties leading to abnormal endothelial activation.

Abnormal endothelial vasomotor function

The regulation of the vascular tone in cross-talk with vascular smooth muscle cells (VSMCs) is a key feature of the endothelium. This is achieved by secretion of vasodilatory substances such as NO, prostacyclin, and endothelial-derived hyperpolarization factor (EDHF), which induce relaxation of VSMCs (Fig. 113.1A). However, in chronic kidney disease (CKD), substances such as homocysteine, endogenous methylarginines (e.g. asymmetric and symmetric dimethylarginine), or modified lipoproteins inhibit eNOS resulting in a reduced NO bioavailability. Moreover, some of them activate endothelial oxidases (e.g. nicotinamide adenine dinucleotide phosphate, reduced (NADPH) oxidase, xanthine oxidase) to produce reactive oxygen species (ROS), which can directly act on vascular smooth muscle cells, react with NO to form the peroxynitrite radical, or induce uncoupling of eNOS to produce ROS. In addition, cyclooxygenase-derived factors and endothelin-1 are released, causing together with ROS a contraction of the smooth muscle cells (Fig. 113.1B) (Forstermann, 2008; Shi and Vanhoutte, 2009; Vanhoutte, 2011; Feletou et al., 2012).

Abnormal endothelial secretory function

CKD is characterized by abnormal endothelial activation. Several substances circulating in the plasma of patients with impaired kidney function activate the transcription of distinct pro-inflammatory genes acting on endothelial transcription factors like nuclear factor kappa B (NF-κB). The release of pro-coagulatory proteins (e.g. tissue factor) and activation of platelets induce a prothrombotic state. Vice versa, activated platelets secrete cytokines (e.g. IL-1β, RANTES), which further promote endothelial activation. Activated endothelial cells also produce cytokines, which act in an autocrine and paracrine manner by stimulation and chemotaxis of circulating leucocytes. Endothelial cell adhesion molecules enable adhesion and transmigration of mononuclear cells and T lymphocytes resulting in endothelial inflammation (Endemann and Schiffrin, 2004; Rocha and Libby, 2009). Finally, abnormal endothelial activation leads to progressive endothelial apoptosis and damage with shedding of endothelial microparticles and detachment of endothelial cells (Fig. 113.2) (Martinez et al., 2005).

Pathophysiology of endothelial dysfunction in chronic kidney disease

Reduced kidney function leads to accumulation of compounds which are normally excreted by the healthy kidneys. They are referred as uraemic toxins when they impair biological functions (Vanholder and De Smet, 1999; Vanholder et al., 2003). As they circulate in the blood of the patients, it is obvious that some of them may exert direct effects on the vascular endothelium. Several *in vitro* experiments documented that exposure of endothelial cells to serum of uraemic patients induced abnormal endothelial activation

Table 113.1 Vascular functions affected by endothelial cells and selected mediators

Function	Factors
Regulation of vascular tone	Nitric oxide
	Cyclooxygenase-derived products (e.g. prostacyclin)
	Endothelial-derived hyperpolarizing factor (EDHF)
	Endothelial-derived contracting factor (EDCF)
	Endothelin-1
	Angiotensin II
	C-type natriuretic peptide
	Bradykinin
	Adrenomedullin
Regulation of thrombosis and haemostasis	Nitric oxide
	Tissue plasmin activator (tPA)
	Thrombomodulin
	Prostaglandin
	Plasminogen activator inhibitor-1 (PAI-1)
	Tissue factor (TF)
	Tissue factor pathway inhibitor (TFPI)
	Platelet activating factor (PAF)
	Von Willebrand factor (vWF)
	Endothelial protein C receptor
Regulation of vascular inflammation	Monocyte chemotactic factor-1 (MCP-1)
	Cell adhesion molecules (VCAM-1, ICAM-1, E-selectin)
	Interleukin 1, 6, 18
	Tumour necrosis factor alpha
Regulation of cell proliferation	Nitric oxide
	Transforming growth factor beta
	Endothelin-1
	Angiotensin II
	Platelet-derived growth factor (PDGF)
	Basic fibroblast growth factor
	Insulin-like growth factor

(Carbo et al., 2008). Furthermore, CKD interferes considerably with several metabolic pathways leading to post-translational modifications of (lipo)proteins (Endemann and Schiffrin, 2004). In the following sections, endothelial effects of selected uraemic toxins and metabolites will be reviewed. Uraemic toxins in general are reviewed in Chapter 254.

p-Cresyl sulphate and indoxyl sulphate

Both uraemic toxins are generated during bacterial fermentation of tryptophan- and tyrosine-containing proteins in the large intestine. They bind to albumin resulting in a reduced clearance by dialysis treatment. Moreover, their serum levels correlate well with cardiovascular mortality and progression of CKD (Barreto et al., 2009; Meijers et al., 2009; Wu et al., 2012). It was demonstrated that p-cresyl sulphate and indoxyl sulphate attenuate proliferation and migration of endothelial cells leading to endothelial damage with shedding of microparticles (Dou et al., 2004; Meijers et al., 2009). Furthermore, indoxyl sulphate may contribute to endothelial ROS production and promote vascular inflammation by expression of endothelial cell adhesion molecules (Dou et al., 2007; Ito et al., 2010).

Phosphate

High serum phosphate levels are related to cardiovascular events in the general population as well as in CKD patients (Ganesh et al., 2001; Tonelli et al., 2005). Beside its role in the pathogenesis of vascular calcifications, phosphate may directly interfere with endothelial function. It increases endothelial ROS production by NADPH oxidases and diminishes NO bioavailability resulting in a decreased flow-mediated vasodilation in humans (Shuto et al., 2009).

Homocysteine

Homocysteine is a sulphur amino acid, biosynthesized from methionine. It belongs to the group of protein-bound uraemic toxins and is thought to be a cardiovascular risk factor. Several observational trials revealed an association between hyperhomocysteinaemia and cardiovascular morbidity and mortality, although homocysteine-lowering therapies did not reduce the rate of cardiovascular events in large randomized controlled trials in CKD and non-CKD patients (Zoccali, 2006; Zoccali and Mallamaci, 2006; Heinz et al., 2010). Nevertheless, a great many of *in vitro* and *in vivo* studies demonstrated that homocysteine may interact with distinct endothelial functions. Homocysteine activates endothelial NADPH oxidases and leads to uncoupling of eNOS. Moreover, reduced expression of antioxidative enzymes like glutathione peroxidase and superoxide dismutase further enhances endothelial ROS production. Notably, homocysteine was shown to attenuate flow-mediated vasodilation *in vivo* (Papatheodorou and Weiss, 2007).

Methylarginines

The methylarginines asymmetric and symmetric dimethylarginine (ADMA, SDMA) are generated *in vivo* by methylation of arginine residues in proteins by protein arginine methyltransferases. Type 1 protein arginine methyltransferase induces methylation of ADMA, whereas type 2 protein arginine methyltransferase induces methylation of SDMA. Methylarginines are released during protein degradation and circulate as free methylarginines in the serum. Whereas SDMA is mainly excreted by urine, ADMA undergoes enzymatic degradation by dimethylaminohydrolase (DDAH). Both methylarginines are thought to be protein bound to a substantial degree. Therefore as DDAH enzyme activity and expression are reduced in kidney disease, it is reasonable that both methylarginines, ADMA and SDMA, accumulate when kidney function decreases. Elevated methylarginine levels are particularly detectable in patients with incipient kidney disease. SDMA correlates well with the glomerular filtration rate, while this association is much weaker for ADMA. Moreover, both methylarginines are predictors for cardiovascular events in patients with CKD as well as in other clinical conditions such as diabetes, hypertension, and coronary artery disease.

ADMA and SDMA interfere with cellular NO bioavailability. ADMA was shown to reduce endothelial NO production by direct inhibition of eNOS and thereby induces endothelial dysfunction. Although SDMA treatment of endothelial cells reduced NO

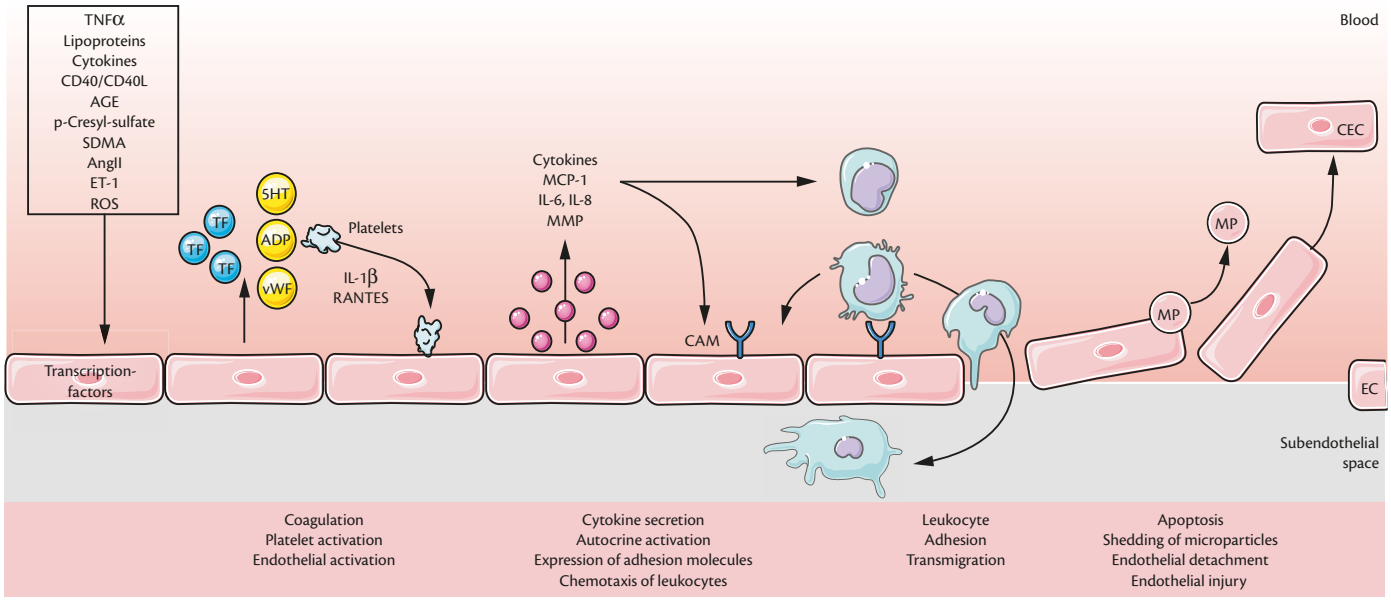

Fig. 113.1 Cross-talk between endothelial cells (ECs) and vascular smooth muscle cells (VSCMs) in health and chronic kidney disease. (A) In healthy subjects, endothelial-derived factors like nitric oxide (NO), endothelial-derived hyperpolarizing factor (EDHF), and prostacyclin (PGI_2) induce relaxation of vascular smooth muscle cells. (B) In chronic kidney disease, several substances inhibit endothelial NO production und induce production of reactive oxygen species (ROS) resulting in VSMC contraction. ADMA = asymmetric dimethylarginine; AGE = advanced glycation end product; SDMA = symmetric dimethylarginine; PG = prostaglandins; AngII = angiotensin II, TGFβ = transforming growth factor beta; TNFα = tumour necrosis factor alpha; TXA_2 = thromboxane A_2.

production, a direct inhibition of eNOS has not yet been demonstrated. However, both substances reduce the L-arginine transport into endothelial cells by the transporters for cationic amino acids (CAT-1/2) resulting in a diminished substrate availability for eNOS. Hence, ADMA and SDMA may be involved into the pathogenesis of CKD-associated endothelial dysfunction (Fig. 113.3) (Fliser et al., 2003; Kielstein et al., 2009; Leiper and Nandi, 2011; Schwedhelm and Boger, 2011).

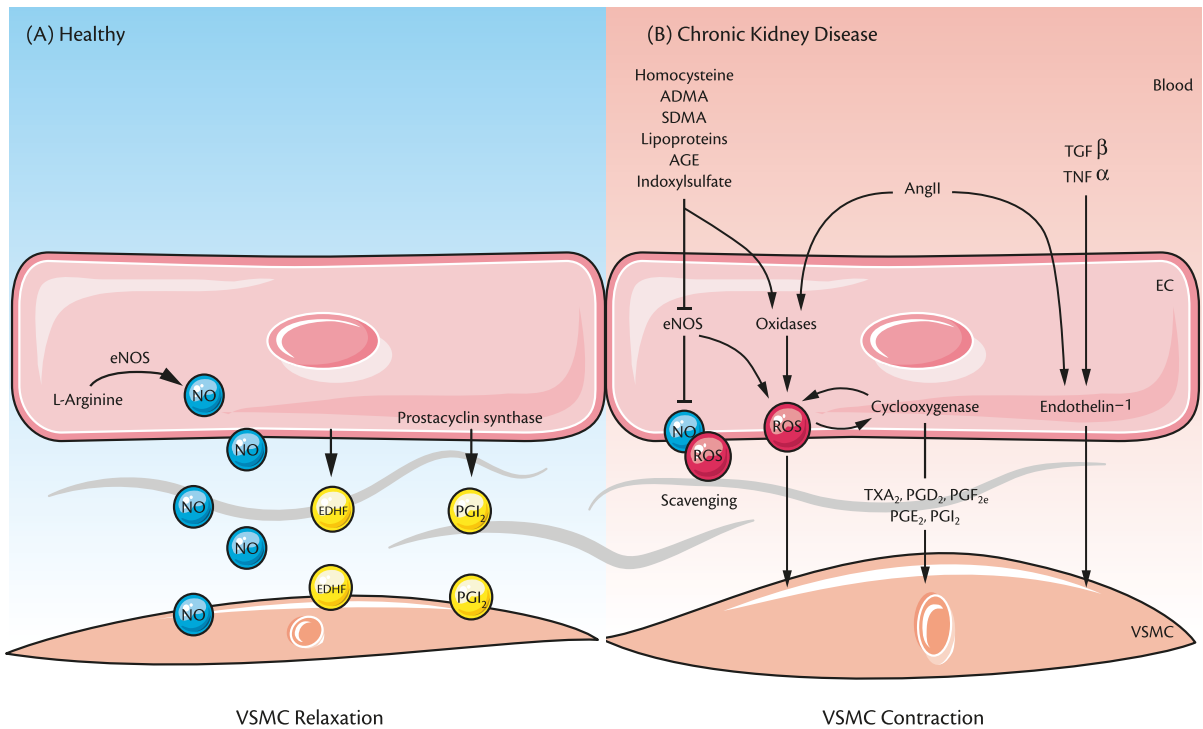

Fig. 113.2 Abnormal endothelial function. 5HT = serotonin; ADP = adenosine diphosphate; CAM = cell adhesion molecules; CEC = circulating endothelial cell; IL-6/8 = interleukin 6/8; MCP-1 = monocyte chemotactic protein; MMP = matrix metalloproteases; MP = microparticles; TF = tissue factor; vWF = von Willebrand factor.

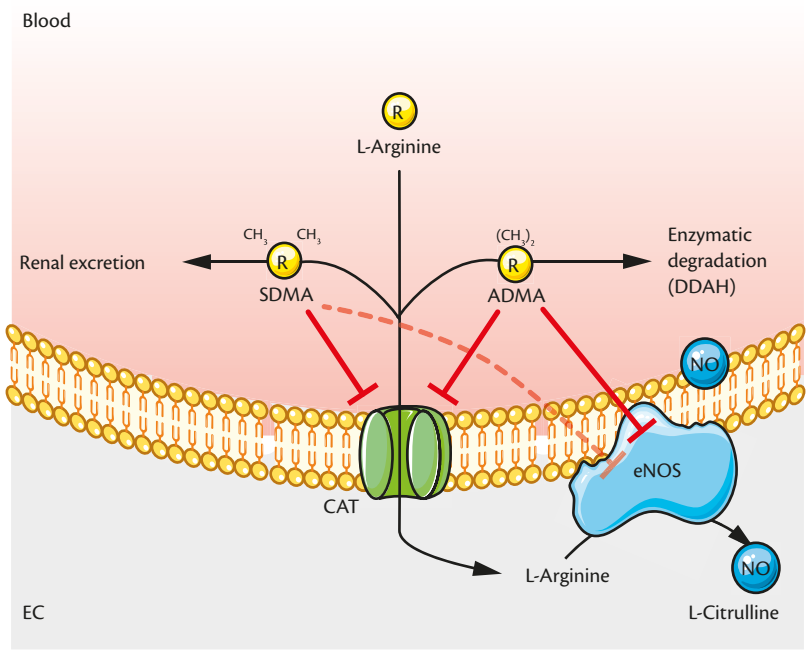

Fig. 113.3 Metabolism and role of the methylarginines asymmetric and symmetric dimethylarginine (ADMA and SDMA) in the regulation of the nitric oxide (NO) bioavailability. CAT = cationic amino acid transporter; DDAH = dimethylaminohydrolase; EC = endothelial cell; eNOS = endothelial nitric oxide synthase.

Lipoproteins

Dyslipidaemia is a common feature of patients with CKD (see Chapter 102), which is characterized by rather normal blood levels of low-density lipoproteins (LDLs), but low blood levels of high-density lipoproteins (HDLs) (see Chapter 102). Beside their role as lipid transporters, lipoproteins may exert several direct vascular effects: HDL is known to preserve endothelial integrity and function mainly by stimulation of endothelial NO production (Navab et al., 2011). In contrast, fatty streak formation by LDL cholesterol-loaded macrophages plays a crucial role in the development of atherosclerotic lesions (Rocha and Libby, 2009). However, CKD may induce substantial changes of lipoprotein composition and function.

Oxidative stress as it occurs in kidney disease (see Chapter 112) leads to oxidation of LDL and HDL. Oxidized LDL (oxLDL) promotes a proinflammatory and procoagulatory endothelial phenotype mediated by the endothelial lectin-like oxLDL receptor (LOX-1). Moreover, oxLDL deteriorates endothelial-dependent vasodilation by reducing NO bioavailability (Heeringa and Tervaert, 2002).

Another recently identified post-translational modification of lipoproteins in CKD patients is carbamylation. Urea (non-enzymatically) or myeloperoxidase (enzymatically) trigger the carbamylation of HDL and LDL lysine residues (Wang et al., 2007). Carbamylated lipoproteins were found in atherosclerotic lesions of animals with experimental CKD. It was shown that carbamylated LDL may induce endothelial apoptosis and promote endothelial inflammatory activation (Apostolov et al., 2010; Speer et al., 2014). Although vascular effects of carbamylated lipoproteins are only partially understood, they might play an important role in CKD-associated endothelial dysfunction.

Notably, HDL—which is commonly referred to as 'good cholesterol'—undergoes considerable changes in CKD patients. In contrast to LDL, the protein composition of HDL is quite complex. Proteomic analysis revealed that uraemia causes changes of HDL-associated proteins affecting its functional properties. The activity of HDL-associated antioxidative proteins is reduced, resulting in a diminished capacity of HDL to prevent oxidation of LDL (Kalantar-Zadeh et al., 2007; Vaziri et al., 2009; Holzer et al., 2011). Furthermore, HDL from CKD patients may promote endothelial adhesion of mononuclear cells and thereby endothelial inflammatory activation. In addition, levels of apolipoprotein A1, which is mainly responsible for the endothelial protective effects of HDL, are reduced in patients with CKD (Vaziri et al., 2010; Speer et al., 2013) (see Chapter 102).

Clinical assessment of endothelial function

Endothelial dysfunction is the first crucial step in the pathogenesis of atherosclerosis and is commonly accepted as a cardiovascular risk factor. It was convincingly demonstrated that endothelial dysfunction might be a predictor for cardiovascular events in the general population and particularly in patients with CKD (Suwaidi et al., 2000). Vice versa, endothelial dysfunction caused by hypertension or diabetes was shown to predict worsening of kidney function, revealing that endothelial dysfunction might be a systemic

rather than a local phenomenon (Malyszko, 2010; Rabelink et al., 2010; Nakagawa et al., 2011). Therefore, it is conceivable that measuring endothelial function might be an important and useful strategy to estimate cardiovascular risk and to assess effects of vascular-targeted therapies in CKD patients (Brunner et al., 2005; Deanfield et al., 2005).

Invasive methods

Quantitative angiography

Assessment of the vessel diameter by quantitative coronary angiography in combination with Doppler flow measurements after infusion of acetylcholine represents the gold standard for the clinical assessment of endothelial function. If the endothelium is intact, acetylcholine or other agonists (e.g. bradykinin, prostacyclin) induce endothelial release of NO leading to vasodilation. However, in patients with endothelial dysfunction, acetylcholine causes a vasoconstriction. Endothelial-independent vasodilation can be assessed by application of adenosine. Because of its invasiveness, the range of application is restricted (Deanfield et al., 2005; Hogas et al., 2010).

Venous occlusion plethysmography

Venous occlusion plethysmography to measure the blood flow is usually performed in the forearm vascular bed after arterial infusion of NO agonists, as in quantitative angiography. This technique utilizes the fact that endothelial dysfunction represents a systemic disorder. It was demonstrated that there is a correlation between acetylcholine response in coronary arteries and in forearm blood vessels. As arterial cannulation is required, the usability of this procedure is limited (Deanfield et al., 2005; Hogas et al., 2010).

Non-invasive methods

The development and validation of non-invasive techniques brought clinical assessment of endothelial function to a broad field of application resulting in a variety of trials studying endothelial function under many different conditions. Today, the most widely used is probably flow-mediated vasodilation, but there are several other methods to assess endothelial function in patients, of which some are summarized in Table 113.2.

Table 113.2 Non-invasive methods to evaluate endothelial function in patients

Method	Principle
Forearm blood flow	Measurement of forearm blood flow by strain gauge plethysmography after application of endothelium-dependent vasodilators or reactive hyperaemia
Applanation tonometry	Measurement of markers of arterial stiffness (see Chapter 111) (e.g. aortic pulse wave velocity and augmentation index) after β_2-adrenoceptor stimulation
Laser digital Doppler	Measurement of skin microcirculation during reactive hyperaemia or local application of endothelium-dependent vasodilators by iontophoresis

Flow-mediated vasodilation

As described by Deanfield and colleagues (1992), this method currently represents the most widely used technique to assess endothelial function *in vivo*. The diameter of the brachial artery is measured after reactive hyperaemia causing a release of NO by an increase of shear stress. To induce reactive hyperaemia, a sphygmomanometer cuff, which is placed distal to the brachial artery, is inflated to 200 mmHg and released 5 minutes later. Accordingly, endothelial-independent vasodilation can be tested after sublingual application of nitroglycerine. Comparable to venous occlusion plethysmography, flow-mediated vasodilation was shown to correlate well with invasive measurements of endothelial-dependent vasodilation in the coronary circulation (Fig. 113.4). Although the principle of this technique is quite simple, accurate performance necessitates highly experienced operators. Furthermore, environmental factors like alimentation and exercise training affecting the results have to be ruled out (Landmesser et al., 2004; Deanfield et al., 2005; Hogas et al., 2010).

Circulating (bio)markers of endothelial function

Beside invasive and non-invasive methods to assess endothelial function in the clinical setting, there are several markers reflecting dysfunctional activation of endothelial cells circulating in the blood of patients with CKD. Mostly they are endothelial products or metabolites which are released when endothelial function deteriorates (Rabelink et al., 2010). Their serum levels are shown to be elevated in CKD patients and some of them are related to cardiovascular morbidity and mortality. Table 113.3 gives an overview about several circulating markers and their vascular function.

Circulating endothelial microparticles

Blood levels of endothelial microparticles are elevated in CKD patients. Endothelial microparticles are membrane vesicles of 0.1–1.0 μm diameter. Several pro-inflammatory factors like tumour necrosis factor alpha (TNFα) and thrombin induce shedding of

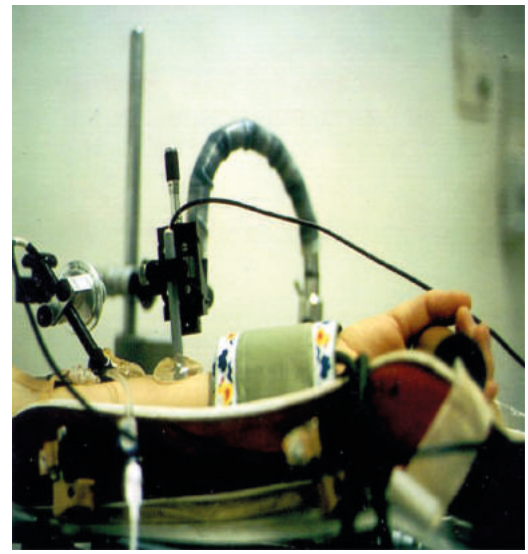

Fig. 113.4 Assessment of flow-mediated vasodilation in response to reactive hyperaemia.
Courtesy of Prof. Ulf Landmesser, Charite, Berlin, Germany.

Table 113.3 Circulating (bio)markers of endothelial dysfunction and their vascular function

Marker	Vascular function
Circulating adhesion molecules	
ICAM-1	Intercellular adhesion molecule 1 Stabilizing endothelial cell-cell interactions Leucocyte transmigration
VCAM-1	Vascular cell adhesion molecule 1 Endothelial adhesion of leucocytes
E-selectin	Endothelial adhesion and rolling of leucocytes
P-selection	Endothelial adhesion of leucocytes Recruitment and aggregation of platelets
sCD40 ligand	Expressed on $CD4^+$ T-cells and platelets Adhesion to CD40 on endothelial cells
CD146	Control of endothelial cohesion
Cytokines	
Interleukin 6	Endothelial inflammatory activation
TNFα	Production of proinflammatory cytokines Expression of cell adhesion molecules
High-sensitive CRP	Endothelial inflammatory activation
Pentraxin 3	Endothelial inflammatory activation
sTWEAK	Soluble tumour necrosis factor-like weak inducer of apoptosis Induction of apoptosis Production of proinflammatory cytokines
Endothelin 1	Contraction of vascular smooth muscle cells
Coagulation markers	
vWF	Binding to factor VIII, collagen, platelets Platelet adhesion
Thrombomodulin	Cofactor in thrombin-induced activation of protein C
Tissue factor	Activation of factor X thereby initiation of thrombin formation
Other markers	
ADMA, SDMA	Inhibition of endothelial NO production
Visfatin	Adipokine Associated with endothelial dysfunction
Adiponectin	Adipokine Associated with endothelial dysfunction
Circulating cells/particles	
Endothelial microparticles	Released in response to proinflammatory stimuli Activation of endothelial cells and coagulation
Endothelial cells	Released during advanced endothelial damage
Endothelial repair cells	Surrogate marker for endothelial damage Heterogeneous group of cells Repair of injured endothelial layer mainly by paracrine effects

microparticles from endothelial cells in a NF-κB-dependent manner. They contain several endothelial constituents like tissue factors, cell adhesion molecules, enzymes, and chemokines. Endothelial microparticles may impair endothelial-dependent vasodilation and promote pro-coagulatory activation. They express endothelial surface markers like VE-cadherin, CD146, and endoglin, and can be numerated by flow cytometry (Rabelink et al., 2010; Dignat-George and Boulanger, 2011).

Circulating endothelial cells

Sustained endothelial activation causes detachment of endothelial cells by changes in cell adhesion molecules, matrix molecules, and subsequent endothelial injury. Circulating endothelial cells represent a surrogate marker for advanced endothelial damage. They can be identified by expression of endothelial adhesion molecules like CD146 and VE-cadherin and absence of haematopoietic (CD45 and CD14) and progenitor (CD133) markers. The number of circulating endothelial cells is elevated in patients on dialysis and CKD which are associated with abnormal endothelial activation like vasculitis. Their number strongly correlates with plasma markers of endothelial injury and a reduced flow-mediated vasodilation in patients. Although their effects on healthy endothelial cells are poorly understood, there is a growing body of evidence suggesting that circulating endothelial cells may promote endothelial inflammatory activation and aggravate endothelial dysfunction (Boos et al., 2006; Woywodt et al., 2008; Rabelink et al., 2010).

References

Apostolov, E. O., Ray, D., Savenka, A. V., *et al.* (2010). Chronic uremia stimulates LDL carbamylation and atherosclerosis. *J Am Soc Nephrol*, 21(11), 1852–7.

Barreto, F. C., Barreto, D. V., Liabeuf, S., *et al.* (2009). Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. *Clin J Am Soc Nephrol*, 4(10), 1551–8.

Boos, C. J., Lip, G. Y., and Blann, A. D. (2006). Circulating endothelial cells in cardiovascular disease. *J Am Coll Cardiol*, 48(8), 1538–47.

Brunner, H., Cockcroft, J. R., Deanfield, J., *et al.* (2005). Endothelial function and dysfunction. Part II: Association with cardiovascular risk factors and diseases. A statement by the Working Group on Endothelins and Endothelial Factors of the European Society of Hypertension. *J Hypertens*, 23(2), 233–46.

Carbo, C., Arderiu, G., Escolar, G., *et al.* (2008). Differential expression of proteins from cultured endothelial cells exposed to uremic versus normal serum. *Am J Kidney Dis*, 51(4), 603–12.

Deanfield, J., Halcox, J. P., and Rabelink, T. J. (2005). Endothelial function and dysfunction. Part I: Methodological issues for assessment in the different vascular beds: a statement by the Working Group on Endothelin and Endothelial Factors of the European Society of Hypertension. *J Hypertens*, 23(1), 7–17.

Dignat-George, F. and Boulanger, C. M. (2011). The many faces of endothelial microparticles. *Arterioscler Thromb Vasc Biol*, 31(1), 27–33.

Dou, L., Bertrand, E., Cerini, C., *et al.* (2004). The uremic solutes p-cresol and indoxyl sulfate inhibit endothelial proliferation and wound repair. *Kidney Int*, 65(2), 442–51.

Dou, L., Jourde-Chich, N., Faure, V., *et al.* (2007). The uremic solute indoxyl sulfate induces oxidative stress in endothelial cells. *J Thromb Haemost*, 5(6), 1302–8.

Endemann, D. H. and Schiffrin, E. L. (2004). Endothelial dysfunction. *J Am Soc Nephrol*, 15(8), 1983–92.

Feletou, M., Kohler, R., and Vanhoutte, P. M. (2012). Nitric oxide: orchestrator of endothelium-dependent responses. *Ann Med*, 44, 694–716.

Fleming, I. and Busse, R. (2003). Molecular mechanisms involved in the regulation of the endothelial nitric oxide synthase. *Am J Physiol Regul Integr Comp Physiol*, 284(1), R1–12.

Fliser, D., Kielstein, J. T., Haller, H., *et al.* (2003). Asymmetric dimethylarginine: a cardiovascular risk factor in renal disease? *Kidney Int Suppl*, 84, S37–40.

Forstermann, U. (2008). Oxidative stress in vascular disease: causes, defense mechanisms and potential therapies. *Nat Clin Pract Cardiovasc Med*, 5(6), 338–49.

Ganesh, S. K., Stack, A. G., Levin, N. W., *et al.* (2001). Association of elevated serum PO_4, Ca × PO_4 product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol*, 12(10), 2131–8.

Heeringa, P. and Tervaert, J. W. (2002). Role of oxidized low-density lipoprotein in renal disease. *Curr Opin Nephrol Hypertens*, 11(3), 287–93.

Heinz, J., Kropf, S., Domröse, U., *et al.* (2010). B vitamins and the risk of total mortality and cardiovascular disease in end-stage renal disease: results of a randomized controlled trial. *Circulation*, 121(12), 1432–8.

Hogas, S. M., Voroneanu, L., Serban, D. N., *et al.* (2010). Methods and potential biomarkers for the evaluation of endothelial dysfunction in chronic kidney disease: a critical approach. *J Am Soc Hypertens*, 4(3), 116–27.

Holzer, M., Birner-Gruenberger, R., Stojakovic, T., *et al.* (2011). Uremia alters HDL composition and function. *J Am Soc Nephrol*, 22(9), 1631–41.

Ito, S., Osaka, M., Higuchi, Y., *et al.* (2010). Indoxyl sulfate induces leukocyte-endothelial interactions through up-regulation of E-selectin. *J Biol Chem*, 285(50), 38869–75.

Kalantar-Zadeh, K., Kopple, J. D., Kamranpour, N., *et al.* (2007). HDL-inflammatory index correlates with poor outcome in hemodialysis patients. *Kidney Int*, 72(9), 1149–56.

Kielstein, J. T., Fliser, D., and Veldink, H. (2009). Asymmetric dimethylarginine and symmetric dimethylarginine: axis of evil or useful alliance? *Semin Dial*, 22(4), 346–50.

Landmesser, U., Hornig, B., and Drexler, H. (2004). Endothelial function: a critical determinant in atherosclerosis? *Circulation*, 109(21 Suppl 1), II27–33.

Leiper, J. and Nandi, M. (2011). The therapeutic potential of targeting endogenous inhibitors of nitric oxide synthesis. *Nat Rev Drug Discov*, 10(4), 277–91.

Malyszko, J. (2010). Mechanism of endothelial dysfunction in chronic kidney disease. *Clin Chim Acta*, 411(19–20), 1412–20.

Martinez, M. C., Tesse, A., Zobairi, F., *et al.* (2005). Shed membrane microparticles from circulating and vascular cells in regulating vascular function. *Am J Physiol Heart Circ Physiol*, 288(3), H1004–9.

Meijers, B. K., Van Kerckhoven, S., Verbeke, K., *et al.* (2009). The uremic retention solute p-cresyl sulfate and markers of endothelial damage. *Am J Kidney Dis*, 54(5), 891–901.

Munzel, T., Sinning, C., Post, F., *et al.* (2008). Pathophysiology, diagnosis and prognostic implications of endothelial dysfunction. *Ann Med*, 40(3), 180–96.

Nakagawa, T., Tanabe, K., Croker, B. P., *et al.* (2011). Endothelial dysfunction as a potential contributor in diabetic nephropathy. *Nat Rev Nephrol*, 7(1), 36–44.

Navab, M., Reddy, S. T., Van Lenten, B. J., *et al.* (2011). HDL and cardiovascular disease: atherogenic and atheroprotective mechanisms. *Nat Rev Cardiol*, 8(4), 222–32.

Papatheodorou, L. and Weiss, N. (2007). Vascular oxidant stress and inflammation in hyperhomocysteinemia. *Antioxid Redox Signal*, 9(11), 1941–58.

Rabelink, T. J., de Boer, H. C., and van Zonneveld, A. J. (2010). Endothelial activation and circulating markers of endothelial activation in kidney disease. *Nat Rev Nephrol*, 6(7), 404–14.

Rao, R. M., Yang, L., Garcia-Cardena, G., *et al.* (2007). Endothelial-dependent mechanisms of leukocyte recruitment to the vascular wall. *Circ Res*, 101(3), 234–47.

Rocha, V. Z. and Libby, P. (2009). Obesity, inflammation, and atherosclerosis. *Nat Rev Cardiol*, 6(6), 399–409.

Ross, R. (1999). Atherosclerosis—an inflammatory disease. *N Engl J Med*, 340(2), 115–26.

Schwedhelm, E. and Boger, R. H. (2011). The role of asymmetric and symmetric dimethylarginines in renal disease. *Nat Rev Nephrol*, 7(5), 275–85.

Shi, Y. and Vanhoutte, P. M. (2009). Reactive oxygen-derived free radicals are key to the endothelial dysfunction of diabetes. *J Diabetes*, 1(3), 151–62.

Shuto, E., Taketani, Y., Tanaka, R., *et al.* (2009). Dietary phosphorus acutely impairs endothelial function. *J Am Soc Nephrol*, 20(7), 1504–12.

Speer, T., Owala, F. O., Holy, E. W., *et al.* (2014). Carbamylated low-density lipoprotein induces endothelial dysfunction. *Eur Heart J*, 35(43), 3021–32.

Speer, T., Rohrer, L., Blyszczuk, P., *et al.* (2013). Abnormal high-density lipoprotein induces endothelial dysfunction via activation of Toll-like receptor-2. *Immunity*, 38(4), 754–68.

Suwaidi, J. A., Hamasaki, S., Higano, S. T., *et al.* (2000). Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation*, 101(9), 948–54.

Tonelli, M., Sacks, F., Pfeffer, M., *et al.* (2005). Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation*, 112(17), 2627–33.

Vanholder, R. and De Smet, R. (1999). Pathophysiologic effects of uremic retention solutes. *J Am Soc Nephrol*, 10(8), 1815–23.

Vanholder, R., De Smet, R., Glorieux, G., *et al.* (2003). Review on uremic toxins: classification, concentration, and interindividual variability. *Kidney Int*, 63(5), 1934–43.

Vanhoutte, P. M. (2011). Endothelium-dependent contractions in hypertension: when prostacyclin becomes ugly. *Hypertension*, 57(3), 526–31.

Vaziri, N. D., Moradi, H., Pahl, M. V., *et al.* (2009). In vitro stimulation of HDL anti-inflammatory activity and inhibition of LDL pro-inflammatory activity in the plasma of patients with end-stage renal disease by an apoA-1 mimetic peptide. *Kidney Int*, 76(4), 437–44.

Vaziri, N. D., Navab, M., and Fogelman, A. M. (2010). HDL metabolism and activity in chronic kidney disease. *Nat Rev Nephrol*, 6(5), 287–96.

Wang, Z., Nicholls, S. J., Rodriguez, E. R., *et al.* (2007). Protein carbamylation links inflammation, smoking, uremia and atherogenesis. *Nat Med*, 13(10), 1176–84.

Woywodt, A., Kirsch, T., and Haubitz, M. (2008). Circulating endothelial cells in renal disease: markers and mediators of vascular damage. *Nephrol Dial Transplant*, 23(1), 7–10.

Wu, I. -W., Hsu, K. -H., Hsu, H. -J., *et al.* (2012). Serum free p-cresyl sulfate levels predict cardiovascular and all-cause mortality in elderly hemodialysis patients—a prospective cohort study. *Nephrol Dial Transplant*, 27(3), 1169–75.

Zoccali, C. (2006). Traditional and emerging cardiovascular and renal risk factors: an epidemiologic perspective. *Kidney Int*, 70(1), 26–33.

Zoccali, C. and Mallamaci, F. (2006). Homocysteine and risk in end-stage renal disease: a matter of context. *Kidney Int*, 69(2), 204–6.

CHAPTER 114

Endothelins and their antagonists in chronic kidney disease

Neeraj Dhaun and David J. Webb

The endothelin system

Endothelin (ET) was discovered in 1988 (Yanagisawa et al., 1988) and is now known to be a family of three 21-amino acid peptides, each with distinct genes and tissue distributions, with powerful vasoconstrictor and pressor properties (Yanagisawa et al., 1988; Inoue et al., 1989; Arinami et al., 1991). Of the three peptides, ET-1 is the major endothelial isoform and, in the human kidney, the only one so far shown to be expressed at the protein level (Karet and Davenport, 1996). Its main site of vascular production is the endothelial cell but it is also produced by other cell types including vascular smooth muscle cells and epicardial cells (Eid et al., 1994). Within the kidney, it is produced by glomerular epithelial and mesangial cells, and renal tubular and medullary collecting duct cells (Kohan, 1997). The renal medulla contains among the highest concentrations of immunoreactive ET-1 of any organ (Morita et al., 1991).

Regulation of ET synthesis occurs at the level of gene transcription, with the gene product being the 212-amino acid pre-pro-ET-1. Enhanced gene transcription occurs with a wide range of stimuli (Wesson et al., 1998; Attina et al., 2005). Those pertinent to chronic kidney disease (CKD) include other vasoactive hormones, such as angiotensin and vasopressin, the cytokine interleukin-1, oxidized low-density lipoprotein, reduced extracellular pH, and ciclosporin. In contrast, prostacyclin, nitric oxide (NO), and the natriuretic peptides all inhibit gene transcription. Pre-pro-ET-1 is cleaved to big ET-1 (38 amino acids) which is largely biologically inactive (Haynes and Webb, 1994). Endothelin converting enzyme then splits big ET-1 to the biologically active ET-1 and C-terminal fragment. Once synthesized, the secretion of mature ET-1 from endothelial cells is largely abluminal (Yoshimoto et al., 1991), towards the adjacent vascular smooth muscle, suggesting an autocrine or paracrine mechanism of action.

ET-1 acts by binding to two cognate receptors, the ET_A and ET_B receptors (Arai et al., 1990; Sakurai et al., 1990) (see Tables 114.1 and 114.2). Within blood vessels, both receptors are found on smooth muscle cells and their activation results in vasoconstriction. ET_B receptors are, however, predominantly found on the vascular endothelium where their activation results in vasodilatation via prostacyclin and NO (DeNucci et al., 1988). Because most ET-1 is released abluminally, plasma concentrations of ET-1 do not accurately reflect ET-1 production. However, some is released into the circulation and the ET_B receptor also acts as a clearance receptor for this circulating ET-1. Therefore, reduction in ET_B number, or ET_B receptor blockade, may reduce ET-1 clearance, increasing plasma concentrations without altering production. ET receptors are widely distributed within the human kidney, with the ET_A subtype localized to vascular smooth muscle, notably in the glomeruli, vasa recta, and arcuate arteries, whereas ET_B receptors are more numerous (ET_B to ET_A ratio 2:1), and more widespread, with a high concentration in the collecting system (Karet and Davenport, 1996; Kuc et al., 2004).

Plasma ET-1 is elevated in CKD (Koyama et al., 1989; Dhaun et al., 2009a). This is likely due to a combination of reduced clearance and increased production. Evidence exists for renal and vascular ET-1 acting as two independent systems (Serneri et al., 1995). After systemic infusion of radiolabelled ET-1, labelled compound makes up < 1% of total urinary ET-1 (Benigni et al., 1991). Therefore, neither glomerular filtration nor tubular secretion of plasma ET-1 accounts for urinary ET-1, which is therefore assumed to be primarily of renal origin. Urinary excretion of ET-1 is thus thought to reflect renal ET-1 production. Renal ET-1 is thought to have a role in the paracrine/autocrine regulation of renal and intrarenal blood flow, glomerular haemodynamics, sodium and water homeostasis (Kohan and Padilla, 1993), and acid–base balance (Wesson, 2001).

Endothelin receptor antagonists

A number of selective ET_A and mixed $ET_{A/B}$ receptor antagonists are in clinical development and active use, and several have a proven role in the management of pulmonary hypertension. Selectivity is usually calculated from *in vitro* competitive receptor assays. 'Mixed' antagonists have a ratio of ET_A to ET_B affinity < 100-fold greater for ET_A than ET_B (Davenport and Maguire, 2006; Davenport et al., 2014), compared with ≥ 100-fold for ET_A selective agents. Thus, selectivity may depend on dose, with higher doses of marginally ET_A selective antagonists providing functionally important inhibitory effects at the ET_B receptor.

In models of disease where ET-1 generation is increased, it has been generally found that excess ET_A receptor activation is harmful, so its pharmacological antagonism may be clinically useful. Studies with ET_B receptor knockouts and selective ET_B antagonists suggest that selective ET_B receptor antagonism is unlikely to be a useful therapeutic approach, though with exceptions (Lahav et al., 1999). There remains then the question of any potential benefit of additional ET_B receptor blockade when the ET_A receptor is blocked. This will depend on the balance of ET_B receptor activity,

Table 114.1 Actions of ET-1 in the systemic vasculature—animal studies. This table shows the receptor responsible for each action but, particularly in the case of ET_A receptor-mediated actions, does not exclude a small contribution from the ET_B receptor

ET_A receptor	ET_B receptor
Vasoconstriction	Vasoconstriction
Increased arterial stiffness	Endothelium-dependent vasodilatation
Endothelial dysfunction	ET-1 clearance
Inflammation	
Atherosclerosis	
Cardiac hypertrophy	

particularly vascular smooth muscle cell ET_B vasoconstrictor activity, and is likely to be tissue and disease specific. Ultimately, only direct head-to-head comparisons of selective ET_A and equipotent (with respect to the dose of ET_A antagonist) mixed $ET_{A/B}$ receptor antagonists will inform us as to the additional impact of additional ET_B receptor blockade in disease states. Such studies are currently not available.

Glomerulopathies, proteinuric nephropathies, and chronic kidney disease

Glomerular injury is frequently associated with progressive CKD. This process typically involves glomerulosclerosis and interstitial fibrosis and occurs regardless of the nature of the initial renal insult. The mechanisms responsible for this continued renal deterioration are not fully understood (see Chapter 136), but likely involve a number of common pathways and may be distinct from those responsible for the original injury. There is substantial preclinical data (e.g. see Dhaun et al., 2006) that ET may be an important mediator in these processes, and some supportive clinical observations (Barton, 2008). Some of this evidence is summarized below.

Table 114.2 Actions of ET-1 in the kidney—animal studies

ET_A receptor	ET_B receptor	Receptor uncertain
Renal vasoconstriction	Renal vasodilatation	Podocyte de-differentiation
Cortical vasoconstriction	Medullary vasodilatation	Diuresis
Afferent arteriolar constriction	Afferent arteriolar constriction	Acid–base balance
Efferent arteriolar constriction	Efferent arteriolar dilatation	
Mesangial cell contraction	Natriuresis	
Mesangial cell proliferation		
Extracellular matrix accumulation		
Interstitial fibrosis		

Box 114.1 Animal models of CKD improved by ET receptor antagonism

- Streptozocin-induced diabetes mellitus
- Renal mass reduction
- Proliferative glomerulonephritis
- Lupus nephritis
- Hypertensive nephrosclerosis
- Chronic ciclosporin administration
- Hypokalaemic nephropathy.

Animal studies of endothelin antagonism in renal disease

In a mouse model of immunoglobulin A (IgA) nephropathy, both ET-1 and ET receptor message increased alongside progression of the nephritis, and treatment with a selective ET_A receptor antagonist ameliorated the histopathological lesions and proteinuria observed in this model (Nakamura et al., 1996).

In a rat model of proliferative nephritis, upregulation of ET-1 protein and receptors has been shown at the level of the glomerulus (Yoshimura et al., 1995), and in this case non-selective ET receptor blockade reduced both the mesangial expansion and proteinuria characteristic of this model.

Similarly, in a murine model of lupus nephritis, again defined by abnormal glomerular proliferation, selective blockade of the ET_A receptor improved glomerular structure and function translating to an overall benefit in renal function (Nakamura et al., 1995).

Finally, in rats with accelerated passive Heymann nephritis, a model of membranous glomerulonephritis, combined blockade of the ET and angiotensin systems showed greater renoprotective benefit than either treatment alone (Benigni et al., 1998). Other models of CKD that benefit from ET receptor antagonism are listed in Box 114.1.

Clinical studies of endothelin antagonism in renal disease

The management of CKD in the clinic focuses on blood pressure (BP) and proteinuria reduction, both key parameters that limit CKD progression and reduce the associated cardiovascular risk (see Table 114.3). In addition, there are a number of other areas of CKD where there may be a role for the ET system and so where ET receptor antagonism may offer beneficial effects—these include endothelial dysfunction, atherosclerosis, arterial stiffness, and mineral bone disease. Clinical trials with ET receptor antagonists using these parameters as endpoints CKD are limited.

Hypertension

In non-diabetic hypertensive CKD patients the systemic vasodilatation seen with acute ET_A receptor blockade (associated with a reduction in BP of ~ 10mmHg) (Dhaun et al., 2009b), is attenuated by concomitant ET_B receptor antagonism (Goddard et al., 2004), suggesting that, at least in this disease state, vasoconstrictor ET_B receptor activity is less important than ET_B vasodilatory function.

Acute ET_A receptor antagonism also improves renal haemodynamics with a fall in renal vascular resistance and an increase in renal blood flow (Dhaun et al., 2009b). These changes are accompanied by no measurable effect on glomerular filtration rate (GFR). There is a concomitant fall in the filtration fraction suggesting that ET-1 induces an ET_A receptor-mediated vasoconstriction, preferentially affecting the efferent arterioles as with angiotensin 2, although not excluding and effects on mesangial cells and the filtration coefficient (Dhaun et al., 2009b).

In a similar non-diabetic proteinuric population, chronic dosing with a selective ET_A receptor antagonist also reduces BP albeit to a lesser extent (Dhaun et al., 2011). In this study a similar fall in systolic, diastolic and mean BP of approximately 4 mmHg was observed. Of note, in this trial patients already had good BP control (~ 125/75 mmHg) conforming to current CKD guidelines. Interestingly, in both these acute and chronic studies (Dhaun et al., 2009b, 2011) the majority of patients studied were already taking angiotensin-converting enzyme (ACE) inhibitors. Data from healthy subjects suggest a synergy between ET_A receptor antagonism and ACE inhibition that is not only dependent on an unblocked ET_B receptor but is also associated with a significant natriuresis (Goddard et al., 2004). This is important clinically because patients with CKD are generally prescribed ACE inhibitors, not only for BP control but also for their renoprotective effects. With regards to mixed $ET_{A/B}$ antagonism, sub-group analysis of the DORADO study, which looked at the mixed antagonist darusentan in resistant hypertension, suggests that a combined $ET_{A/B}$ blocking strategy may also be of benefit in lowering BP in non-diabetic CKD (Weber et al., 2009). In diabetic nephropathy, only one study has shown a fall in BP. This used the ET_A selective antagonist atrasentan (ET_A:ET_B receptor selectivity of ~ 1200:1) and patients were dosed for 8 weeks. There was a fall in systolic BP of approximately 8 mmHg and diastolic BP of approximately 6 mmHg (vet al., 2011).

Proteinuria

Proteinuria is one of the manifestations of glomerular hypertension (see Chapter 50). Albuminuria is incrementally associated with increased cardiovascular risk in both individuals with pre-existing risk (such as hypertensive patients) (Ibsen et al., 2005) and in individuals with no known risk factors (Wang et al., 2005). This is true even in the presence of normal renal function (Freedman et al., 2005). Importantly, in patients with hypertension, reduction of albuminuria—at least with blockers of the renin–angiotensin system—confers cardiovascular protection (Ibsen et al., 2005).

Both acute (Goddard et al., 2004; Dhaun et al., 2009b) and chronic (Dhaun et al., 2011) selective ET_A blockade have been shown to reduce proteinuria in patients with non-diabetic proteinuric CKD. In the acute studies these effects were abolished by concomitant ET_B receptor antagonism (Goddard et al., 2004). As for BP reduction, mixed $ET_{A/B}$ antagonism has also been shown to reduce proteinuria in non-diabetic CKD (Weber et al., 2009). However, all these subjects had, at most, microalbuminuria compared to the chronic dosing study with the selective ET_A antagonist (Dhaun et al., 2011) which included not only a wide range of non-diabetic proteinuric renal diagnoses (e.g. membranous glomerulopathy, IgA nephropathy, and focal segmental glomerulosclerosis) but also varying proteinuria (0.3–8 g/day).

The largest studies looking at the efficacy of ET receptor antagonism in reducing proteinuria have been in patients with diabetic nephropathy. The first of these was a phase 2 study investigating the effects of 12 weeks of treatment with avosentan, a relatively ET_A-selective antagonist (ET_A:ET_B blockade ~ 300:1), on albuminuria in 286 patients with diabetic nephropathy already receiving renin–angiotensin system blockade. Subjects had a creatinine clearance of approximately 80mL/min and albuminuria of approximately 1500 mg/day (Wenzel et a., 2009). Avosentan, at all doses used, reduced albuminuria by 20–30%. Fluid retention was a problematic side effect, however, and was more apparent at the higher doses of avosentan. Based on their interpretation of the data, the pharmaceutical company launched a phase 3 trial (Avosentan on doubling of Serum Creatinine, End stage renal disease and death in Diabetic Nephropathy (ASCEND)) examining the effects of avosentan on renal disease progression or death in type 2 diabetic nephropathy (Mann et al., 2010). A total of 1392 patients were enrolled and avosentan reduced urine albumin to creatinine ratio (ACR) by 40–50% compared to the 10% reduction seen with placebo. However, the trial was terminated early due to greater serious adverse cardiovascular events in the avosentan groups, including a threefold increase in the incidence of congestive heart failure (see 'Adverse effects of endothelin receptor antagonists'). It is likely that the doses of avosentan used were too high and so blocked the ET_B receptor as well as the ET_A, an effect that would be predicted to promote fluid retention (Kohan et al., 2011). Furthermore, the ASCEND trial involved patients with advanced kidney disease who may have been more likely to retain fluid.

The failure of the ASCEND trial underscored the importance of careful patient selection and ET antagonist dosing in CKD. A subsequent study evaluated the effects of varying doses of atrasentan or placebo given for 8 weeks on ACR in 89 subjects with diabetic nephropathy receiving stable doses of renin–angiotensin system inhibitors (Kohan et al., 2011). Atrasentan reduced ACR by approximately 40% compared to the 11% reduction seen with placebo. The only adverse event was mild to moderate peripheral oedema that was dose related.

As yet, it remains unclear as yet to what extent these effects on proteinuria are explained by BP reduction alone. In both the acute and chronic dosing studies in non-diabetic CKD using a selective ET_A receptor blocking approach there was, as expected, a correlation between the changes in BP and proteinuria, with a greater fall in urinary protein seen in those patients with the greater fall in BP. However, both studies also had an active control which matched the reduction in BP seen with ET_A antagonism. Despite a similar fall in BP with both the active control and the ET_A antagonist, proteinuria

Table 114.3 ET receptor antagonist studies in CKD patients

	Effect	ET receptor blockade	Dosing
↓ forearm blood flow	ET_A		Acute
↓ blood pressure	ET_A	$ET_{A/B}$	Acute and chronic
↓ renal vascular resistance, ↓ proteinuria	ET_A		Acute
↓ proteinuria	ET_A	$ET_{A/B}$	Acute and chronic

fell to a greater extent with the latter supporting a BP-independent effect. Furthermore, a renal haemodynamic study following chronic selective ET_A antagonism suggests that falls in both GFR and filtration fraction are in part responsible for the reduction in proteinuria (Dhaun et al., 2011). This is similar to the effects seen with ACE inhibitors and so may translate to longer-term renoprotection. In the atrasentan study in diabetic nephropathy the reduction in ACR was evident after 1 week of treatment and was associated with a fall in BP, suggesting that the initial antiproteinuric effect of atrasentan may be haemodynamic.

Broader cardiovascular risk: endothelial dysfunction, atherosclerosis, and arterial stiffness

The endothelium is a crucial regulator of vascular tone (Endemann and Schiffrin, 2004) and its function is impaired in CKD, with a shift towards reduced vasodilatation, associated with a pro-inflammatory and pro-thrombotic state (see Chapter 113). Endothelial dysfunction is recognized to be a key early determinant in the progression to atherosclerosis, and is now well established to be independently associated with increased cardiovascular risk (Lerman and Zeiher, 2005) and GFR loss (Perticone et al., 2010). Animal models show that ET-1 contributes to endothelial dysfunction (Amiri et al., 2004) and ET receptor antagonism, predominantly with selective ET_A antagonists, improves NO-mediated endothelial function (Barton et al., 1998; Best et al., 1999; Bauersachs et al., 2000). In addition to its effects on BP, ET-1 is pro-inflammatory (Dhaun et al., 2006) and is implicated in the development of atherosclerosis. Several animal models have shown benefit of both selective and mixed ET receptor antagonism in the development of atherosclerotic lesions (Kowala et al., 1995; Barton et al., 1998; Babaei et al., 2000; D'Uscioet al., 2002). There are currently no patient studies that focus on endothelial function in CKD. There are data that support a role for the ET_A receptor in coronary vascular tone and endothelial dysfunction in coronary artery disease (Halcox et al., 2001, 2007). Furthermore, CKD is a feature of ageing, and in these subjects compared to younger ET-1 contributes to endothelial dysfunction (Westby et al., 2011). Also, in older subjects with early atherosclerosis, long-term administration of a selective ET_A receptor antagonist improves coronary endothelial dysfunction (Reriani et al., 2010).

Arterial stiffness (see Chapter 111) is linked to endothelial dysfunction (Oliver and Webb, 2003) and the two commonly coexist in patients at increased cardiovascular risk. A number of interventions that reduce arterial stiffness also improve endothelial function (Oliver and Webb, 2003). To date, there have been few studies addressing the relationship between these two markers of cardiovascular disease after treatment. However, both animal and human studies suggest that the endothelium is an important regulator of arterial stiffness. ET-1 increases arterial stiffness in animals (Amiri et al., 2004) and humans (Dhaun et al., 2009c). There are only two studies, one acute (Dhaun et al., 2009b) and one chronic (Dhaun et al., 20011), both using a selective ET_A receptor antagonist approach, in non-diabetic CKD. These show a reduction in arterial stiffness with treatment but the extent to which this is independent of BP is unclear. Interestingly, in the acute study (Dhaun et al., 2009b) the reduction in arterial stiffness seen with ET antagonism was greater in those taking dual ACE inhibitor/angiotensin receptor blocker treatment than in those receiving an ACE inhibitor alone (Dhaun et al., 2009c). Indeed, there was a similar effect for proteinuria in this study. These findings support a role for ET antagonists to be considered in the multimodal regimen of the remission clinic.

Adverse effects of endothelin receptor antagonists

Side effects with ET receptor antagonists in clinical trials are common. The most frequently reported clinical adverse events are headache, dizziness, nausea, nasal congestion, and dyspnoea. These appear to be class effects and likely relate to vasodilatation. Liver toxicity is also common and is dose dependent. This has been particularly reported to occur with sulphonamide-derived compounds such as avosentan and sitaxsentan. Indeed, sitaxsentan was voluntarily withdrawn due to this side effect. Importantly, successful switching from a sulphonamide ET receptor antagonist that has caused liver enzyme derangement to a non-sulphonamide agent, such as ambrisentan, is an option for those patients requiring continued therapy (McGoon et al., 2009).

The mechanism of peripheral oedema with ET receptor antagonism remains unclear. ET-1 acts in the renal tubule via the ET_B receptor to promote natriuresis and diuresis. Thus, peripheral oedema associated with vasodilatation could be aggravated by mixed $ET_{A/B}$ antagonists due to the reported ET_B-mediated downregulation of the renal tubular epithelial sodium channel (Kohan et al., 2011). However, in clinical trials fluid retention appears to occur with both selective ET_A and mixed $ET_{A/B}$ receptor antagonists. It is clearly of importance in studies with CKD patients. However, the DORADO study, using the ET receptor antagonist darusentan in patients with resistant hypertension, has shown this to be manageable (Weber et al., 2009).

Finally, all ET antagonists are contraindicated in pregnancy as they are teratogenic. As these drugs have only been available for a relatively short period of time their balance of risks and benefits remains incompletely understood. Longer-term observational studies of individual ET receptor antagonists will be of benefit in this regard.

References

Amiri, F., Virdis, A., Neves, M. F., *et al.* (2004). Endothelium-restricted overexpression of human endothelin-1 causes vascular remodeling and endothelial dysfunction. *Circulation*, 110, 2233–40.

Arai, H., Hori, S., Aramori, I., *et al.* (1990). Cloning and expression of a cDNA encoding an endothelin receptor. *Nature*, 348, 730–2.

Arinami, T., Ishikawa, M., Inoue, A., *et al.* (1991). Chromosomal assignments of the human endothelin family genes: The endothelin-1 gene (EDN1) to 6p23–p24, the endothelin-2 gene (EDN2) to 1p34, and the endothelin-3 gene (EDN3) to 20q13.2–q13.3. *Am J Hum Genet*, 48, 990–6.

Attina, T., Camidge, R., Newby, D. E., *et al.* (2005). Endothelin antagonism in pulmonary hypertension, heart failure, and beyond. *Heart*, 91, 825–31.

Babaei, S., Picard, P., Ravandi, A., *et al.* (2000). Blockade of endothelin receptors markedly reduces atherosclerosis in LDL receptor deficient mice: role of endothelin in macrophage foam cell formation. *Cardiovasc Res*, 48, 158–67.

Barton, M., Haudenschild, C. C., D'Uscio, L. V., *et al.* (1998). Endothelin ET(A) receptor blockade restores NO-mediated endothelial function and inhibits atherosclerosis in apolipoprotein E-deficient mice. *Proc Nat Acad Sci U S A*, 95, 14367–72.

Barton, M. (2008). Reversal of proteinuric renal disease and the emerging role of endothelin. *Nat Clin Pract Nephrol*, 4, 490–501.

Bauersachs, J., Fraccarollo, D., Galuppo, P., *et al*. (2000). Endothelin-receptor blockade improves endothelial vasomotor dysfunction in heart failure. *Cardiovasc Res*, 47, 142–9.

Benigni, A., Corna, D., Maffi, R., *et al.* (1998). Renoprotective effect of contemporary blocking of angiotensin II and endothelin-1 in rats with membranous nephropathy. *Kidney Int*, 54, 353–9.

Benigni, A., Perico, N., Gaspari, F., *et al.* (1991). Increased renal endothelin production in rats with reduced renal mass. *Am J Physiol*, 260, F331–9.

Best, P. J. M., McKenna, C. J., Hasdai, D., *et al.* (1999). Chronic endothelin receptor antagonism preserves coronary endothelial function in experimental hypercholesterolaemia. *Circulation*, 99, 1747–52.

D'Uscio, L. V., Barton, M., Shaw, S., *et al.* (2002). Chronic ET(A) receptor blockade prevents endothelial dysfunction of small arteries in apolipoprotein E-deficient mice. *Cardiovasc Res*, 53, 487–95.

Davenport, A. P. and Maguire, J. J. (2006). Endothelin. *Handb Exp Pharmacol*, 2006, 295–329.

Davenport, A. P., D'Orléans-Juste, P., Godfraind, T., *et al.* (2014). *Endothelin Receptors: ET_A receptor. IUPHAR/BPS Guide to Pharmacology*. [Online] http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=219.

DeNucci, G., Thomas, R., D'Orleans-Juste, P., *et al*. (1988). Pressor effects of circulating endothelin are limited by its removal in the pulmonary circulation and by the release of prostacyclin and endothelium-derived relaxing factor. *Proc Natl Acad Sci U S A*, 85, 9797–800.

Dhaun, N., Goddard, J., and Webb, D. J. (2006). The endothelin system and its antagonism in chronic kidney disease. *J Am Soc Nephrol*, 17, 943–55.

Dhaun, N., Lilitkarntakul, P., Macintyre, I. M., *et al*. (2009a). Urinary endothelin-1 in chronic kidney disease and as a marker of disease activity in lupus nephritis. *Am J Physiol*, 296, F1477–83.

Dhaun, N., MacIntyre, I. M., Kerr, D., *et al.* (2011). Selective endothelin-A receptor antagonism reduces proteinuria, blood pressure, and arterial stiffness in chronic proteinuric kidney disease. *Hypertension*, 57, 772–9.

Dhaun, N., Macintyre, I. M., Melville, V., *et al.* (2009b). Blood pressure-independent reduction in proteinuria and arterial stiffness after acute endothelin-a receptor antagonism in chronic kidney disease. *Hypertension*, 54, 113–19.

Dhaun, N., Macintyre, I. M., Melville, V., *et al.* (2009c). Effects of endothelin receptor antagonism relate to the degree of renin-angiotensin system blockade in chronic proteinuric kidney disease. *Hypertension*, 54, e19–20.

Eid, H., de Bold, M. L., Chen, J. H., *et al*. (1997). Epicardial mesothelial cells synthesize and release endothelin. *J Cardiovasc Pharmacol*, 24, 715–20.

Endemann, D. H. and Schiffrin, E. L. (2004). Endothelial dysfunction. *J Am Soc Nephrol*, 15, 1983–92.

Freedman, B. I., Langefeld, C. D., Lohman, K. K., *et al.* (2005). Relationship between albuminuria and cardiovascular disease in type 2 diabetes. *J Am Soc Nephrol*, 16, 2156–61.

Goddard, J., Eckhart, C., Johnston, N. R., *et al.* (2004). Endothelin A receptor antagonism and angiotensin-converting enzyme inhibition are synergistic via an endothelin B receptor-mediated and nitric oxide-dependent mechanism. *J Am Soc Nephrol*, 15, 2601–10.

Goddard, J., Johnston, N. R., Hand, M. F., *et al.* (2004). Endothelin-A receptor antagonism reduces blood pressure and increases renal blood flow in hypertensive patients with chronic renal failure: a comparison of selective and combined endothelin receptor blockade. *Circulation*, 109, 1186–93.

Halcox, J. P., Nour, K. R., Zalos, G., *et al*. (2001). Coronary vasodilation and improvement in endothelial dysfunction with endothelin ET(A) receptor blockade. *Circ Res*, 89, 969–76.

Halcox, J. P., Nour, K. R., Zalos, G., *et al.* (2007). Endogenous endothelin in human coronary vascular function. Differential contribution of endothelin receptor types A and B. *Hypertension*, 49, 1–8.

Haynes, W. G. and Webb, D. J. (1994). Contribution of endogenous generation of endothelin-1 to basal vascular tone. *Lancet*, 344, 852–4.

Ibsen, H., Olsen, M. H., Wachtell, K., *et al.* (2005). Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. *Hypertension*, 45, 198–202.

Inoue, A., Yanagisawa, M., Kimura, S., *et al*. (1989). The human endothelin family: three structurally and pharmacologically distinct isopeptides predicted by three separate genes. *Proc Nat Acad Sci U S A*, 86, 2863–7.

Karet, F. E. and Davenport, A. P. (1996). Localization of endothelin peptides in human kidney. *Kidney Int*, 49, 382–7.

Kohan, D. E. (1997). Endothelins in the normal and diseased kidney. *Am J Kid Dis*, 29, 2–26.

Kohan, D. E. and Padilla, E. (1993). Osmolar regulation of endothelin-1 production by rat inner medullary collecting duct. *J Clin Invest*, 91, 1235–40.

Kohan, D. E., Pritchett, Y., Molitch, M., *et al.* (2011). Addition of atrasentan to renin-angiotensin system blockade reduces albuminuria in diabetic nephropathy. *J Am Soc Nephrol*, 22, 763–72.

Kohan, D. E., Rossi, N. F., Inscho, E. W., *et al.* (2011). Regulation of blood pressure and salt homeostasis by endothelin. *Physiol Rev*, 91, 1–77.

Kowala, M. C., Rose, P. M., Stein, P. D., *et al.* (1995). Selective blockade of the endothelin subtype A receptor decreases early atherosclerosis in hamsters fed cholesterol. *Am J Pathol*, 146, 819–26.

Koyama, H., Tabata, T., Nishzawa, Y., *et al*. (1989). Plasma endothelin levels in patients with uraemia. *Lancet*, 333, 991–2.

Kuc, R. and Davenport, A. P. (2004). Comparison of endothelin-A and endothelin-B receptor distribution visualized by radioligand binding versus immunocytochemical localization using subtype selective antisera. *J Cardiovasc Pharmacol*, 44, 224–6.

Lahav, R., Heffner, G., and Patterson, P. H. (1999). An endothelin receptor B antagonist inhibits growth and induces cell death in human melanoma cells in vitro and in vivo. *Proc Natl Acad Sci U S A*, 96, 11496–500.

Lerman, A. and Zeiher, A. M. (2005). Endothelial function: cardiac events. *Circulation*, 111, 363–8.

Mann, J. F., Green, D., Jamerson, K., *et al.* (2010). Avosentan for overt diabetic nephropathy. *J Am Soc Nephrol*, 21, 527–35.

McGoon, M. D., Frost, A. E., Oudiz, R. J., *et al.* (2009). Ambrisentan therapy in patients with pulmonary arterial hypertension who discontinued bosentan or sitaxsentan due to liver function test abnormalities. *Chest*, 135, 122–9.

Morita, S., Kitamura, K., Yamamoto, Y., *et al.* (1991). Immunoreactive endothelin in human kidney. *Ann Clin Biochem*, 28, 267–71.

Nakamura, T., Ebihara, I., Fukui, M., *et al.* (1996). Effect of a specific endothelin receptor A antagonist on glomerulonephritis of ddY mice with IgA nephropathy. *Nephron*, 72, 454–60.

Nakamura, T., Ebihara, I., Tomino, Y., *et al.* (1995). Effect of a specific endothelin A receptor antagonist on murine lupus nephritis. *Kidney Int*, 47, 481–9.

Oliver, J. J. and Webb, D. J. (2003). Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. *Arterioscler Thrombos Vasc Biol*, 23, 554–66.

Perticone, F., Maio, R., Perticone, M., *et al*. (2010). Endothelial dysfunction and subsequent decline in glomerular filtration rate in hypertensive patients. *Circulation*, 122, 379–84.

Reriani, M., Raichlin, E., Prasad, A., *et al*. (2010). Long-term administration of endothelin receptor antagonist improves coronary endothelial function in patients with early atherosclerosis. *Circulation*, 122, 958–66.

Sakurai, T., Yanagisawa, M., Takuwa, Y., *et al.* (1990). Cloning of a cDNA encoding a non-isopeptide selective subtype of the endothelin receptor. *Nature*, 348, 732–5.

Serneri, G. G. N., Modesti, P. A., Cecioni, I., *et al.* (1995). Plasma endothelin and renal endothelin are two distinct systems involved in volume homeostasis. *Am J Physiol*, 268, H1829–37.

Vuurmans, T. J., Boer, P., and Koomans, H. A. (2003). Effects of endothelin-1 and endothelin-1 receptor blockade on cardiac output,

aortic pressure, and pulse wave velocity in humans. *Hypertension*, 41, 1253–8.

Wang, T. J., Evans, J. C., Meigs, J. B., *et al.* (2005). Low-grade albuminuria and the risks of hypertension and blood pressure progression. *Circulation*, 111, 1370–6.

Weber, M. A., Black, H., Bakris, G., *et al.* (2009). A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. *Lancet*, 374(9699), 1423–31.

Wenzel, R. R., Littke, T., Kuranoff, S., *et al.* (2009). Avosentan reduces albumin excretion in diabetics with macroalbuminuria. *J Am Soc Nephrol*, 20, 655–64.

Wesson, D. E. (2001). Endogenous endothelins mediate increased acidification in remnant kidneys. *J Am Soc Nephrol*, 12, 1826–35.

Wesson, D. E., Simoni, J., and Green, D. F. (1998). Reduced extracellular pH increases endothelin-1 secretion by human renal microvascular endothelial cells. *J Clin Invest*, 101, 578–83.

Westby, C. M., Weil, B. R., Greiner, J. J., *et al.* (2011). Endothelin-1 vasoconstriction and the age-related decline in endothelium-dependent vasodilation in men. *Clin Sci (Lond)*, 120(11), 485–91.

Yanagisawa, M., Kurihara, H., Kimura, S., *et al.* (1988). A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature*, 332, 411–15.

Yoshimoto, S., Ishizaki, Y., Sasaki, T., *et al.* (1991). Effect of carbon dioxide and oxygen on endothelin production by cultured porcine cerebral endothelial cells. *Stroke*, 22, 378–83.

Yoshimura, A., Iwasaki, S., Inui, K., *et al.* (1995). Endothelin-1 and endothelin B type receptor are induced in mesangial proliferative nephritis in the rat. *Kidney Int*, 48, 1290–7.

CHAPTER 115

Chronic kidney disease-mineral and bone disorder: overview

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Background

In normal individuals, serum concentrations of phosphorus (P) and calcium (Ca) are maintained through the interaction of three hormones: parathyroid hormone (PTH), 1,25-$(OH)_2$D (calcitriol), the active metabolite of vitamin D, and phosphatonins, of which fibroblast growth factor 23 (FGF23) is the best characterized. These hormones act on three primary target organs: bone, kidney, and intestine. The kidneys play a critical role in maintaining normal serum Ca and P concentrations; thus, derangements in mineral metabolism are common in patients with chronic kidney disease (CKD). Abnormalities are initially observed in patients with a glomerular filtration rate (GFR) of < 60 mL/min and are nearly uniform as the GFR becomes < 30 mL/min (Levin et al., 2007). With the progressive development of CKD, the body attempts to maintain normal serum concentrations of Ca and P with altered production of calcitriol, PTH, and FGF23. Disturbances of mineral metabolism include hyperparathyroidism, phosphate retention, hypocalcaemia, and vitamin D deficiency. These disturbances are associated with bone loss, fractures, cardiovascular disease, immune suppression, and increased mortality. In 2006, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) created a consensus group to better define the diseases associated with altered mineral metabolism in CKD, which was termed 'chronic kidney disease-mineral and bone disorder' (CKD-MBD). It is a systemic disorder of mineral and bone metabolism found in patients with CKD, manifested by either one or a combination of the following:

- Abnormalities of Ca, P, PTH, or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Vascular or soft tissue calcification.

It is important to note that this list was not intended to be all-encompassing and could expand as our understanding of disordered mineral metabolism evolves (Moe et al., 2006).

Abnormalities of calcium, phosphorus, vitamin D, and parathyroid hormone

Increased PTH concentrations are generally the first clinically measured abnormality observed in patients with evolving CKD (Levin et al., 2007). Increases in PTH concentrations in the early stages of CKD are an adaptive mechanism to help maintain the serum Ca and P concentrations in the normal range. In addition to the increase in PTH, there is also an early increase in FGF23 concentrations (Westerberg et al., 2007), as well as a decrease in calcitriol (Levin et al., 2007). It is not until the development of CKD stages 4–5 that measurable abnormalities of Ca and P become apparent (Levin et al., 2007).

Calcium

In patients with CKD stages 3–4 there are no data to support an increased risk of mortality or fracture with increasing serum Ca concentrations. However, studies in dialysis patients show that variable degrees of hypercalcaemia become significantly associated with increased all-cause mortality (Block et al., 2004; Kestenbaum et al., 2005; Young et al., 2005; Kalantar-Zadeh et al., 2006; Tentori et al., 2008). In regards to hypocalcaemia, there is little evidence of an increase in relative risk until serum levels fall below 8.4 mg/dL (Tentori et al., 2008); however, one study did demonstrate that the increased relative risk of mortality with low serum Ca was reversed when adjusted for covariates (Block et al., 2004). It is therefore unclear at what degree of hypocalcaemia there is an increased risk.

Phosphorus

In patients with CKD stages 2–5 who are not undergoing dialysis, higher concentrations of serum P, even within the normal range, have been associated with increased risk of all-cause or cardiovascular mortality (Kestenbaum et al., 2005). There are multiple studies in patients on dialysis with similar results, although slight differences in the levels at which serum P becomes significantly associated with increased mortality (Block et al., 2004; Kimata Young et al., 2005; Kalantar-Zadeh et al., 2006; Tentori et al., 2008). Although a specific serum P concentration at which increased risk of mortality has not been defined, there is clear epidemiologic data supporting that lower serum P concentration is associated with better outcomes. Unfortunately, no study has demonstrated that lowering the serum P concentration to a specific value leads to improved outcomes. A meta-analysis found that, of the serum parameters of mineral metabolism, P had the greatest effect on mortality, followed by PTH (Covic et al., 2009).

FGF23 is a phosphate-regulating hormone that is secreted by bone cells. Both PTH and FGF23 inhibit renal tubular phosphate reabsorption. In the setting of CKD, the actions of both PTH and FGF23 maintain P balance by increasing the excretion of

P. However, with progressive loss of kidney function, these hormones can no longer have a significant effect on renal P excretion; in fact, increased level of PTH may now have a negative effect on P balance, as it leads to increased bone P resorption. FGF23 levels continue to rise progressively with worsening renal dysfunction.

Vitamin D

Vitamin D deficiency in patients with CKD has generally been defined as 25-OH-vitamin D (calcidiol) levels of < 30 ng/mL (National Kidney Foundation, 2003). Such deficiency is common in CKD, being reported in 71% of stage 3 and 83% of stage 4 CKD subjects (LaClair et al., 2005). This prevalence of vitamin D deficiency in an ambulatory CKD population is similar to that in non-CKD nursing home residents, hospitalized patients, and elderly women with hip fractures. The prevalence of severe vitamin D deficiency (< 10 ng/mL) is 14% and 26% in stage 3 and 4 CKD, respectively (LaClair et al., 2005). Several other investigators have confirmed widespread vitamin D deficiency in CKD, although not all of them have identified a correlation with the CKD stage (Gonzalez et al., 2004; LaClair et al., 2005; Elder and Mackun, 2006; Levin et al., 2007). Vitamin D deficiency in patients with CKD stages 3 and 4 is associated with increased serum PTH (LaClair et al., 2005; Elder and Mackun, 2006; Zisman et al., 2007; Tomida et al., 2009). It has also been associated with increased mortality in incident dialysis patients (Wolf et al., 2007) and increased cardiovascular events in peritoneal dialysis patients (Wang et al., 2008). These data have led the Kidney Disease Improving Global Outcomes (KDIGO) to recommend systematic measurements (Table 115.1) of calcidiol levels in CKD patients; however, KDIGO authors conclude that there is insufficient data to suggest an optimal level of vitamin D for these patients, while noting that there is also no reason to assume that they would require different levels for non-endocrine effects of vitamin D (KDIGO, 2009). Furthermore, definitive studies demonstrating that treatment with vitamin D leads to improvement in secondary hyperparathyroidism or other complications in patients with CKD are lacking.

Table 115.1 Summary of the KDIGO guidelines and commentary

	KDIGO 2009 guidelines[a]	KDIGO 2010 commentary[b]
Monitoring biochemical components	Start at CKD 3 Include Ca, P, PTH, alkaline phosphatase (ALP)	Suggest using ALP as adjunct test
Goal PTH	CKD 3–4: unknown CKD 5: 2–9 times upper limit of normal for the assay When PTH above upper limits of normal, evaluate correctable factors like P, Ca, vitamin D	Suggest a range corresponding to approximately 130–600 ng/mL
Goal P	CKD 3–4: normal range CKD 5: towards normal range	Suggest lowering towards the reference range
Goal Ca	Normal Suggest to stay away from Ca × P product	Suggest monitoring in the reference range
Goal 25(OH) vitamin D	Start at CKD 3 Correct as in general population	Suggest expanded testing as well as treatment of 25(OH) vitamin D deficiency
PTH assay	Clinical labs should report assay method handling and sampling Recommend 2nd-generation assay	Recommend evolution in assay
Bone-specific ALP	In CKD 3–5D. Suggest testing bone-specific ALP in certain individuals. Very high or low levels predict underlying bone turnover	Suggest testing bone-specific ALP in certain individuals
Bone biopsy	In CKD 3–5D. Reasonable to perform bone biopsy in various settings and before therapy with bisphosphonates in CKD-MBD patients	Expanded indications for bone biopsy, including before treatment with bisphosphonates
BMD testing	CKD 3–5D. Suggest not routinely testing for BMD	Suggest restricted testing for BMD
Screening for vascular calcification	No recommendation given for routine screening for vascular calcification	–

[a] Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009).

[b] Uhlig et al. (2010).

Regulation of mineral metabolism is predominately due to circulating calcitriol levels, which mediates its cellular function via both non-genomic and genomic mechanisms. Calcitriol facilitates the uptake of Ca in intestinal and renal epithelium, by increasing the activity of voltage-dependent Ca channels. Calcitriol then enhances the transport of Ca through and out of these cells, by upregulating the Ca transport protein calbindin and the basolateral Ca-ATPase (Hoenderop and Bindels, 2008; Boros et al., 2009). In addition, calcitriol also directly suppresses PTH synthesis (Silver et al., 1986; Brown et al., 2006) and is important for normal bone turnover (Goltzman et al., 2004; Anderson and Atkins, 2008). The predominant source of circulating calcitriol is from activation of calcidiol by 1-α-hydroxylase (CYP27B1) in the kidney. This enzyme is stimulated by PTH and inhibited by both calcitriol and FGF23. Other factors that are involved in the regulation of calcitriol include low Ca, low P, oestrogen, prolactin, and growth hormone (Shimada et al., 2005). Most cells in the body, other than renal cells, have the CYP27B1 enzyme and can produce calcitriol; however, this only acts as a local autocrine/paracrine factor and does not significantly contribute to the circulating calcitriol levels or affect mineral metabolism (Stubbs et al., 2010). Calcitriol is degraded by the kidney enzyme 24,25-hydroxylase (CYP24), providing the primary metabolism of the active compound. Elevated serum levels of PTH increase CYP27B1 activity in the kidney (and possibly in other cells), thereby raising serum calcitriol levels and, subsequently, serum Ca. In its turn, calcitriol inhibits PTH secretion by the parathyroid glands, thus completing a typical endocrine feedback loop. As CKD progresses, there is a progressive decrease in calcitriol production (Levin et al., 2007).

Parathyroid hormone

Serum PTH has long been considered a surrogate marker for bone disease and its ability to predict low- and high-turnover bone disease was the rationale for the target range of 150–300 pg/mL

in the K/DOQI guidelines for CKD stage 5D (National Kidney Foundation, 2003). Unfortunately, the assay used for those analyses is no longer available and subsequent studies have demonstrated that PTH levels within a range of 150–300 pg/mL are not predictive of underlying bone histology (Barreto et al., 2008). Similar to other biochemical parameters of CKD-MBD, observational studies have found an association of all-cause mortality with various levels of PTH, concentrations > 600 pg/mL being associated with increased mortality (Block et al., 1998; Kimata et al., 2005; Young et al., 2005). However, at least one study showed an increased risk of all-cause mortality with PTH concentrations approaching 400 pg/mL (Kalantar-Zadeh et al., 2006). Based on these observational data and considering the limitations associated with various PTH assays, the KDIGO guidelines suggested that target PTH concentrations should be assay specific and should range between two and nine times the upper limit of normal for the PTH assay being utilized. The guidelines also suggest that values within that range should be interpreted by evaluating trends and recommend interventions according to these trends (KDIGO, 2009). It is important to recognize that there are no randomized clinical trials which demonstrate that treatment to achieve specific PTH targets results in improved outcomes.

The immediate signal that regulates parathyroid glands to secrete PTH is changes in serum ionized Ca concentration. The PTH-Ca relationship is very tightly regulated, such that a very small decrease in the serum ionized Ca concentration will cause a maximal PTH secretion and vice versa (Goodman et al., 1995). The parathyroid gland is able to sense changes in the ionized serum Ca concentration via the activity of Ca-sensing receptor (Brown et al., 1993), which directly inhibits PTH secretion. PTH maintains normal serum Ca concentrations through both direct and indirect actions. PTH directly increases serum Ca via increasing bone resorption and renal tubular Ca absorption. Indirectly, PTH increases serum Ca by stimulating the renal synthesis of calcitriol, which is responsible for the absorption of Ca from the gastrointestinal tract.

The 2009 KDIGO guideline (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009) and the 2010 KDIGO commentary (Uhlig et al., 2010) agreed that the control of serum Ca, P, vitamin D, and PTH is central to the management of CKD-MBD. A retrospective study in 2008 showed that being out of target for any of these parameters is associated with an increased risk of mortality. Furthermore, as more parameters are out of control, the higher the associated risk for mortality (Danese et al., 2008).

Abnormalities in bone turnover, mineralization, volume, linear growth, and strength

Renal osteodystrophy consists of abnormalities in bone morphology occurring as a result of CKD. Its clinical manifestations include bone pain, muscle weakness, and fractures. Renal osteodystrophy starts early in the course of CKD, with minor changes in bone histology found in patients with only mildly increased PTH (Hamdy, 1995). Besides elevations in PTH, disorders of Ca and P, vitamin D deficiency, and elevated FGF23 have also been shown to be associated with renal osteodystrophy (Juppner et al., 2010). The importance of bone disease in CKD is due to the increased risk of fractures, which, in turn, are associated with increased mortality. The incidence of hip fractures is higher in patients on dialysis. The risk increases with age (especially > 80 years old) and time on dialysis (> 4 years) and is higher in patients with low body mass index and in white females (Alem et al., 2000; Stehman-Breen et al., 2000). Therefore, early diagnosis of bone disease in CKD patients is essential and it requires the use of several tools, including the following:

- Biochemical markers: serum PTH, Ca, P, and FGF23
- Markers of bone formation (alkaline phosphatase and osteocalcin) and bone resorption (tartrate-resistant acid phosphatase (TRAP), urine hydroxyproline, and N-terminal telopeptide (NTx))
- Bone imaging (bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DEXA) scan, quantitative computed tomography (qCT) or micro-magnetic resonance imaging (μ-MRI))
- Bone biopsy.

Biochemical markers like PTH, Ca and P suggest an association with bone disease; however, these markers are not very specific and correlate poorly with bone histomorphometry. Markers of bone formation and bone resorption could have a potential role in assessing bone disease; however, there is marked diurnal variation in their levels and this makes it hard to interpret the results. Bone-specific or total alkaline phosphatase may provide useful information, in conjunction with PTH measurements, in assessing bone formation (Moe et al., 2006).

Bone strength and ultimately fracture risk is determined by two factors: the density and the quality of the bone. The 'density of the bone' is determined by the bone mass, while the 'quality of the bone' is determined by its architecture, turnover, and mineralization.

In non-CKD populations, the diagnosis of osteoporosis (loss of bone density/mass) is based on the results of BMD measurements, using DEXA. Fracture risk increases approximately 1.6-fold for every SD decrement in BMD, irrespective of gender (Cummings et al., 2006; Rivadeneira et al., 2007). Although CKD patients have decreased BMD, the degree of bone loss is not directly associated with the decrease in estimated GFR (Jamal et al., 2010). Interestingly, BMD measurements are not able to discriminate between the histological or microarchitectural abnormalities seen in CKD and thus have not been able to consistently discriminate between ESRD patients who fracture from those who do not fracture (Jamal et al., 2007; Jamal, 2010).

As BMD accounts for only part of the variation seen in bone strength and only some of the observed reduction in fracture risk that occurs with treatment, recent developments have focused more on measuring bone structure and quality of trabecular and cortical bone rather than bone mass alone. This is done with the knowledge that a measure encompassing bone quality and structure along with bone mass will provide a better prediction of fracture risk than bone mass alone. Recent advances in high-resolution imaging technologies, notably qCT and μ-MRI, enable direct visualization and quantification of both trabecular and cortical bone. qCT measuring the forearm may be useful, as it could separate cortical from trabecular bone loss, and at least one study demonstrated that cortical bone density loss in dialysis patients may be associated with increased fracture risk (Jamal et al., 2006). However, qCT is not a readily available technology and places the patient at an increased

exposure to radiation compared with traditional measurements of BMD. μ-MRI has the advantage of being free of radiation and has been shown to provide high spatial resolution. In fact, it is possible to obtain a three-dimensional representation of trabecular bone architecture in a volume of interest selected from a high-resolution set of contiguous slices, which thus can be analysed analogous to a physical bone biopsy (Wehrli et al., 2002, 2004). These recent advances in high-resolution imaging technologies will require further validation in larger patient studies to determine its ultimate clinical potential as an alternative to invasive biopsy in the evaluation of patients with renal osteodystrophy.

It is important to remember that there are many potential causes for decreased bone density in CKD patients, including hypogonadism, sedentary lifestyle, smoking, use of steroids, poor protein intake, vitamin D deficiency, diabetes and Ca deficiency. Thus, in dialysis patients, fractures are not necessarily related to osteoporosis. In a study that looked at 26 femoral neck fractures in 19 chronic haemodialysis patients, the pathology was variable, with amyloidosis, aluminium toxicity, osteoporosis and steroid necrosis as the cause of fracture, in decreasing order of frequency (Hardy et al., 1994). Dialysis-related amyloidosis most commonly affects the synovial, but can produce cystic/lytic lesions in the long bone that mimic the changes of hyperparathyroidism. The recommendations of KDIGO, as well as the subsequent KDOQI commentary on KDIGO, conclude that BMD studies do not predict the type of renal osteodystrophy in patients with CKD-MBD and recommends against routine BMD testing in this patient population (Moe et al., 2006; Uhlig et al., 2010).

As mentioned above, the gold standard to assess bone quality and to diagnose renal osteodystrophy is bone histomorphometry on a transcortical bone biopsy from the iliac crest, with double tetracycline labelling (Moe et al., 2006; Gal-Moscovici et al., 2008). Classically, bone disease in CKD has been classified in four major categories:

- Osteitis fibrosa cystica (high turnover)
- Mixed uremic osteodystrophy
- Adynamic bone disease (low turnover bone disease)
- Osteomalacia.

In 2006, the KDIGO consensus group came up with the TMV classification, so that bone biopsies are not classified via descriptive parameters, but scored on a quantitative assessment based on bone turnover, mineralization and volume. The TMV classification is as follows (Moe et al., 2006):

1. Turnover—low, normal, or increased
2. Mineralization—normal, or abnormal
3. Volume—decreased, normal, or increased.

The role of bone biopsies in renal osteodystrophy is further discussed in Chapter 122.

Vascular and soft tissue calcification

Extraskeletal deposition of Ca commonly occurs in patients with long-standing CKD. This may involve vascular, peri-articular, visceral, or subcutaneous deposition of Ca. Vascular calcification also occurs in disease states that do not involve the kidney. There are several pathologic mechanisms which result in the development of vascular calcification. In patients with atherosclerotic disease, the typical lesion is intimal calcification. The pathogenesis of intimal calcification involves the deposition of Ca in the atherosclerotic plaques within the intima of blood vessels. This is generally a progressive process that leads to vascular occlusion and commonly occurs in absence of renal disease (Amann, 2008). The other form of vascular calcification, which is common in patients with long-standing CKD is called Mönckeberg calcification or medial calcinosis (Proudfoot et al., 1998). The Ca deposits within the media form a linear deposit in the vessel wall, while the lumen of the vessel generally remains open. This leads to very stiff arteries and has been associated with increased cardiac afterload, left ventricular hypertrophy, and increased pulse wave velocity, all of which may have adverse effects on clinical outcomes of renal patients.

Pathophysiology of vascular calcification was initially thought to be a passive process and only a function of increased Ca × P product; however, recent evidence suggests that vascular calcification is a tightly regulated process that resembles mineralization in bone (Moe and Chen, 2008). The current working hypothesis is that vascular smooth muscle cells de-differentiate or transform into osteocyte/chondrocyte-like cells. These cells then lay down an extracellular matrix of collagen and non-collagenous proteins and make matrix vesicles that somehow attach to the extracellular matrix and initiate mineralization. This process is regulated by the cells, the extracellular matrix proteins, and inhibitors that may act locally or systemically (Moe and Chen, 2008).

Even though the medial calcification is more frequently associated with CKD, there is a broad overlap of both intimal and medial calcification in the ESRD patient population. The factors that are involved in vascular calcification are increasing age, diabetes, time on dialysis, increased P levels, increased use of Ca-containing P binders, and high PTH levels (Goodman et al., 2000; Raggi et al., 2002). Worsening secondary hyperparathyroidism is associated with increased coronary calcification in dialysis patients, independently of Ca and P abnormalities (Coen et al., 2007). In dialysis patients, the presence of vascular calcifications, whether intimal or medial, is associated with decreased survival (London et al., 2003). However, it may be premature to embark on a screening programme in the CKD population with plain radiographs or CT scanning until data are available regarding therapeutic interventions to prevent or treat vascular calcifications. KDIGO 2009 does not recommend routine screening for vascular calcifications (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009).

Calciphylaxis (calcific uraemic arteriolopathy) is characterized by spontaneous ischaemic necrosis of the skin, muscles, and/or subcutaneous fat (Rogers et al., 2007). This occurs almost exclusively in patients with ESRD, most of whom are on haemodialysis; however, peritoneal dialysis has been reported to pose an even greater risk (Cordova et al., 2009). The classical presentation of calciphylaxis was associated with severe hyperphosphataemia and hyperparathyroidism and demonstrated marked clinical improvement within days of parathyroidectomy (Rogers et al., 2007). Although this clinical presentation continues to occur, it is relatively rare since the introduction of aggressive management of hyperparathyroidism. Unlike the earlier presentation of calciphylaxis, current presentation is not necessarily associated with very high PTH concentrations or improvement with parathyroidectomy (Rogers et al., 2007). Calciphylaxis is a disease with high morbidity and mortality and

with few effective treatments. Supportive care should emphasize aggressive wound debridement, systemic pain management, and normalization of serum Ca and P levels. Therapy with sodium thiosulfate has also been shown to be helpful (Cicone et al., 2004).

Post-transplant chronic kidney disease-mineral and bone disorder

Bone disease continues to be a major problem after renal transplantation, resulting in accelerated loss of BMD, leading to osteopenia, osteoporosis, and increased risk of fractures. These complications occur predominantly in the first 6–12 months following transplantation (Grotz et al., 1995; Moreno et al., 1999). Osteoporosis has been reported in up to 30% of renal transplant recipients.

Factors associated with increased risk of bone loss include long duration of dialysis and presence of renal osteodystrophy prior to transplantation, hypogonadism, lower body mass index, high cumulative dose of glucocorticoids, vitamin D deficiency, high FGF23, and high PTH levels prior to transplantation (Alshayeb et al., 2013).

After successful renal transplantation, serum PTH decreases significantly in the first 3 months after surgery, but tends to stabilize at elevated levels after 1 year. Higher pre-transplant PTH and longer time on dialysis predict higher post-transplant PTH. The prevalence of hyperparathyroidism among renal transplant patients is estimated to be around 30–50%. Persistent hyperparathyroidism is a risk factor for hypercalcaemia, hypophosphataemia, worsening of bone disease, and possibly acute tubular necrosis after kidney transplant.

Hypophosphataemia is observed frequently after renal transplantation (up to 90% in some reports) and it is an important risk factor for fractures. Decreased P reabsorption in the proximal tubules seems to be the main mechanism for hypophosphataemia, which in turn affects bone mineralization, by increasing osteoblast apoptosis, diminishing osteoblast activity and inhibiting osteoblast proliferation. In addition to high PTH, high FGF23 also contributes to the renal P wasting. In fact, the risk of developing severe hypophosphataemia during the immediate post-transplant period is more closely linked to FGF23 than to PTH levels. The pre-transplant serum levels of FGF23 are thought to be the single most important predictor of post-transplant FGF23 levels. FGF23 remains significantly increased even at 6 months post transplant (Bhan et al., 2006; Huang and Sprague, 2009).

Steroids may affect bone metabolism by increasing osteoclastic resorption and decreasing osteoblastic activity, as well as by promoting apoptosis of osteoblasts. Therefore, low-turnover bone disease appears to be common in kidney transplant recipients. The role of calcineurin inhibitors in post-transplant bone disease remains controversial.

In renal transplant patients with an eGFR > 30 mL/min/1.73 m^2 (CKD stages 1–3T), the KDIGO guidelines suggest measuring BMD in the first 3 months after transplantation, if they receive corticosteroids or have risk factors for osteoporosis. In patients with CKD stages 4–5T, the same guidelines suggest that BMD testing should not be performed routinely, because BMD does not predict fracture risk as it does in the general population (Durieux et al., 2002) and BMD does not predict the type of kidney transplant bone disease. Bone biopsy is thought to be the gold standard for the identification and classification of post-transplantation bone disease (Sprague, 2000; Alshayeb et al., 2013).

Calcium and calcitriol therapies have been shown to have beneficial effects in some studies, with one study showing significantly less bone loss in the lumbar spine and increased BMD in the distal radius and femoral neck, compared with post-transplant patients treated with Ca and placebo (Josephson et al., 2004; Weisinger et al., 2006; Huang and Sprague, 2009; Kalantar-Zadeh et al., 2012).

Cinacalcet, a calcimimetic, has been shown to correct hypercalcaemia and refractory hyperparathyroidism post transplant, with no side effects on the renal allograft. However, these studies involving cinacalcet are small and more prospective trials are needed. Parathyroidectomy may be indicated in patients who have persistent hypercalcaemia, symptomatic bone disease, fractures, or persistent hyperparathyroidism more than 1 year post transplant (Josephson et al., 2004; Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group, 2009).

Bisphosphonates, particularly if started in the initial months after renal transplantation, have been shown to prevent bone loss. However, there may be an increased risk of developing adynamic bone disease due to the bisphosphonates. Moreover, since the amount of bone loss after transplantation does not necessarily predict fracture risk, the indiscriminate use of bisphosphonates in this population is not recommended.

References

Alem, A. M., Sherrard, D. J., Gillen, D. L., *et al.* (2000). Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int*, 58, 396–9.

Alshayeb, H. M., Josephson, M. A., and Sprague, S. M. (2013). CKD-mineral and bone disorder management in kidney transplant recipients. *Am J Kidney Dis*, 61, 310–25.

Amann, K. (2008). Media calcification and intima calcification are distinct entities in chronic kidney disease. *Clin J Am Soc Nephrol*, 3, 1599–605.

Anderson, P. H. and Atkins, G. J. (2008). The skeleton as an intracrine organ for vitamin D metabolism. *Mol Aspects Med*, 29, 397–406.

Barreto, F. C., Barreto, D. V., Moyses, R. M., *et al.* (2008). K/DOQI-recommended intact PTH levels do not prevent low-turnover bone disease in hemodialysis patients. *Kidney Int*, 73, 771–7.

Bhan, I., Shah, A., Holmes, J., *et al.* (2006). Post-transplant hypophosphatemia: tertiary 'hyper-phosphatoninism'? *Kidney Int*, 70(8), 1486–94.

Block, G. A., Hulbert-Shearon, T. E., Levin, N. W., *et al.* (1998). Association of serum P and Ca × phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*, 31, 607–17.

Block, G. A., Klassen, P. S., Lazarus, J. M., *et al.* (2004). Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*, 15, 2208–18.

Boros, S., Bindels, R. J., and Hoenderop, J. G. (2009). Active Ca^{2+} reabsorption in the connecting tubule. *Pflugers Arch*, 458, 99–109.

Brown, A. J., Ritter, C. S., Knutson, J. C., *et al.* (2006). The vitamin D prodrugs 1alpha(OH)D_2, 1alpha(OH)D_3 and BCI-210 suppress PTH secretion by bovine parathyroid cells. *Nephrol Dial Transplant*, 21, 644–50.

Brown, E. M., Gamba, G., Riccardi, D., *et al.* (1993). Cloning and characterization of an extracellular Ca^{2+}-sensing receptor from bovine parathyroid. *Nature*, 366, 575–80.

Cicone, J. S., Petronis, J. B., Embert, C. D., *et al.* (2004). Successful treatment of calciphylaxis with intravenous sodium thiosulfate. *Am J Kidney Dis*, 43, 1104–8.

Coen, G., Manni, M., Mantella, D., *et al.* (2007). Are PTH serum levels predictive of coronary calcifications in haemodialysis patients? *Nephrol Dial Transplant*, 22, 3262–7.

Cordova, K. B., Oberg, T. J., Malik, M., *et al.* 92009). Dermatologic conditions seen in end-stage renal disease. *Semin Dial*, 22, 45–55.

Covic, A., Kothawala, P., Bernal, M., *et al.* (2009). Systematic review of the evidence underlying the association between mineral metabolism disturbances and risk of all-cause mortality, cardiovascular mortality

and cardiovascular events in chronic kidney disease. *Nephrol Dial Transplant*, 24, 1506–23.
Cummings, S. R., Cawthon, P. M., Ensrud, K. E., *et al.* (2006). BMD and risk of hip and nonvertebral fractures in older men: a prospective study and comparison with older women. *J Bone Miner Res*, 21, 1550–6.
Danese, M. D., Belozeroff, V., Smirnakis, K., *et al.* (2008). Consistent control of mineral and bone disorder in incident hemodialysis patients. *Clin J Am Soc Nephrol*, 3, 1423–9.
Durieux, S., Mercadal, L., Orcel, P., *et al.* (2002). Bone mineral density and fracture prevalence in long-term kidney graft recipients. *Transplantation*, 74, 496–500.
Elder, G. J. and Mackun, K. (2006). 25-Hydroxyvitamin D deficiency and diabetes predict reduced BMD in patients with chronic kidney disease. *J Bone Miner Res*, 21, 1778–84.
Gal-Moscovici, A. and Sprague, S. M. (2008). Role of bone biopsy in stages 3 to 4 chronic kidney disease. *Clin J Am Soc Nephrol*, 3 Suppl 3, S170–4.
Goltzman, D., Miao, D., Panda, D. K., *et al.* (2004). Effects of Ca and of the vitamin D system on skeletal and Ca homeostasis: lessons from genetic models. *J Steroid Biochem Mol Biol*, 89–90, 485–9.
Gonzalez, E. A., Sachdeva, A., Oliver, D. A., *et al.* (2004). Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. *Am J Nephrol*, 24, 503–10.
Goodman, W. G., Belin, T., Gales, B., *et al.* (1995). Ca-regulated parathyroid hormone release in patients with mild or advanced secondary hyperparathyroidism. *Kidney Int*, 48, 1553–8.
Goodman, W. G., Goldin, J., Kuizon, B. D., *et al.* (2000). Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med*, 342, 1478–83.
Grotz, W. H., Mundinger, F. A., Gugel, B., *et al.* (1995). Bone mineral density after kidney transplantation. A cross-sectional study in 190 graft recipients up to 20 years after transplantation. *Transplantation*, 59, 982–6.
Hamdy, N. A. (1995). The spectrum of renal bone disease. *Nephrol Dial Transplant*, 10 Suppl 4, 14–8.
Hardy, P., Benoit, J., Donneaud, B., *et al.* (1994). [Pathological fractures of the femoral neck in hemodialyzed patients. Apropos of 26 cases]. *Rev Chir Orthop Reparatrice Appar Mot*, 80, 702–10.
Hoenderop, J. G. and Bindels, R. J. (2008). Calciotropic and magnesiotropic TRP channels. *Physiology (Bethesda)*, 23, 32–40.
Huang, M. and Sprague, S. M. (2009). Bone disease in kidney transplant patients. *Semin Nephrol*, 29(2), 166–73
Jamal, S. A. (2010). Bone mass measurements in men and women with chronic kidney disease. *Curr Opin Nephrol Hypertens*, 19, 343–8.
Jamal, S. A., Gilbert, J., Gordon, C., *et al.* (2006). Cortical pQCT measures are associated with fractures in dialysis patients. *J Bone Miner Res*, 21, 543–8.
Jamal, S. A., Hayden, J. A., and Beyene, J. (2007). Low bone mineral density and fractures in long-term hemodialysis patients: a meta-analysis. *Am J Kidney Dis*, 49, 674–81.
Jamal, S. A., Swan, V. J., Brown, J. P., *et al.* (2010). Kidney function and rate of bone loss at the hip and spine: the Canadian Multicentre Osteoporosis Study. *Am J Kidney Dis*, 55, 291–9.
Josephson, M. A., Schumm, L. P., Chiu, M. Y., *et al.* (2004). Calcium and calcitriol prophylaxis attenuates posttransplant bone loss. *Transplantation*, 78(8), 1233–6
Juppner, H., Wolf, M., and Salusky, I. B. (2010). FGF-23: more than a regulator of renal phosphate handling? *J Bone Miner Res*, 25, 2091–7.
Kalantar-Zadeh, K., Kuwae, N., Regidor, D. L., *et al.* (2006). Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int*, 70, 771–80.
Kalantar-Zadeh, K., Molnar, M. Z., Kovesdy, C. P., *et al.* (2012). Management of mineral and bone disorder after kidney transplantation. *Curr Opin Nephrol Hypertens*, 21(4), 389–403.
KDIGO (2009). Clinical practice guidelines for the management of CKD-MBD. *Kidney Int*, 76, S1–130.
Kestenbaum, B., Sampson, J. N., Rudser, K. D., *et al.* (2005). Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol*, 16, 520–8.
Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009). KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int, Suppl*, S1–130.
Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group (2009). KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*, 9 Suppl 3, S1–155.
Kimata, N., Akiba, T., Pisoni, R. L., *et al.* (2005). Mineral metabolism and haemoglobin concentration among haemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*, 20, 927–35.
LaClair, R. E., Hellman, R. N., Karp, S. L., *et al.* (2005). Prevalence of calcidiol deficiency in CKD: a cross-sectional study across latitudes in the United States. *Am J Kidney Dis*, 45, 1026–33.
Levin, A., Bakris, G. L., Molitch, M., *et al.* (2007). Prevalence of abnormal serum vitamin D, PTH, Ca, and P in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int*, 71, 31–8.
London, G. M., Guerin, A. P., Marchais, S. J., *et al.* (2003). Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol, Dial, Transplant*, 18, 1731–40.
Moe, S., Drueke, T., Cunningham, J., *et al.* (2006). Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*, 69, 1945–53.
Moe, S. M. and Chen, N. X. (2008). Mechanisms of vascular calcification in chronic kidney disease. *J Am Soc Nephrol*, 19, 213–6.
Moreno, A., Torregrosa, J. V., Pons, F., *et al.* (1999). Bone mineral density after renal transplantation: long-term follow-up. *Transplant Proc*, 31, 2322–3.
National Kidney Foundation (2003). K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*, 42, S1–201.
Proudfoot, D., Shanahan, C. M., and Weissberg, P. L. (1998). Vascular calcification: new insights into an old problem. *J Nephrol*, 185, 1–3.
Raggi, P., Boulay, A., Chasan-Taber, S., *et al.* (2002). Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol*, 39, 695–701.
Rivadeneira, F., Zillikens, M. C., De Laet, C. E., *et al.* (2007). Femoral neck BMD is a strong predictor of hip fracture susceptibility in elderly men and women because it detects cortical bone instability: the Rotterdam Study. *J Bone Miner Res*, 22, 1781–90.
Rogers, N. M., Teubner, D. J., and Coates, P. T. (2007). Calcific uremic arteriolopathy: advances in pathogenesis and treatment. *Semin Dial*, 20, 150–7.
Shimada, T., Yamazaki, Y., Takahashi, M., *et al.* (2005). Vitamin D receptor-independent FGF23 actions in regulating phosphate and vitamin D metabolism. *Am J Physiol Renal Physiol*, 289, F1088–95.
Silver, J., Naveh-Many, T., Mayer, H., *et al.* (1986). Regulation by vitamin D metabolites of parathyroid hormone gene transcription in vivo in the rat. *J Clin Invest*, 78, 1296–301.
Sprague, S. M. (2000). The role of the bone biopsy in the diagnosis of renal osteodystrophy. *Semin Dial*, 13, 152–5.
Stehman-Breen, C. O., Sherrard, D. J., Alem, A. M., *et al.* (2000). Risk factors for hip fracture among patients with end-stage renal disease. *Kidney Int*, 58, 2200–5.
Stubbs, J. R., Idiculla, A., Slusser, J., *et al.* (2010). Cholecalciferol supplementation alters calcitriol-responsive monocyte proteins and decreases inflammatory cytokines in ESRD. *J Am Soc Nephrol*, 21, 353–61.
Tentori, F., Blayney, M. J., Albert, J. M., *et al.* (2008). Mortality risk for dialysis patients with different levels of serum Ca, P, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*, 52, 519–30.
Tomida, K., Hamano, T., Mikami, S., *et al.* (2009). Serum 25-hydroxyvitamin D as an independent determinant of 1-84 PTH and bone mineral density in non-diabetic predialysis CKD patients. *Bone*, 44, 678–83.

Uhlig, K., Berns, J. S., Kestenbaum, B., *et al.* (2010). KDOQI US commentary on the 2009 KDIGO clinical practice guideline for the diagnosis, evaluation, and treatment of ckd-mineral and bone disorder (CKD-MBD). *Am J Kidney Dis*, 55, 773–99.

Wang, A. Y., Lam, C. W., Sanderson, J. E., *et al.* (2008). Serum 25-hydroxyvitamin D status and cardiovascular outcomes in chronic peritoneal dialysis patients: a 3-y prospective cohort study. *Am J Clin Nutr*, 87, 1631–8.

Wehrli, F. W., Leonard, M. B., Saha, P. K., *et al.* (2004). Quantitative high-resolution magnetic resonance imaging reveals structural implications of renal osteodystrophy on trabecular and cortical bone. *J Magn Reson Imaging*, 20, 83–9.

Wehrli, F. W., Saha, P. K., Gomberg, B. R., *et al.* (2002). Role of magnetic resonance for assessing structure and function of trabecular bone. *Top Magn Reson Imaging*, 13, 335–55.

Weisinger, J. R., Carlini, R. G., Rojas, E., *et al.* (2006). Bone disease after renal transplantation. *Clin J Am Soc Nephrol*, 1(6), 1300–13.

Westerberg, P. A., Linde, T., Wikstrom, B., *et al.* (2007). Regulation of fibroblast growth factor-23 in chronic kidney disease. *Nephrol Dial Transplant*, 22, 3202–7.

Wolf, M., Shah, A., Gutierrez, O., *et al.* (2007). Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int*, 72, 1004–13.

Young, E. W., Albert, J. M., Satayathum, S., *et al.* (2005). Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. *Kidney Int*, 67, 1179–87.

Zisman, A. L., Hristova, M., Ho, L. T., *et al.* (2007). Impact of ergocalciferol treatment of vitamin D deficiency on serum parathyroid hormone concentrations in chronic kidney disease. *Am J Nephrol*, 27, 36–43.

CHAPTER 116

Imaging for detection of vascular disease in chronic kidney disease patients

Paolo Raggi and Luis D'Marco

Introduction

The well-known severity of cardiovascular disease in patients suffering from chronic kidney disease (CKD) requires an accurate risk stratification of these patients in several clinical situations. Imaging has been used successfully for such purpose in the general population and it has demonstrated excellent potential among CKD patients as well. Both traditional risk factors for atherosclerosis and factors more closely associated with progressive loss of renal function contribute to the high incidence of cardiovascular complications seen in these patients. As a result, two main forms of arterial pathology develop in patients with CKD: atherosclerosis, with accumulation of inflammatory cells, lipids, fibrous tissue and calcium in the subintimal space, and arteriosclerosis. The latter is characterized by accumulation of deposits of hydroxyapatite and amorphous calcium crystals in the muscular media of the vessel wall, and is believed to be more closely associated with alterations of mineral metabolism than with traditional atherosclerosis risk factors. The result is the development of what appears to be premature arterial ageing, with loss of elastic properties, increased stiffness, and increased overall fragility of the arterial system. Despite intensifying research and increasing awareness of these issues, the underlying pathophysiology of the aggressive vasculopathy of CKD remains largely unknown (Drüeke and Massy, 2010). As a consequence, there are currently very limited pathways to prevent progression of vascular damage in CKD. This chapter explores the indications, strengths and weaknesses of several imaging modalities employed to evaluate vascular disease in CKD, focusing on coronary arterial circulation and the peripheral arteries, with the exclusion of the intracranial arteries.

Non-invasive modalities

Cardiac computed tomography for vascular calcification

Cardiac computed tomography (CT) is considered the reference standard to assess the presence and quantify the extent of cardiovascular calcification. Although initially performed with electron-beam CT (EBCT), a technology no longer available on the market, imaging of cardiovascular calcification is currently performed with multi-detector CT (MDCT) scanners. The MDCT technology operates on the basis of a different imaging platform, but is considered of equivalent accuracy and reproducibility compared to EBCT (Stanford et al., 2004). Image acquisition is slower with MDCT than with EBCT (lower temporal resolution), but the spatial resolution is higher (better image quality), although MDCT provides a higher radiation dose (1.5–2.5 mSv or 40–200 chest X-rays vs 0.6 mSv with EBCT) (Owen et al., 2011). Careful application of several methods to reduce radiation exposure can render the MDCT technology similar to EBCT even under this aspect.

Quantification of calcification is performed on stand-alone workstations after image acquisition implementing one of three scores: the Agatston score (Agatston et al., 1990), the volume score (Callister et al., 1998), or the mass score (Rumberger and Kaufman, 2003). The Agatston score is the most frequently reported and is calculated as the product of a calcified plaque area by its peak attenuation (or density, which in CT is measured in Hounsfield units). The sum of all scores in each calcified lesion identified along the course of the coronary arteries constitutes the total score. The volume and mass score are more reproducible than the Agatston score, but are less sensitive to the calcium content of the plaque that may be of interest in CKD patients.

In the general population, several retrospectives and prospective studies in asymptomatic subjects have shown that the presence and extent of coronary artery calcium (CAC) are independently associated with the risk of cardiovascular events and all-cause mortality within 3–5 years of screening (Budoff et al., 2006, 2007). In contrast, a CAC score of zero is associated with a very low risk of events (Shareghi et al., 2007).

The first CT observation in CKD patients was made by Braun et al. (1996); they described a higher prevalence and larger extent of CAC in CKD patients, in comparison with healthy subjects and patients with coronary artery disease (CAD) and normal renal function (Fig. 116.1). In patients with CKD, the prevalence of CAC increases with worsening renal failure (Kramer et al., 2005)—from 40% in CKD stage 4 patients (Russo et al., 2004) to approximately 85% in maintenance haemodialysis patients (Raggi et al., 2002). In a comparison of 60 haemodialysis and 28 peritoneal dialysis patients there was no difference in prevalence and extent of CAC between dialysis modalities (70% and 73%, respectively) (Sigrist

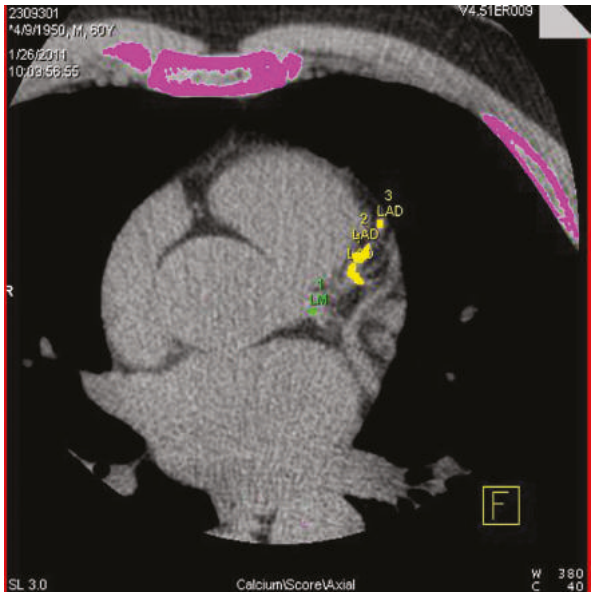

Fig. 116.1 Computerized tomography axial image of the chest and heart showing calcium deposits in the left main trunk (green) and left anterior descending coronary artery (yellow).

et al., 2006). Extensive CAC has been reported not only in adults, but in paediatric patients and young adults as well (Oh et al., 2002). Matsuoka et al. followed 102 chronic haemodialysis patients and evaluated the impact of CAC on survival. After a 5-year follow-up, the cumulative survival was significantly lower in the high (score ≥ 200) than in the low (< 200) CAC group (84% and 68%) (Matsuoka et al., 2004). Similarly, Block et al. showed a higher mortality risk with a high CAC score (> 400) among 127 hemodialysis patients followed for nearly 5 years from the time of screening (Block et al., 2007). More recently, Shantouf et al. reported a high mortality risk in haemodialysis patients with both CAC score 101–400 and > 400, compared to a score of 0 (hazard ratio (HR) 8.5; 95% confidence interval (CI) 1.1–48.1, P = 0.02; and HR 13.3; 95% CI 1.3–65.1, P = 0.01, respectively). This association was independent of demographic characteristics, comorbidities, and other traditional and uremic-related risk factors (Shantouf et al., 2010).

The thoracic and abdominal aortas have also been explored for the presence and extent of calcification by means of CT imaging. A prospective evaluation of 101 Japanese patients with moderate to severe CKD (stages 3–5) found an association between declining estimated glomerular filtration rate (eGFR) and presence and extent of abdominal aortic calcification (Hanada et al., 2010). The extent of aortic calcification was associated with the occurrence of *de novo* cardiovascular events. Aortic calcification is prevalent and is predictive of future cardiovascular events even among renal transplant recipients (DeLoach et al., 2008).

Although CT imaging provides an accurate and quantitative assessment of the cardiovascular calcification burden in patients with CKD, there are some inherent limitations to this technique. High equipment cost and radiation exposure for the patient are the main limitations, along with the inability to perform imaging in the office setting and the need for advanced image training. Finally, although desirable, these techniques do not differentiate intimal (i.e. atherosclerotic) from medial calcification. Thus, other methods have been used to assess vascular damage in CKD, and some simple tools have compared favourably with CT as far as the ability to detect calcification and predict outcome (Bellasi et al., 2006; Okuno et al., 2007).

Computed tomography angiography

Coronary artery CT angiography (CCTA) is an emerging non-invasive technology utilized for the identification of obstructive CAD, as well as non-calcified atherosclerotic plaques (Achenbach and Raggi, 2010). The presence of obstructive as well as non-obstructive CAD detected with this technology has been linked with unfavourable outcomes (Chow et al., 2010). Additionally, the excellent negative predictive value of CCTA for the presence of CAD renders it a very valuable tool to exclude the presence of disease in symptomatic patients with low-to-intermediate pre-test likelihood of CAD (Hoffmann et al., 2004).

Patients with CKD have been largely excluded from CCTA research protocols mostly due to the risk of iodine dye nephrotoxicity. Furthermore, the heavy vascular calcification typically found in these patients may hamper the interpretability of the scans. Thus, the role of CCTA in CKD patients remains to be fully explored. In a prospective study of 4297 asymptomatic patients submitted to CCTA, 651 patients suffered from CKD stages 1–3; the investigators showed that the early stages of CKD are not independently associated with obstructive CAD (Cho et al., 2010). Mao et al. investigated 28 patients on maintenance haemodialysis undergoing pre-transplant evaluation for risk stratification; they reported that patients with no CAC (36%) had no evidence of obstructive CAD (Mao et al., 2010). However, patients with extensive CAC showed significant stenosis of one or more coronary arteries, defined as > 50% of the vessel lumen. The CCTA was feasible and the image quality was sufficiently good in every patient to confidently exclude significant CAD in the main coronary arteries. In 704 patients with normal or minimally abnormal renal function (N = 635; eGFR ≥ 60 mL/min/1.73 m^2) and mild-to-moderate CKD (N = 69; eGFR: 30–59 mL/min/1.73 m^2) the optimal cut-off value of CAC to predict obstructive CAD was 140 (sensitivity 73% and specificity of 70%) (Yiu et al., 2013). The same research group provided initial evidence of the prognostic utility of CCTA in CKD. In 85 CKD patients with moderate CKD (eGFR: 30–59 mL/min/1.73m^2), both renal dysfunction and obstructive CAD on CCTA were independent predictors of cardiovascular events after 2.5 years of follow-up (Yiu et al., 2011). Furthermore, moderate CKD added incremental prognostic value to obstructive CAD.

CT angiography is often used to obtain detailed images of the entire aorta, renal arteries, and iliofemoral axis (Fig. 116.2); these are of aid in planning interventions such as placement of aortic endografts and peripheral stents or gauging the size of peripheral arteries prior to introducing large-bore catheters for the performance of interventional procedures.

At the time of this writing the role of CCTA remains unclear in patients with advanced renal failure; it may represent an acceptable alternative to invasive coronary angiography in patients with early CKD stages, provided that care is taken to prevent dye nephrotoxicity. CCTA may be helpful in CKD stage 1–3 patients with atypical symptoms of CAD or in cases with an indeterminate stress test result, to exclude CAD. There is currently no indication for CCTA as a non-invasive screening test for CAD.

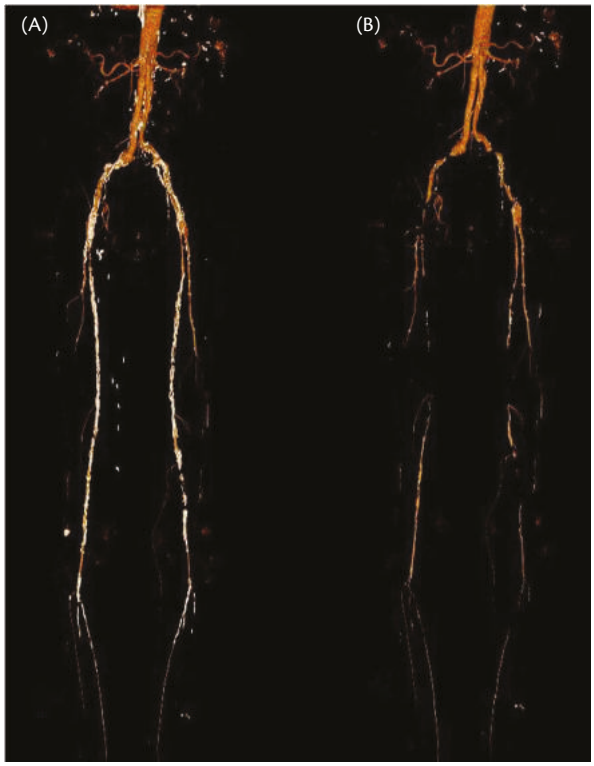

Fig. 116.2 Computerized tomography angiography of the abdominal aorta and arteries of the inferior limbs (volume rendering technique). (A) Image contains numerous areas of calcification along the arterial tree. (B) The areas of calcification have been removed and only the contrast filled lumen is now visible. This haemodialysis patient demonstrates extensive vasculopathy throughout the vascular tree.

Myocardial perfusion imaging

Performed via either positron emission tomography (PET) or single-photon emission computed tomography (SPECT), myocardial perfusion imaging (MPI) is the reference standard for the non-invasive assessment of coronary circulatory function. Radioactive tracers are injected intravenously at rest and after stress and are extracted by the myocardium proportional to the extent of coronary blood flow. This technology provides information on global and segmental myocardial perfusion, as well as myocardial function (Fig. 116.3). PET further allows a precise assessment of coronary flow reserve, an index of coronary vasodilator capacity. Although MPI has traditionally been used to identify perfusion abnormalities due to coronary disease, it has become apparent that perfusion abnormalities may occur in the absence of critical stenoses. In this case the abnormalities are considered secondary to microcirculatory or endothelial dysfunction (Karohl and Raggi, 2011).

Several studies have demonstrated the diagnostic and prognostic utility of MPI in various stages of CKD, including incident and prevalent dialysis patients (Hatta et al., 2009; Momose et al., 2009). Venkataraman et al. reported that haemodialysis patients had a worse prognosis than patients with normal renal function for any myocardial perfusion defect size; furthermore, MPI performed better than invasive coronary angiography for risk stratification (Venkataraman et al., 2008). Of interest, CKD patients with perfusion defects on SPECT, but non-obstructive coronary artery disease on invasive coronary angiography, were shown to have a higher cardiovascular risk than non-CKD subjects with non-obstructive coronary artery disease (Alqaisi et al., 2008). This suggests that, even in the absence of critical coronary luminal stenoses, CKD patients may be at greater cardiovascular risk due to greater endothelial dysfunction and increased vascular stiffness compared to non-CKD patients.

Patel et al. retrospectively examined the cardiovascular outcome of 174 patients with CKD submitted to SPECT MPI for risk stratification prior to renal transplantation. Patients with normal SPECT studies had a significantly lower cardiac event rate than those with abnormal studies (P = 0.006). The cardiac event-free survival after 42 months of follow-up was 97% and 85% for patients with normal and abnormal MPI, respectively; furthermore, an abnormal MPI was the single best predictor of an unfavourable outcome (Patel et al., 2003). It should be noted, however, that a few others studies suggested that MPI does not offer any advantage over clinical evaluation and/or invasive angiography in assessing cardiac risk in CKD patients. De Lima et al. showed no additional benefit of MPI over a direct invasive angiogram to predict cardiovascular risk in 126 renal transplant candidates (De Lima et al., 2003). Similarly, Patel et al. could not prove any benefit of screening for myocardial ischaemia for the purpose of performing a revascularization procedure in 300 patients submitted to stress testing prior to renal transplantation (Patel et al., 2008). It would appear, therefore, that the debate is far from being set as to the most appropriate indication for MPI in advanced CKD.

Whether stress MPI should be performed to risk stratify advanced CKD patients, with the goal of initiating a targeted therapy, or whether it should be performed as a pre-transplant evaluation to reduce future cardiovascular risk, remains unclear at this stage. To date, the only patients with accepted indications for MPI are those with advanced CKD with clinical and electrocardiographic evidence of CAD and patients with prior incomplete revascularization (KDOQI Workgroup 2005).

Planar roentgenography

Single plane radiography (planar X-ray) is the most widely available method to evaluate vascular calcification. It has been proposed that planar X-ray can be used to differentiate medial from intimal arterial calcification. Usually, the involvement of the arterial media appears as linear, railroad calcifications that delineate the wall of the artery; intimal calcification, instead, appears as patchy areas of calcification in affected regions (London et al., 2003). Planar radiography has been used to image the aorta, radial, digital, and iliac arteries and has provided outcome information when utilized at each one of these sites.

Semi-quantitative approaches were developed to render the technique less subjective. Perhaps the most popular is the one introduced by Kauppila et al. (1997). On lateral X-rays of the lumbar spine, areas of calcification are visualized along the profile of the abdominal aorta; focusing on aortic segments extending from the first to the fourth lumbar vertebra, several scores can be derived based on the number of plaques and the extent of calcification. With another semi-quantitative method, the femoral, iliac, radial and digital arteries are given a score of 1 for the presence of calcification and 0 for absence of calcification, with a maximum score of 8 (Adragao et al., 2004). Finally, Hashimoto et al. validated a method to quantitate aortic arch calcification from 0 to 3, which

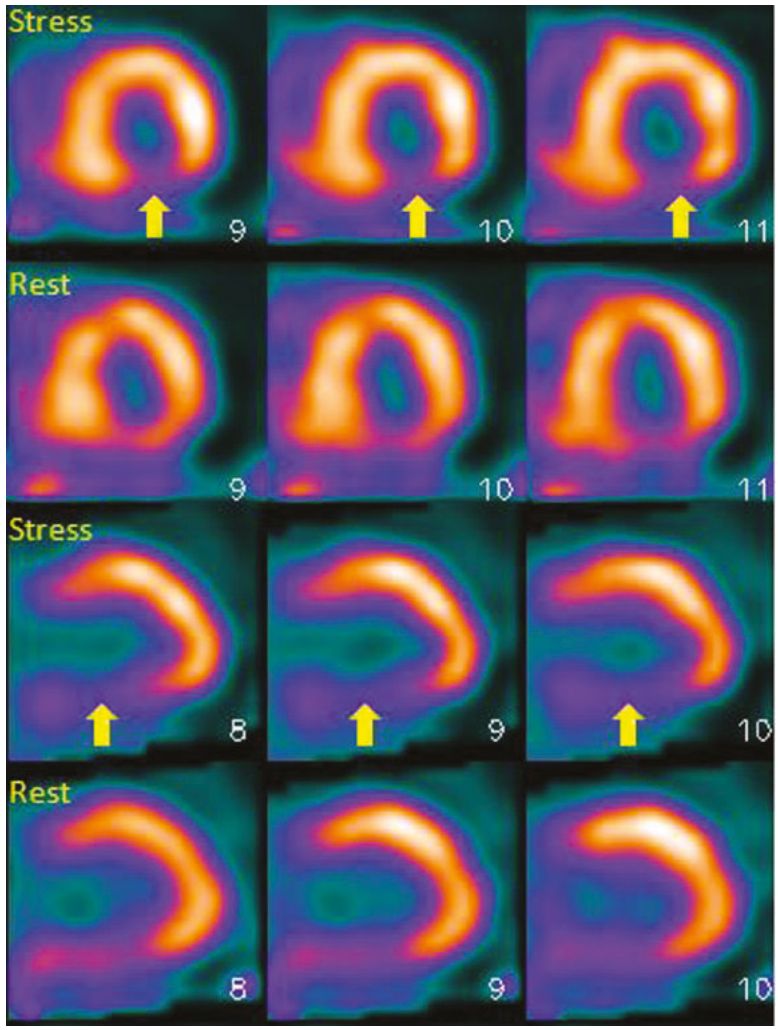

Fig. 116.3 Stress and rest SPECT images of a patient with end-stage renal disease being evaluated for renal transplantation. After stress there is a perfusion abnormality in the inferior and basal segments of the left ventricle (arrows). The perfusion abnormality is only partially reversible at rest, suggesting a combination of scar from prior myocardial infarction and ischaemia in the territory of the right coronary artery.

demonstrated a good correlation with CT measurements of aortic calcification (Hashimoto et al., 2009).

All scores have been shown to carry a prognostic value in CKD patients. In the study by Okuno et al., 515 maintenance haemodialysis patients were followed for 51 ± 17 months after undergoing a lateral abdominal X-ray for detection of abdominal aorta calcification (AAC) (Okuno et al., 2007). During this period there were 103 deaths from all causes (41 were from cardiovascular disease) and the cardiovascular event rate was greater in patients with AAC (27.8% vs 9.8% death rate; and 11.6% vs 3.1% cardiovascular event rate, respectively). Kaplan–Meier analysis showed that both all-cause and cardiovascular mortality were significantly greater in patients with AAC compared to those without ($P < 0.0001$, log-rank test).

In a multicentre study conducted in 47 European dialysis centres, 1084 dialysis patients were submitted to AAC scoring and measurement of carotid-femoral pulse wave velocity (PWV) (Verbeke et al., 2010). During a 2-year follow-up, there were 234 deaths and 91 non-fatal cardiovascular events. The risk of an adverse event increased 3.7-fold in patients with an AAC score of 5–15 (middle tertile) and 8.6-fold in patients with a score of 16–24 (top tertile) compared with the lowest tertile. Similarly, an X-ray score based on the number of calcified limb arteries was independently associated with coronary disease events ($P < 0.008$), peripheral arterial disease events ($P < 0.001$), and cardiovascular hospitalizations ($P = 0.02$) (Adragao et al., 2004).

Finally, Inoue et al. retrospectively evaluated a semi-quantitative aortic arch score as a predictor of events in 197 patients undergoing chronic haemodialysis (Inoue et al., 2012). During a follow-up period of 69 ± 45 months, 89 patients suffered a cardiovascular event and the score was a significant independent predictor of an adverse outcome. Additionally, the progression of aortic arch calcification was a predictor of all-cause and cardiovascular mortality in another study of 65 patients on haemodialysis (Ogawa et al., 2010).

As mentioned earlier in this chapter, in a cross-sectional study, Bellasi et al. showed a good correlation between the AAC score described by Kauppila et al. (1997) and CAC burden assessed by cardiac CT, in 140 chronic haemodialysis patients (Bellasi et al., 2006). These findings showed that a simple imaging method such as planar X-rays can be utilized to provide valid diagnostic and prognostic data in patients with CKD and could therefore play an

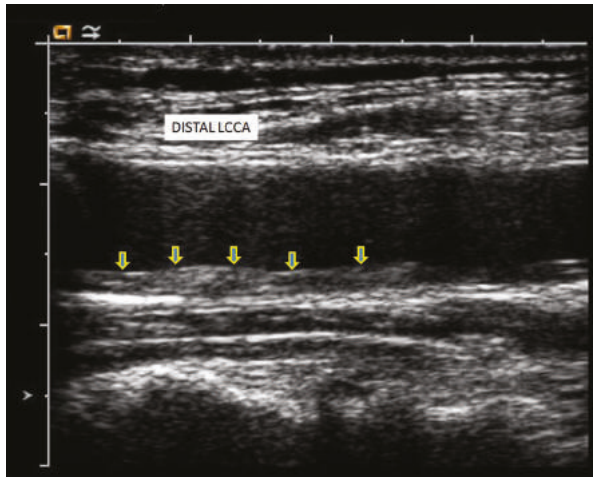

Fig. 116.4 Long-axis bidimensional ultrasound view of the left common carotid artery showing increased intima-media thickness of the far wall of the vessel (arrows).

important role in the management of cardiovascular diseases in CKD patients. Advantages of the planar X-ray techniques include wide availability, ease of performance, low cost, and low radiation exposure. However, given their qualitative or semi-quantitative nature, their reproducibility is limited and highly operator dependent.

Ultrasonography

Carotid and ilio-femoral artery imaging

The ease of access of superficial vessels such as the carotid and ilio-femoral arteries, the non-invasive nature and relatively low cost of ultrasound (US)-based imaging methodologies and the ability to perform in-office evaluations make this technology a useful screening method for vascular disease in CKD. Duplex ultrasonography (bidimensional imaging with Doppler flow measurements) has been utilized for several years to estimate the severity of arterial luminal stenosis. However, besides quantification of stenosis, vascular ultrasonography can be used to assess cardiovascular risk via other indirect markers of disease.

Quantification of carotid stenosis by Duplex is helpful in selecting the most appropriate CKD patients for endarterectomy. Recent evidence suggests that endarterectomy for severe carotid stenosis is more effective in lowering the risk of stroke in patients with mild-to-moderate CKD than in patients from the general population (number needed to treat to avoid one stroke: four for CKD patients and 10 for patients with normal renal function) (Mathew et al., 2009). Nevertheless, more severe CKD states show worse prognosis with severe carotid stenosis than in cases with normal renal function (Tarakji et al., 2006). In a cohort of 1011 patients Debind and Van Den Brande reported that perioperative mortality was significantly higher in dialysis patients undergoing endarterectomy compared to patients with normal renal function (3.9% vs 1.0%, P = 0.013) (Debing and Van den Brande, 2006). Multivariate logistic regression analysis showed that haemodialysis was the best independent predictor of 30-day mortality (odds ratio = 3.76, P = 0.032). Duplex US has also been used very successfully to assess the severity of peripheral vascular disease (Hosokawa et al., 2005), as well as to follow the status of a renal graft after transplantation. In a retrospective evaluation of 113 kidney transplant patients, abnormal Duplex results showed a correlation with histopathological changes; interlobar arteries showed atypical ultrasonographic changes that correlated with the presence of interstitial fibrosis/tubular atrophy and vascular/glomerular sclerosis on biopsy (Gao et al., 2011).

Arterial intima-media thickness (IMT) was first quantified by B-mode US in the femoral arteries in the late 1980s. It quickly became known as a surrogate marker of subclinical atherosclerosis and several studies established the value of carotid artery IMT (Fig. 116.4) as an independent and non-invasive marker of risk of atherosclerotic events and stroke in the general population. Carotid IMT measurement has been applied, although not extensively, to the study of vascular pathology in patients with CKD (Tanaka et al., 2012). Increased carotid IMT has been linked with declining renal function. In a study of 1003 patients with CKD a mild reduction in eGFR (mean 67.9 mL/min/1.73 m^2) was associated with an increase in carotid IMT; the association was independent of classical atherosclerosis risk factors and the presence of proteinuria (Tanaka et al., 2012). Other investigators confirmed that this association is independent of risk factors such as body mass index, smoking, hypertension, dyslipidaemia, and diabetes (Kawamoto et al., 2008); however, in at least one study there was no independent association between IMT and CKD stages (Zhang et al., 2007).

During a mean follow-up of 29 months, Benedetto et al. showed a close association of baseline IMT with the occurrence of cardiovascular and all-cause mortality in 138 haemodialysis patients (Benedetto et al., 2001). Nishizawa et al. followed prospectively 438 haemodialysis patients for an average of 30 months and recorded 82 deaths, of which 44 were cardiovascular (Nishizawa et al., 2003). Patients with moderately increased carotid IMT (1.0–2.0 mm) and those with severely increased IMT (≥ 2.0 mm) showed a significantly higher risk of death from cardiovascular causes. Szeto et al. measured carotid IMT in 203 Chinese patients with stage 3–4 CKD and followed them for 48 months (Szeto et al., 2007). The cardiovascular event-free survival was 94.4%, 89.8%, 77.7%, and 65.9% for the 1st to the 4th IMT quartile, respectively (log rank test, P = 0.006). Each quartile of IMT conferred an additional 41.6% (95% CI 6.4–88.4%; P = 0.017) excess hazard of cardiovascular events.

When performing bidimensional ultrasound imaging to measure IMT, a localized wall thickness > 1.5 mm is considered evidence of focal atherosclerotic plaque. Carotid plaques, and especially echolucent ones, purportedly representing lipid-rich plaques, have been associated with a high risk of stroke and cardiovascular events in the general population. In a histological study of specimens collected during carotid endarterectomy performed for severe vessel stenosis (> 70%), the composition of carotid plaques of 107 patients on dialysis was characterized by a high content of calcium (Fig. 116.5), a low collagen content, and no increase in non-calcified plaque frequency compared to patients with normal renal function (Pelisek et al., 2010). The presence of plaques carries an adverse prognostic value in CKD, as well as in patients with normal renal function. In an observational study, 167 chronic haemodialysis patients were followed for an average of 13 years after having been submitted to carotid artery imaging for identification of focal plaques (both calcified and non-calcified) (Schwaiger et al., 2006). The investigators reported that cardiovascular events increased proportional to the number of plaques (from 21% for those without plaques to 43% for

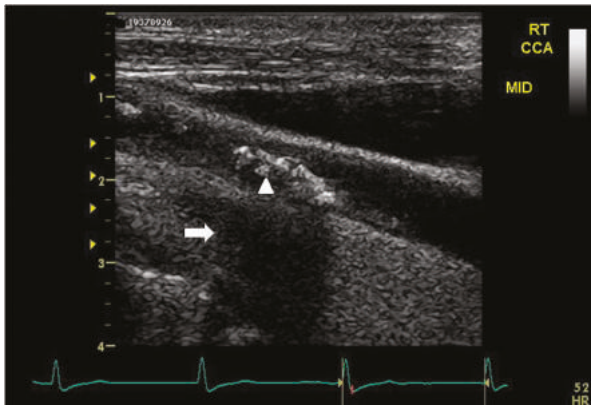

Fig. 116.5 Long-axis bidimensional ultrasound view of the right common carotid artery showing a densely calcified atherosclerotic plaque (arrow head) casting a shadow on the vessel wall behind it (arrow).

those with the largest number of plaques; P = 0.005). The number of plaques was also associated with the rapidity with which an event occurred after the index imaging test.

In a study investigating the prognostic value of the progression of IMT and carotid plaques in 103 haemodialysis patients, the appearance of new plaques was largely independent of changes in IMT; furthermore the development of new plaques was an independent predictor of incident cardiovascular events after adjustment for baseline plaque burden and other risk factors, while IMT was not (Benedetto et al., 2008). The growth rate of new atherosclerotic plaques was significantly associated with all-cause mortality (HR (one plaque/year increase) 1.25; 95% CI, 1.04–1.50; P = 0.02) and the occurrence of fatal and nonfatal cardiovascular events (HR (one plaque/year increase) 1.32; 95% CI, 1.14–1.52; P = 0.001). Therefore, both mortality and cardiovascular events were more frequent in patients forming new plaques (21 deaths per 100 patient-years and 35 cardiovascular events per 100 patient-years) than in those who did not (10 deaths per 100 patient-years and 13 cardiovascular events per 100 patient-years).

Bidimensional ultrasonography imaging provides an opportunity to qualitatively or semi-quantitatively evaluate the presence and extent of arterial calcification. A simple score based on the number of arterial sites showing calcification was devised for this purpose for patients suffering from CKD (Blacher et al., 2001). The score is based on a combination of US and planar X-ray techniques to detect and quantify arterial calcification: it is computed by adding a factor of 1 for the presence of calcification at each of the following sites: common carotid arteries, abdominal aorta, ilio-femoral arteries, and lower limb arteries. The total score varies from 0 (complete absence of calcification) to 4 (calcification is present at each of the above sites). Blacher et al. (2001) used this method to follow 110 haemodialysis patients for 53 ± 21 months in an observational prospective study. There was a stepwise increase in risk of death for each numerical increase in score.

Limited evidence suggests that an increased IMT and the presence of carotid plaques are associated with the burden of coronary artery calcium in CKD patients. In a cross-sectional study of 47 maintenance haemodialysis subjects, 70% of the patients showed CAC (mean score: 1055 ± 232) and 80% had an increased IMT (mean thickness: 0.96 ± 0.21 mm), as well as carotid plaques. The investigators described a positive correlation between the thickness of atherosclerotic plaques and CAC (P = 0.001) (Kurnatowska et al., 2010). In a retrospective evaluation in 91 CKD stage 5 patients listed for kidney transplant, 81% (N = 74) of the patients had carotid plaques and their presence was significantly associated with the severity of CAC in univariate analysis (P = 0.008); this association remained significant after adjustment for age, gender, race, CKD aetiology, and dialysis vintage (P = 0.025) (D'Marco et al., 2011). These findings suggest that measurement of IMT and detection of carotid plaques could serve as a surrogate marker for CAC in CKD (Yildiz et al., 2004).

Like all other non-invasive imaging techniques, bidimensional ultrasonography cannot be used to differentiate intima from media calcification; however, it is fully non-invasive, widely available, and its cost is moderate.

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) has become established as the most accurate non-invasive method to assess left ventricular mass, volume, and ejection fraction without need for contrast administration. CMR further allows the assessment of severity of valvular regurgitation and stenosis with a high degree of accuracy (Stewart et al., 1999).

Similarly, magnetic resonance angiography (MRA) provides high-quality imaging of the aorta and peripheral vessels and has in many cases replaced conventional invasive angiography. The obvious advantage of MRA over conventional angiography and CT angiography is that it does not require iodine-based contrast media and does not use ionizing radiation. Nonetheless, the paramagnetic medium gadolinium, used for vascular imaging and delayed enhancement of the myocardium to demonstrate the presence of scar and inflammation, has been associated with the occurrence of a lethal complication (nephrogenic systemic fibrosis) in advanced CKD and is therefore contraindicated in these patients. The application of specific flow-dependent sequences (i.e. time-of-flight) allows imaging of short vascular segments (typically the carotid arteries) without the need for intravascular contract injection; this renders non-contrast-enhanced MRA ideal for the evaluation of patients with impaired renal function. In a retrospective study of 104 patients with end-stage renal disease, contrast-enhanced MRA (Fig. 116.6) showed an excellent negative and a good positive predictive value for the diagnosis of obstructive peripheral arterial disease, despite an extremely low complication rate (Perriss et al., 2005). Hence, if carefully planned, MRA to assess severity of peripheral arterial disease may be safe in some CKD patients.

Finally, cardiovascular MR has been demonstrated to be an accurate method for assessment of aortic distensibility and stiffness in the general population and CKD patients. Zimmerli et al. reported that in the absence of symptomatic CAD, patients with CKD have significantly reduced aortic compliance compared to normal subjects as measured by magnetic resonance imaging (Zimmerli et al., 2007).

Invasive studies

Angiography

Invasive coronary angiography (CA) remains the gold standard for the assessment of obstructive coronary and peripheral artery disease in the general population and in CKD patients. Patients

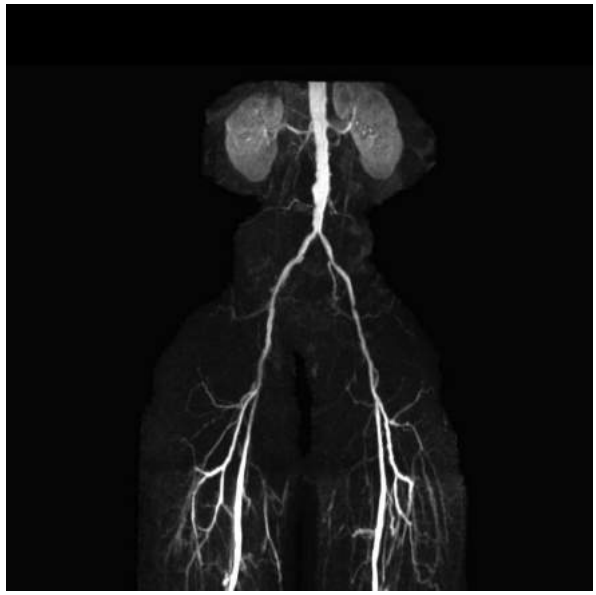

Fig. 116.6 Magnetic resonance angiography of the abdominal aorta, iliac, and femoral arteries (maximal intensity projection technique). The image shows severe stenosis of the aortic bifurcation and several areas of critical stenosis of the superficial femoral arteries bilaterally.

with CKD tend to have more severe and more extensive obstructive CAD than patients with normal renal function (Liu et al., 2012). Chonchol et al. reported an increasing prevalence of CAD with decreasing levels of renal function (51% in patients with eGFR ≥ 90 mL/min/1.73 m^2 and 84% with eGFR < 30 mL/min/1.73 m^2; P = 0.0046). CKD was associated with a greater likelihood of obstructive CAD even after logistic regression analyses controlling for demographic and comorbidity factors (Chonchol et al., 2008). The presence of obstructive CAD has a significant prognostic impact in patients with CKD. Gowdak et al. evaluated 301 patients receiving haemodialysis and awaiting kidney transplant, and found obstructive CAD in 136 patients. Independent predictors of obstructive CAD were a history of diabetes mellitus, peripheral arterial disease, and prior myocardial infarction. After 32 months of follow-up, the incidence of major adverse coronary events was 45.2% in patients with CAD and 18.1% in those without CAD (P < 0.0001). Since obstructive CAD was detectable in < 50% of the patients, and in virtually none of the patients without one of the three predictors listed above, invasive angiography could not be recommended as the first-line modality to diagnose CAD in a very sizeable proportion of CKD patients (Gowdaka et al., 2007).

In another investigation, 167 CKD-5D patients were submitted to clinical examination and MPI; invasive angiography was performed in a selected group of patients (De Lima et al., 2010). Absence of anginal symptoms and ischaemia on MPI were associated with an excellent outcome, while the presence of ischaemia, and especially the combination of ischaemia and obstructive CAD was associated with a high incidence of adverse events. Enkiri et al. suggested that the presence of CAD on invasive angiography is a better predictor of outcome than abnormal results on non-invasive testing in patients with advanced stages of CKD. In a small study of 57 patients listed for kidney transplantation, the event-free survival after 3 years of follow-up was 50% and 73% for patients with and without CAD on invasive angiography, while non-invasive imaging failed to predict events effectively (Enkiri et al., 2010).

Intravascular ultrasound

Intravascular ultrasound (IVUS) is an invasive, catheter-based imaging modality, which provides high-resolution cross-sectional images of the coronary arteries. The IVUS catheters emit high-frequency ultrasound waves and the reflection of such waves is used to reconstruct high-resolution images of the vessel wall (Fig. 116.7). Conventional invasive angiography has obvious limitations in the diagnosis of coronary atherosclerosis. Angiography displays only an opacified luminal silhouette, while IVUS permits imaging of both the lumen and vessel wall and allows some characterization of plaque composition (Bourantas et al., 2011). Indeed, it is fairly easy to differentiate an echolucent (dark), lipid-rich plaque from a dense, bright, echo-reflective, calcified plaque. However, when intimal calcification is present, it casts a shadow that may obscure the presence of underlying medial calcification, thus rendering the identification of the two types of calcification difficult, even by IVUS. Although IVUS provides accurate quantitative and qualitative information, it is not routinely used during coronary angiography or angioplasty procedures, because of its risk:benefit ratio (cost, length of procedure, risk of complications). Nevertheless, there are situations where IVUS is extremely valuable for both diagnosis and management of CAD, such as accurate assessment of luminal stenosis, appropriate deployment of an intracoronary stent (Bourantas et al., 2010), and visualization of the calcium content of an atherosclerotic plaque, to plan the appropriate type of intervention (Maehara and Fitzgerald, 2000). Indeed, in the presence of extensive intimal calcification, dissection of the coronary artery wall can be expected during an angioplasty procedure (Fitzgerald et al., 1992).

The impact of renal function on coronary plaque composition has been evaluated with IVUS. Gruber et al. reported that patients with CKD on dialysis have more positive (outward) remodelling of the coronary arteries and larger arcs of calcium (i.e. degrees along the vessel luminal circumference covered by calcium) than patients with eGFR >70, 50–69, and <50 mL/min/1.73 m^2 (P < 0.05 for all comparisons) (Gruberg et al., 2005). In an IVUS study of 89 CKD patients, the lipid volume was larger and the fibrous volume was smaller in coronary plaques of patients with an eGFR < 60 mL/min/1.73 m^2 compared to those with an eGFR > 60 mL/min/1.73 m^2 (Miyagi et al., 2009). Recently, Kono et al. identified the characteristics of coronary plaques in 78 patients with increasing severity of CKD (Kono et al., 2012). Using virtual histology-IVUS, researchers found a decreased necrotic core/dense calcium ratio in advanced CKD. Thus, plaque composition of coronary plaques changed from fragile (core rich in necrotic and pultaceous material) to extensively calcified as the renal function decreased. Of note, total plaque volume was significantly higher in patients with acute myocardial infarction and unstable angina pectoris than in those with stable angina pectoris. Finally, in a subanalysis of 989 patients recruited in several IVUS trials, there was no difference in atheroma volume at baseline and no difference in atheroma progression between patients with an eGFR < 60 mL/min/1.73 m^2 or > 60 mL/min/1.73 m^2 during follow-up (Nicholls et al., 2007).

Optical coherence tomography

Optical coherence tomography (OCT) is a catheter-based imaging technique that utilizes advanced photonics and fibreoptic wires to

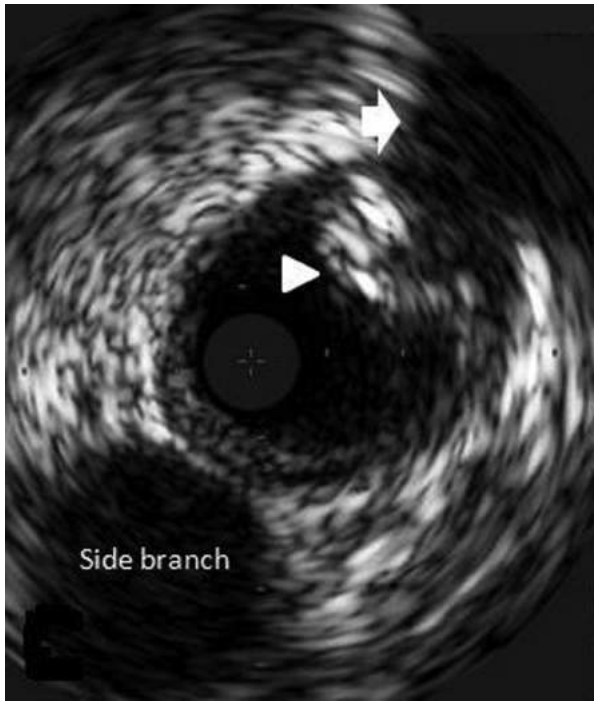

Fig. 116.7 Intravascular ultrasound image of a coronary artery of a patient with CKD showing dense calcification of an atherosclerotic plaque (arrow head) casting a shadow on the vessel wall behind it (arrow).

characterize tissue composition on a microscopic scale (Takashi and Takashi, 2008). The fibreoptic wire emits light at a predetermined wavelength towards the vessel wall and a mirror; when the reflected beams coincide an interference occurs. Eventually an image is obtained by recording the backscatter of light from the vessel wall (Bezerra et al., 2009; Eshtehardi et al., 2011). This method provides IVUS-like images but with approximately 10 times higher resolution than IVUS, and more detailed structural information of the arterial wall that any other clinically available modality (Takashi and Takashi, 2008) (Fig. 116.8). Despite its high resolution, OCT is limited by its tissue penetration of only 1–3 mm (Regar et al., 2010). The main clinical application of OCT in the general population is the assessment of coronary atherosclerosis and plaque characterization, the identification of intravascular thrombus, as well as to guide stents deployment. Several studies have compared OCT and *ex vivo* coronary histology in the general population. The reported sensitivity and specificity of OCT for detecting thin-capped fibroatheromas (i.e. prone to rupture causing an acute intravascular thrombosis) are 92% and 75% respectively (Yabushita, 2002). OCT has also been used to evaluate the effect of medical interventions, such as statin therapy, on the atherosclerotic plaque burden and composition. At this time there is no information regarding the specific use of OCT for the study of coronary artery disease in CKD. Investigators from Switzerland recently evaluated 32 renal arteries after a denervation procedure for treatment of resistant hypertension (Templin et al., 2013). The presence of thrombus was high following ablation (67% vs 18% prior to ablation, $P < 0.001$). Endothelial-intimal oedema (96% of the cases) and vasospasm (42%) were also frequently noted. The authors concluded that OCT visualizes vascular lesions not apparent on angiography.

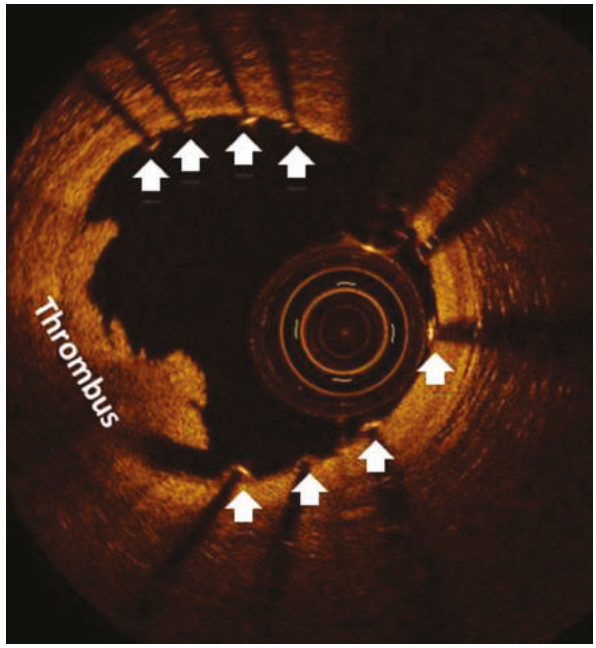

Fig. 116.8 Intracoronary optical coherence tomography image of a patient with prior stent implantation (arrows point at the stent's struts) demonstrating the presence of thrombus in the lumen of the coronary artery.

Angioscopy

This technique utilizes an angioscope (i.e. intravascular endoscope) to provide direct visualization of the vessel lumen and detailed information regarding the characteristics of the intimal surface of the artery, such as plaque surface colour, presence of thrombus, and plaque integrity (Ishibashi et al., 2006). Furthermore, angioscopy has been used to evaluate the effect of lipid-lowering drugs on atherosclerosis disease burden (Ohsawa et al., 2002) and to elucidate the mechanism of acute coronary syndromes.

Angioscopy has been employed in patients with CKD to evaluate the renal arteries of an allograft before kidney transplantation, in order to reduce the incidence of graft injuries. L'Hermite et al. (1990) reported a reduction in the incidence of post-transplant renal artery stenosis in 60 consecutive transplants with routine performance of allograft angioscopy prior to surgery. Burgos et al. performed angioscopy in 25 kidney allografts and found subintimal hematomas, intimal tear, atheromatous plaques, venous thrombosis, and vascular injuries that needed microsurgical vascular reconstruction before transplantation in 48% of them (Burgos et al., 1998). Angioscopy is also used in CKD to help performing native arteriovenous fistulas in individuals with a difficult access extremity (Roberts et al., 2005).

Angioscopy relies on transient balloon occlusion of the vessel, which may cause short lived periods of ischaemia, and is restricted to the surface morphology of lesions therefore it is unable to provide information on plaque composition.

Conclusions

The field of vascular disease in CKD is extensive and the vascular pathology of these patients is severe. Numerous imaging modalities are available to help the physician make an accurate diagnosis

and choose the most appropriate therapeutic approach. Each of the modalities discussed in this chapter offers distinct advantages and disadvantages and requires a certain degree of proficiency for appropriate implementation and interpretation. Some of these modalities offer an insight into the mechanisms of vascular disease in CKD, although much remains to be discovered in the field.

References

Achenbach, S. and Raggi, P. (2010). Imaging of coronary atherosclerosis by computed tomography. *Eur Heart J*, 31(12), 1442–8.

Adragao, T., Pires, A., Lucas, C., *et al.* (2004). A simple vascular calcification score predicts cardiovascular risk in haemodialysis patients. *Nephrol Dial Transplant*, 19(6), 1480–8.

Agatston, A., Janowitz, W., Hildner, F. J., *et al.* (1990). Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*, 15(4), 827–32.

Alqaisi, F., Albadarin, F., Jaffery, Z., *et al.* (2008). Prognostic predictors and outcomes in patients with abnormal myocardial perfusion imaging and angiographically insignificant coronary artery disease. *J Nucl Cardiol*, 15(6), 754–61.

Bellasi, A., Ferramosca, E., Muntner, P., *et al.* (2006). Correlation of simple imaging tests and coronary artery calcium measured by computed tomography in hemodialysis patients. *Kidney Int*, 70(9), 1623–8.

Benedetto, F. A., Mallamaci, F., Tripepi, G., *et al.* (2001). Prognostic value of ultrasonographic measurement of carotid intima media thickness in dialysis patients. *J Am Soc Nephrol*, 12, 2458–64.

Benedetto, F. A., Tripepi, G., Mallamaci, F., *et al.* (2008). Rate of atherosclerotic plaque formation predicts cardiovascular events in ESRD. *J Am Soc Nephrol*, 19(4), 757–63.

Bezerra, H. G., Costa, M. A., Guagliumi, G., *et al.* (2009). Intracoronary optical coherence tomography: a comprehensive review. *JACC Cardiovasc Interv*, 2(11), 1035–46.

Blacher, J., Guerin, A. P., Pannier, B., *et al.* (2001). Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension*, 38(4), 938–42.

Block, G. A., Raggi, P., Bellasi, A., *et al.* (2007). Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int*, 71(5), 438–41.

Bourantas, C., Naka, K., Garg, S., *et al.* (2010). Clinical indications for intravascular ultrasound imaging. *Echocardiography*, 27(10), 1282–90.

Bourantas, C. V., Garg, S., Naka, K. K., *et al.* (2011). Focus on the research utility of intravascular ultrasound—comparison with other invasive modalities. *Cardiovasc Ultrasound*, 9(1), 2.

Braun, J., Oldendorf, M., Moshage, W., *et al.* (1996). Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. *J Am Kidney Dis*, 27, 394–401.

Budoff, M. J., Achenbach, S., Blumenthal, R. S., *et al.* (2006). Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation*, 114(16), 1761–91.

Budoff, M. J., Shaw, L. J., Liu, S. T., *et al.* (2007). Long-term prognosis associated with coronary calcification. *J Am Coll Cardiol*, 49(18), 1860–70.

Burgos, F., Marcen, R., Pascual, J., *et al.* (1998). Value of backtable angioscopy previous to kidney transplantation. *Transplant Proc*, 30, 2294.

Callister, T., Cooil, B., Raya, S. P., *et al.* (1998). Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. *Radiology*, 208, 807–14.

Chonchol, M., Whittle, J., Desbien, A., *et al.* (2008). Chronic kidney disease is associated with angiographic coronary artery disease. *Am J Nephrol*, 28(2), 354–60.

Cho, I., Min, H., Chun, E. J., *et al.* (2010). Coronary atherosclerosis detected by coronary CT angiography in asymptomatic subjects with early chronic kidney disease. *Atherosclerosis*, 208(2), 406–11.

Chow, B. J. W., Wells, G. A., Chen, L., *et al.* (2010). Prognostic value of 64-slice cardiac computed tomography. *J Am Coll Cardiol*, 55(10), 1017–28.

D'Marco, L., Karohl, C., and Raggi, P. (2011). Carotid plaques predict presence and severity of coronary artery calcium in chronic kidney disease [Abstract]. *J Am Soc Nephrol*, 22, 158–9.

De Lima, J., Sabbaga, E., Vieira, M. L., *et al.* (2003). Coronary angiography is the best predictor of events in renal transplant candidates compared with noninvasive testing. *Hypertension*, 42(3), 263–8.

De Lima, J. J. G., Gowdak, L. H. W., de Paula, F. J., *et al.* (2010). Influence of coronary artery disease assessment and treatment in the incidence of cardiac events in renal transplant recipients. *Clin Transplant*, 24(4), 474–80.

Debing, E. and Van den Brande, P. (2006). Chronic renal insufficiency and risk of early mortality in patients undergoing carotid endarterectomy. *Ann Vasc Surg*, 20(5), 609–13.

DeLoach, S. S., Joffe, M. M., Mai, X., *et al.* (2008). Aortic calcification predicts cardiovascular events and all-cause mortality in renal transplantation. *Nephrol Dial Transplant*, 24(4), 1314–19.

Drüeke, T. B. and Massy, Z. A. (2010). Atherosclerosis in CKD: differences from the general population. *Nat Rev Nephrol*, 6(12), 723–35.

Enkiri, S. A., Taylor, A. M., Keeley, E. C., *et al.* (2010). Coronary angiography is a better predictor of mortality than noninvasive testing in patients evaluated for renal transplantation. *Catheter Cardiovasc Interv*, 76(6), 795–801.

Eshtehardi, P., Luke, J., McDaniel, M. C., *et al.* (2011). Intravascular imaging tools in the cardiac catheterization laboratory: comprehensive assessment of anatomy and physiology. *J Cardiovasc Transl Res*, 4(4), 393–403.

Fitzgerald, P., Ports, T., and Yock, P. G. (1992). Contribution of localized calcium deposits to dissection after angioplasty. An observational study using intravascular ultrasound. *Circulation*, 86, 64–70.

Gao, J., Rubin, J., Xiang, D. Y., *et al.* (2011). Doppler parameters in renal transplant dysfunction: correlations with histopathologic changes. *J Ultrasound Med*, 30(2), 169–75.

Gowdaka, L., de Paula, F., César, L. A., *et al.* (2007). Screening for significant coronary artery disease in high-risk renal transplant candidates. *Coron Artery Dis*, 18, 553–8.

Gruberg, L., Rai, P., Mintz, G. S., *et al.* (2005). Impact of renal function on coronary plaque morphology and morphometry in patients with chronic renal insufficiency as determined by intravascular ultrasound volumetric analysis. *Am J Cardiol*, 96(7), 892–6.

Hanada, S., Ando, R., Naito, S., *et al.* (2010). Assessment and significance of abdominal aortic calcification in chronic kidney disease. *Nephrol Dial Transplant*, 25(6), 1888–95.

Hashimoto, H., Katsuya, L., Hashimoto, M., *et al.* (2009). Validity and usefulness of aortic arch calcification in chest X-ray. *J Atheroscler Thromb*, 16(3), 256–64.

Hatta, T., Nishimura, S., and Nishimura, T. (2009). Prognostic risk stratification of myocardial ischaemia evaluated by gated myocardial perfusion SPECT in patients with chronic kidney disease. *Eur J Nucl Med Mol Imaging*, 36(11), 1835–41.

Hoffmann, U., Moselewski, F., Cury, R. C., *et al.* (2004). Predictive value of 16-slice multidetector spiral computed tomography to detect significant obstructive coronary artery disease in patients at high risk for coronary artery disease: patient- versus segment-based analysis. *Circulation*, 110(17), 2638–43.

Hosokawa, K., Kuriyama, S., Astumi, Y., *et al.* (2005). Incidence of peripheral arteriosclerotic complications of the lower extremities in diabetic patients with chronic renal failure. *Ther Apher Dial*, 9(2), 161–6.

Inoue, T., Ogawa, T., Ishida, H., *et al.* (2012). Aortic arch calcification evaluated on chest X-ray is a strong independent predictor of cardiovascular events in chronic hemodialysis patients. *Heart Vessels*, 27(2), 135–42.

Ishibashi, F., Aziz, K., Abela, G. S., *et al.* (2006). Update on coronary angioscopy: review of a 20-year experience and potential application for detection of vulnerable plaque. *J Interven Cardiol*, 19, 17–25.

Karohl, C. and Raggi, P. (2011). Cardiovascular imaging in patients with chronic kidney disease. *Blood Purif*, 31(1–3), 130–7.

Kauppila, L., Polak, J., Cupples, L. A., *et al.* (1997). New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: a 25-year follow-up study. *Atherosclerosis*, 132, 245–50.

Kawamoto, R., Ohtsuka, N., Kusunoki, T., *et al.* (2008). An association between the estimated glomerular filtration rate and carotid atherosclerosis. *Intern Med*, 47(5), 391–8.

K/DOQI Workgroup (2005). K/DOQI clinical practice guidelines on cardiovascular disease in dialysis patients. *Am J Kidney Dis*, 45 Suppl 3, 16–153.

Kono, K., Fujii, H., Nakai, K., *et al.* (2012). Composition and plaque patterns of coronary culprit lesions and clinical characteristics of patients with chronic kidney disease. *Kidney Int*, 82(3), 344–51.

Kramer, H., Toto, R., Peshock, R., *et al.* (2005). Association between chronic kidney disease and coronary artery calcification: The Dallas Heart Study. *J Am Soc Nephrol*, 16(2), 507–13.

Kurnatowska, I., Grzelak, P., Stefańczyk, L., *et al.* (2010). Tight relations between coronary calcification and atherosclerotic lesions in the carotid artery in chronic dialysis patients. *Nephrology (Carlton)*, 15(2), 184–9.

L'Hermite, J., Hubert, J., Trackoen, G., *et al.* (1990). Value of arterioscopy in the prevention of renal artery stenosis after transplantation. *Ann Urol*, 24(5), 415–16.

Liu, H., Yan, L., Ma, G. S., *et al.* (2012). Association of chronic kidney disease and coronary artery disease in 1,010 consecutive patients undergoing coronary angiography. *J Nephrol*, 25(2), 219–24.

London, G. M., Guerin, A. P., Marchais, S. J., *et al.* (2003). Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant*, 18(9), 1731–40.

Maehara, A. and Fitzgerald, P. (2000). Coronary calcification: assessment by intravascular ultrasound imaging. *Z Kardiol*, 89(Suppl 2), 112–16.

Mao, J., Karthikeyan, V., Poopat, C., *et al.* (2010). Coronary computed tomography angiography in dialysis patients undergoing pre-renal transplantation cardiac risk stratification. *Cardiol J*, 17(4), 349–61.

Mathew, A., Eliasziw, M., Devereaux, P. J., *et al.* (2009). Carotid endarterectomy benefits patients with CKD and symptomatic high-grade stenosis. *J Am Soc Nephrol*, 21(1), 145–52.

Matsuoka, M., Iseki, K., Tamashiro, M., *et al.* (2004). Impact of high coronary artery calcification score (CACS) on survival in patients on chronic hemodialysis. *Clin Exp Nephrol*, 8(1), 54–8.

Miyagi, M., Ishii, H., Murakami, R., *et al.* (2009). Impact of renal function on coronary plaque composition. *Nephrol Dial Transplant*, 25(1), 175–81.

Momose, M., Babazono, T., Kondo, C., *et al.* (2009). Prognostic significance of stress myocardial ECG-gated perfusion imaging in asymptomatic patients with diabetic chronic kidney disease on initiation of haemodialysis. *Eur J Nucl Med Mol Imaging*, 36(8), 1315–21.

Nicholls, S., Tuzcu, E., Hsu, A., *et al.* (2007). Comparison of coronary atherosclerotic volume in patients with glomerular filtration rates ≤60 versus >60 ml/min/1.73 m2: A meta-analysis of intravascular ultrasound studies. *Am J Cardiol*, 99(6), 813–16.

Nishizawa, Y., Shoji, T., Maekawa, K., *et al.* (2003). Intima-media thickness of carotid artery predicts cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis*, 41(S3), S76–9.

Ogawa, T., Ishida, H., Akamatsu, M., *et al.* (2010). Relation of oral 1α-hydroxy vitamin D3 to the progression of aortic arch calcification in hemodialysis patients. *Heart Vessels*, 25(1), 1–6.

Oh, J., Wunsch, R., Turzer, M., *et al.* (2002). Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. *Circulation*, 106(1), 100–5.

Ohsawa, H., Uchida, Y., Fujimori, Y., *et al.* (2002). Angioscopic evaluation of stabilizing effects of an antilipemic agent, bezafibrate, on coronary plaques in patients with coronary artery disease. *Jpn Heart J*, 43, 319–31.

Okuno, S., Ishimura, E., Kitatani, K., *et al.* (2007). Presence of abdominal aortic calcification is significantly associated with all-cause and cardiovascular mortality in maintenance hemodialysis patients. *Am J Kidney Dis*, 49(3), 417–25.

Owen, D. R. J., Lindsay, A. C., Choudhury, R. P., *et al.* (2011). Imaging of atherosclerosis. *Ann Rev Med*, 62(1), 25–40.

Patel, A., Abo-Auda, W., Davis, J. M., *et al.* (2003). Prognostic value of myocardial perfusion imaging in predicting outcome after renal transplantation. *Am J Cardiol*, 92(2), 146–51.

Patel, R., Mark, P., Johnston, N., *et al.* (2008). Prognostic value of cardiovascular screening in potential renal transplant recipients: a single-center prospective observational study. *Am J Transplant*, 8(8), 1673–83.

Pelisek, J., Assadian, A., Sarkar, O., *et al.* (2010). Carotid plaque composition in chronic kidney disease: a retrospective analysis of patients undergoing carotid endarterectomy. *Eur J Vascular Endovasc Surg*, 39(1), 11–16.

Perriss, R., Løkkegaard, H., Løgager, V., *et al.* (2005). Preliminary experience with contrast-enhanced MR angiography in patients with end-stage renal failure. *Acad Radiol*, 12(5), 652–7.

Raggi, P., Boulay, A., Chasan-Taber, S., *et al.* (2002). Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol*, 39(4), 695–701.

Regar, E., van Soest, G., Bruining, N., *et al.* (2010). Optical coherence tomography in patients with acute coronary syndrome. *EuroIntervention*, 6 Suppl, 154–60.

Roberts, J., Sideman, M., and Jennings, W. C. (2005). The difficult hemodialysis access extremity: proximal radial arteriovenous fistulas and the role of angioscopy and valvulotomes. *Am J Surg*, 190(6), 877–82.

Rumberger, J. A. and Kaufman, L. (2003). A Rosetta stone for coronary calcium risk stratification: agatston, volume, and mass scores in 11,490 individuals. *AJR*, 181, 743–8.

Russo, D., Palmiero, G., De Blasio, A. P., *et al.* (2004). Coronary artery calcification in patients with CRF not undergoing dialysis. *Am J Kidney Dis*, 44(6), 1024–30.

Schwaiger, J., Lamina, C., Neyer, U., *et al.* (2006). Carotid plaques and their predictive value for cardiovascular disease and all-cause mortality in hemodialysis patients considering renal transplantation: a decade follow-up. *Am J Kidney Dis*, 47(5), 888–97.

Shantouf, R., Budoff, M., Ahmadi, N., *et al.* (2010). Total and individual coronary artery calcium scores as independent predictors of mortality in hemodialysis patients. *Am J Nephrol*, 31, 419–25.

Shareghi, S., Ahmadi, N., Young, E., *et al.* (2007). Prognostic significance of zero coronary calcium scores on cardiac computed tomography. *J Cardiovasc Comput Tomogr*, 1(3), 155–9.

Sigrist, M., Bungay, P., Taal, M. W., *et al.* (2006). Vascular calcification and cardiovascular function in chronic kidney disease. *Nephrol Dial Transplant*, 21(3), 707–14.

Stanford, W., Thompson, B., Burns, T. L., *et al.* (2004). Coronary artery calcium quantification at multi–detector row helical CT versus electron-beam CT. *Radiology*, 230, 397–402.

Stewart, G., Foster, J., Cowan, M., *et al.* (1999). Echocardiography overestimates left ventricular mass in hemodialysis patients relative to magnetic resonance imaging. *Kidney Int*, 56, 2248–53.

Szeto, C. C., Chow, K. M., Woo, K. S., *et al.* (2007). Carotid intima media thickness predicts cardiovascular diseases in Chinese predialysis patients with chronic kidney disease. *J Am Soc Nephrol*, 18(6), 1966–72.

Takashi, K. and Takashi, A. (2008). Recent advances in intracoronary imaging techniques: focus in optical coherence tomography. *Expert Rev Med Devices*, 5(6), 691–7.

Tanaka, M., Abe, Y., Furukado, S., *et al.* (2012). Chronic kidney disease and carotid atherosclerosis. *J Stroke Cerebrovasc Dis*, 21, 47–51.

Tarakji, A., McConaughy, A., and Nicholas, G. G. (2006). The risk of carotid endarterectomy in patients with chronic renal insufficiency. *Curr Surg*, 63(5), 326–9.

Templin, C., Jaguszewski, M., Ghadri, J. R., *et al.* (2013). Vascular lesions induced by renal nerve ablation as assessed by optical coherence tomography: pre- and post-procedural comparison with the Simplicity(R) catheter system and the EnligHTN multi-electrode renal denervation catheter. *Eur Heart J*, 34(28), 2141–8, 2148b.

Venkataraman, R., Hage, F., Dorfman, T., *et al.* (2008). Role of myocardial perfusion imaging in patients with end-stage renal disease undergoing coronary angiography. *Am J Cardiol*, 102(11), 1451–6.

Verbeke, F., Van Biesen, W., Honkanen, E., *et al.* (2010). Prognostic value of aortic stiffness and calcification for cardiovascular events and mortality

in dialysis patients: outcome of the calcification outcome in renal disease (CORD) study. *Clin J Am Soc Nephrol*, 6(1), 153–9.

Yabushita, H. (2002). Characterization of human atherosclerosis by optical coherence tomography. *Circulation*, 106(13), 1640–5.

Yildiz, A., Tepe, S., Oflaz, H., *et al*. (2004). Carotid atherosclerosis is a predictor of coronary calcification in chronic haemodialysis patients. *Nephrol Dial Transplant*, 19(4), 885–91.

Yiu, K. H., de Graaf, F. R., Schuijf, J. D., *et al*. (2011). Prognostic value of renal dysfunction for the prediction of outcome versus results of computed tomographic coronary angiography. *Am J Cardiol*, 108(7), 968–72.

Yiu, K. H., de Graaf, F. R., van Velzen, J. E., *et al*. (2013). Different value of coronary calcium score to predict obstructive coronary artery disease in patients with and without moderate chronic kidney disease. *Neth Heart J*, 21(7–8), 347–53.

Zhang, L., Zhao, F., Yang, Y., *et al*. (2007). Association between carotid artery intima-media thickness and early-stage CKD in a Chinese population. *Am J Kidney Dis*, 49(6), 786–92.

Zimmerli, L. U., Mark, P. B., Steedman, T., *et al*. (2007). Vascular function in patients with end-stage renal disease and/or coronary artery disease: a cardiac magnetic resonance imaging study. *Kidney Int*, 71(1), 68–73.

CHAPTER 117

Pathophysiology of chronic kidney disease-mineral and bone disorder

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Phosphate metabolism

Phosphate (P) is an essential mineral in the body, critical for many biological processes, including bone development and bone integrity, cell membrane phospholipid content and function, cell signalling, and energy metabolism. Total adult body store of P equals approximately 700 g. Of total body stores, 85% of P is found in bone, linked with calcium (Ca) as hydroxyapatite crystals, 14% intracellular, and only 1% in the extracellular space. Of extracellular P, 70% represents the organic P fraction, found mainly in phospholipids, and 30% is the inorganic fraction. Fifteen per cent of the inorganic P is bound to plasma proteins, and the rest is complexed with sodium, magnesium, and Ca or circulates in free monohydrogen or dihydrogen forms. The P concentration in the extracellular compartment is the result of the interactions among intestinal uptake, renal excretion, and exchanges with bone and the intracellular compartment (Uribarri et al., 2007).

The average P intake in a developed country population is 1000–1500 mg/day. Sixty to 80% of dietary P is absorbed in all intestinal segments, being maximal in the small intestine. Intestinal P absorption occurs via two routes: a paracellular pathway, involving tight junctions and driven by a passive diffusional flux, and an active, transcellular transport, involving the type II sodium-dependent P cotransporter Npt2b. The energy for this transport process is provided by the sodium gradient induced by the sodium-potassium ATPase cotransporter at the basolateral membrane (Craver et al., 2007). Besides Npt2b, two additional type III sodium-dependent P cotransporters, PiT1 and PiT2, have been found to be expressed in the intestine, but the precise role of these transporters remains to be determined (Sabbagh et al., 2009; Marks et al., 2010). The two major factors that regulate intestinal P absorption are dietary P and 1,25 dihydroxyvitamin D ($1,25(OH)_2D$), although other factors can also play a role, such as oestrogens, glucocorticoids, epidermal growth factor, metabolic acidosis, matrix extracellular phosphoglycoprotein, and fibroblast growth factor 23 (FGF23) (Borowitz and Granrud, 1992; Xu et al., 2001, 2003; Miyamoto et al., 2005; Stauberet al., 2005; Marks et al., 2008).

The kidney plays a major role in maintaining P balance by excreting the net amount of the absorbed P. As P is not significantly bound to albumin, most of the P is filtered freely at the glomerulus. At steady state, 80–90% of the filtered P is reabsorbed by the kidneys. Seventy to 80% of filtered P is reabsorbed in the proximal tubule through type II sodium-P cotransporters Npt2a and Npt2c, expressed at the apical membrane of renal proximal tubule cells. Knockout studies in mice showed that approximately 70% of the renal P absorption is mediated by Npt2a and 30% by Npt2c. Recently, type III P transporter PiT2 has been shown to contribute to P absorption in the proximal tubules. Double-knockout Npt2a/Npt2c mice still exhibit some renal P reabsorption, indicating a role for PiT2 in this process (Beck et al., 1998; Tenenhouse et al., 2003; Segawa et al., 2009; Villa-Bellosta et al., 2009). P transport across the basolateral membrane remains a poorly understood process. Several P transport pathways have been postulated, including a P-anion exchanger, passive diffusion, or P transport via type II sodium-P cotransporters.

Multiple factors have been shown to modulate renal P transport. Factors that stimulate P reabsorption include P depletion, insulin-like growth factor-1, growth hormone, thyroid hormone, and $1,25(OH)_2D$ (Kurnik and Hruska, 1985; Bianda et al., 1997; Villa-Bellosta et al., 2009; Ishiguro et al., 2010). Factors that inhibit P reabsorption include parathyroid hormone (PTH), FGF23, P loading, volume expansion, metabolic acidosis, glucocorticoids, and calcitonin (Laron et al., 1957; Ambuhl et al., 1998; Blaine et al., 2011). The main hormones that regulate renal P handling are PTH and FGF23.

Parathyroid hormone

PTH is an 84-amino acid protein, which is synthesized in the parathyroid glands and stored in secretory granules for release, in response to hypocalcaemia, hyperphosphataemia, and/or $1,25(OH)_2D$ deficiency. Following release, the circulating 1–84 PTH has a relatively short half-life in plasma, of just minutes, and is cleaved into amino-terminal, carboxy-terminal, and mid-region fragments, which are metabolized in the liver and kidney.

The regulation of PTH secretion in response to changes in ionized Ca is mediated by the Ca-sensing receptor (CaSR), which is a seven-membrane-spanning G-protein-coupled receptor. This

receptor is expressed in the parathyroid cells, thyroid C-cells, kidney, and likely bone. The CaSR is activated by elevations in extracellular Ca concentration, leading to inhibition of PTH secretion. High levels of $1,25(OH)_2D$ have a direct inhibitory effect on PTH gene transcription, as well as an indirect effect, by increasing intestinal Ca absorption. Hyperphosphataemia may affect the regulation of intracellular Ca in parathyroid cells, resulting in the inhibition of phospholipase A2 and diminished synthesis of arachidonic acid formation, the latter being a potent inhibitor of PTH release (Almaden et al., 2000). Hyperphosphataemia is also associated with reduced expression of the CaSR, thereby decreasing the ability of the parathyroid gland to respond to changes in ionized Ca (Ritter et al., 2002). In addition, high P intake induces parathyroid cell proliferation and growth through transforming growth factor alpha (TGF-α), mediated via the epidermal growth factor receptor, resulting in parathyroid hyperplasia and the development of secondary hyperparathyroidism (Cozzolino et al., 2005).

PTH binds to type I PTH receptor in proximal tubular cells, to activate cAMP-protein kinase A (AC-PKA) and the phospholipase C-protein kinase C (PKC) signal transduction pathways. Activation of both signalling pathways induces the internalization and catabolism of the sodium-P cotransporters Npt2a and Npt2c, resulting in P wasting. On the other hand, PTH upregulates the transient receptor potential vanilloid (TRPV) transportersTRPV5 and TRPV6, $calbindin_{28\ K}$, the Na^+/Ca^{2+} exchanger-1 (NCX1), and the plasma membrane calcium ATPase-1b (PMCA1b), which results in increased renal Ca reabsorption. In bone, PTH primarily utilizes the AC-PKA pathway in exerting both its catabolic and anabolic effects (Yang et al., 2007).

Fibroblast growth factor 23

FGF23 belongs to a group of molecules called phosphatonins, which are hormones that regulate P excretion. In addition to FGF23, other phosphatonins have been identified: secreted frizzled-related protein 4 (sFRP4), matrix extracellular phosphoglycoprotein (MEPE), and fibroblast growth factor-7 (FGF7) (Cai et al., 1994; Kumar et al., 2000; White et al., 2000; Yamashita et al., 2000; Shimada et al., 2001; Berndt et al., 2003; Jonsson et al., 2003; Rowe et al., 2004). FGF23 is a 32-kDa, 251-amino acid protein, predominately expressed in osteocytes and osteoblasts in the skeleton, but low levels of unclear significance can be found in pericyte-like cells that surround the venous sinusoids of the bone marrow, ventrolateral thalamic nuclei, heart, liver, thymus, and small intestine (Liu et al., 2003, 2006).

The kidney is the main target-organ for FGF23. FGF23 induces phosphaturia by suppressing the expression of Npt2a and Npt2c on the apical surface of the proximal tubular cells. The reduction in the number of Npt2a by FGF23 seems to be independent of PTH (Kuro-o, 2006). FGF23 suppresses the renal production of $1,25(OH)_2D$, by inhibiting the 1-α-hydroxylase enzyme (CYP27B1) in the renal tubule, which stimulates the conversion of 25(OH) D to $1,25(OH)_2D$, and also by enhancing the expression of 24-hydroxylase (CYP24), which inactivates the$1,25(OH)_2D$ (Shimada et al., 2004a, 2004b). FGF23 exerts its biological functions by binding to and activating its cognate FGF receptor (FGFR) in the presence of Klotho, a protein thought to be involved in ageing and being downregulated in CKD (Kuro-o et al., 1997; Kurosu et al., 2006; Urakawa et al., 2006). Klotho expression is restricted to a few tissues, including the distal convoluted tubules in the kidney, the parathyroid glands, the sinoatrial node, the pituitary, and the choroid plexus in the brain. It is still unclear how FGF23 exerts its physiological effects on the proximal tubule in the kidney, while Klotho appears to be expressed in the distal tubular epithelial cells. Klotho is expressed at the cell surface, but is also present in plasma as two secreted forms. The membrane-bound form can be cleaved to generate a second circulating species, and either of these forms of Klotho could possibly bind to FGF23 and FGFRs. In Klotho-deficient mice, the FGF23 concentration is increased, but is ineffective in controlling serum P levels. In conclusion, Klotho is a co-receptor that specifically increases the sensitivity of FGF receptors to FGF23 (Kurosu et al., 2006; Urakawa et al., 2006; Segawa et al., 2007; Prieet al., 2009).

Besides its effect on tubular P handling, FGF23 may affect PTH synthesis and secretion through the mitogen-activated protein kinase (MAPK) pathway. *In vivo* and *in vitro* experiments demonstrated that FGF23 inhibits *PTH* gene expression in parathyroid glands and decreases PTH secretion. In addition, FGF23 increases 1-alpha-hydroxylase expression in bovine parathyroid cells, which may contribute to reduce *PTH* gene transcription (Ben-Dov et al., 2007; Krajisnik et al., 2007; Prie et al., 2009).

FGF23 gene expression in bone is regulated by P and $1,25(OH)_2D$. Experimental and clinical studies showed that several days of dietary P loading lead to an increase in serum FGF23 in both mice and humans. However, extracellular P did not directly stimulate *FGF23* mRNA levels or *FGF23* gene promoter activity in osteoblastic cultures (Ferrari et al., 2005; Perwad et al., 2005; Liu et al., 2006; Nishida et al., 2006; Nakai et al., 2010). $1,25(OH)_2D$ stimulates FGF23 production both *in vivo* and *in vitro*, thought to be mediated through the vitamin D receptor (VDR). VDR-null mice did not show an increase in FGF23 levels after $1,25(OH)_2D$ administration. FGF23 secretion is also regulated by local bone-derived factors, such as P-regulating gene with homologies to endopeptidases on the X chromosome (PHEX) and dentin matrix protein 1 (DMP1) (Liu et al., 2003; Lorenz-Depiereux et al., 2006). $1,25(OH)_2D$ is also able to suppress *PHEX* mRNA levels in bone cells, and reductions in PHEX can result in increased FGF23 expression in osteocytes. Therefore, $1,25(OH)_2D$ may upregulate FGF23 production in part indirectly by downregulation of PHEX expression (Hines et al., 2004; Collins et al., 2005; Saito et al., 2005; Liu and Quarles, 2007; Ramon et al., 2010).

Further details on FGF23 are presented in Chapter 119.

Calcium metabolism

Calcium plays an important role in bone mineralization, as well as a wide range of biological processes. Total adult body stores are approximately 1000 g. Ninety-nine per cent of total body Ca is in the skeleton in the form of hydroxyapatite; the remainder is contained in the extracellular fluid and soft tissues. Fifty per cent of the total serum Ca is free (ionized), 40% is bound to albumin, and 10% is complexed with anions, such as P and citrate. Serum Ca concentration is tightly controlled within a narrow physiologic range that is optimal for proper cellular functions of many tissues affected by Ca. The ionized fraction of Ca is the physiologically important fraction that is regulated by the Ca-regulating hormones—PTH and $1,25(OH)_2D$.

The average dietary intake of Ca is around 1000 mg/day, but there are wide variations. On average, 400 mg of Ca undergo net

absorption from the diet, and the unabsorbed and secreted components appear in the stool. This Ca in the extracellular pool is in dynamic equilibrium with Ca entering and exiting the intestine, bone, and renal tubules.

Intestinal Ca absorption occurs throughout the small intestine and the colon, but the duodenum is the major site of this process. Ca absorption occurs across intestinal epithelium through passive, paracellular diffusional pathways, as well as through active, transcellular, vitamin D-dependent pathway. The active Ca uptake from the lumen across the brush border membrane occurs through TRPV5 and TRPV6, located on the apical membrane. The transport of Ca through the cytosol requires a vitamin D-inducible protein, calbindin$_{9K}$. At the basolateral membrane, Ca is removed from the cell by the Ca^{2+}-ATPase PMCA1b and the Na^{+}/Ca^{2+} exchanger NCX1 (van de Graaf et al., 2006). Each of these steps is regulated by 1,25(OH)$_2$D.

In the kidney, 60% of the filtered Ca is reabsorbed mainly passively in the proximal tubule through paracellular pathways, by convection (solvent drag) and electrochemical gradients. Twenty per cent of Ca is reabsorbed in the thick ascending limb of the loop of Henle, of which about 2/3 is paracellular and 1/3 is transcellular. Fifteen per cent of the filtered Ca is reabsorbed in the distal convoluted tubule, the connecting tubule, and the initial part of the cortical collecting tubule, through transcellular pathways. Luminal Ca enters the cells via the epithelial Ca channels, TRPV5 and TRPV6. Inside the cells, Ca binds with calbindin$_{28\ K}$ and is transported through the basolateral membrane via PMCA1b and NCX1. This active transcellular transport is regulated by PTH, 1,25(OH)$_2$D, Ca intake, and oestrogens. PTH stimulates renal Ca reabsorption by upregulating the expression of the TRPV5, calbindin$_{28\ K}$, NCX1 and PMCA1b (van Abel et al., 2005). Studies performed in VDR-null mice and 1-alpha-hydroxylase-knockout mice showed downregulation of TRPV5 and calbindin$_{28\ K}$, demonstrating an important role of vitamin D in regulating renal Ca absorption (Hoenderop et al., 2003).

Vitamin D metabolism

Vitamin D is a multifunctional hormone that affects many essential biological functions, ranging from immune regulation to mineral ion metabolism. Native vitamin D is available in the diet, either from plant sources, as vitamin D_2 (ergocalciferol), or from animal sources, as vitamin D_3 (cholecalciferol). Vitamin D_3 is also produced in the skin from 7-dehydrocholesterol, by ultraviolet radiation. Both forms of vitamin D require further metabolism to become activated, and their respective metabolism is indistinguishable. Vitamin D is transported into the blood, where it circulates bound to vitamin D-binding protein (DBP) to the liver, and it gets hydroxylated by CYP27A1 (25-hydroxylase) to 25(OH)D (calcidiol). The conversion of 25(OH)D to its most active form of the hormone, 1,25(OH)$_2$D (calcitriol), occurs primarily in the kidney by the action of the CYP27B1 (1-alpha-hydroxylase) after the reabsorption of 25-hydroxyvitamin D together with DBP from tubular fluid by a megalin-dependent mechanism. This hydroxylation step is upregulated by several factors, including PTH, hypocalcaemia, hypophosphataemia, and 1,25(OH)$_2$D itself and is inhibited by FGF23, hypercalcaemia, and hyperphosphataemia. Calcitriol is then released into the peritubular blood, where it circulates in plasma again bound to DBP. Calcitriol production occurs in many tissues and contributes to the circulating levels of calcitriol. Both 25(OH)D and 1,25(OH)$_2$D undergo degradation into the inactive metabolites by another enzyme, 24-hydroxylase (CYP24), which is located in many tissues. FGF23 stimulates the activity of the renal CYP24 enzyme. In CKD, FGF23 levels increase, suggesting that CYP24 can cause reductions in both 25(OH)D and1,25(OH)$_2$D in target-tissues, by increased catabolism, thus decreasing the pool of 25(OH)D available for 1-alpha hydroxylation (Omdahl et al., 2002).

1,25(OH)$_2$D mediates its biological effects through its own member of the nuclear hormone receptor superfamily, the VDR, that acts as a ligand-inducible transcription factor. Ligand-bound VDR functions as a heterodimeric complex with the 9-cis-retinoic acid nuclear receptor retinoid-X-receptor (RXR). The complex binds vitamin D response elements (VDREs) of target genes and regulates the transcription of several genes important in mediating the effects of vitamin D on Ca and skeletal metabolism and its diverse biological effects (Ozono et al., 1991; Lowe et al., 1992). 1,25(OH)$_2$D enhances the uptake of Ca in intestinal and renal distal epithelium by increasing the expression of TRPV5 and TRPV6, the intracellular expression of calbindin (9 kD in intestine and 28 kD in kidney), and the expression of the Ca ATP-ase at the basolateral membrane. It also stimulates the intestinal P absorption. Other effects of 1,25(OH)$_2$D include increased bone formation and resorption. At the level of parathyroid gland, 1,25(OH)$_2$D reduces PTH synthesis and secretion, decreases PTH cell proliferation, and increases the expression of Ca receptor, thereby sensitizing the parathyroid gland to inhibition by Ca (Canaff and Hendy, 2002).

Alterations in mineral metabolism in chronic kidney disease

Alterations in mineral homeostasis occur early in CKD. Transient P retention develops at an early stage of CKD, caused by reduced functioning kidney, with gradual decline in filtered P load. P retention stimulates FGF23 synthesis and secretion by osteocytes, which in turn inhibits tubular P reabsorption, causing increased renal P excretion. FGF23 decreases the production of calcitriol (1,25(OH)$_2$D) and accelerates its metabolism by augmenting 25-hydroxylase activity, which results in limited intestinal Ca and

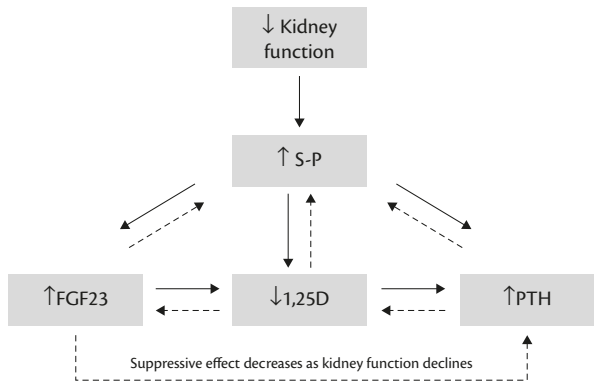

Fig. 117.1 Alterations in mineral metabolism in CKD (dashed lines indicate counter-regulatory pathways). 1,25D = dihydroxyvitamin D (calcitriol); FGF23 = fibroblast growth factor 23; PTH = parathyroid hormone; S-P = serum phosphorus.

P absorption and increases in PTH levels. PTH stimulates the production of $1,25(OH)_2D$, increases urinary Ca reabsorption, to counter the negative Ca balance, and inhibits renal P reabsorption, maintaining serum P levels in early stages of CKD. FGF23 suppresses PTH release via stimulating the dimeric Klotho-FGF receptor at the parathyroid glands, but resistance to the effect of FGF23 appears as kidney function declines, because of decreased Klotho expression in the parathyroid glands and kidney. As CKD progresses, these adaptative mechanisms are overwhelmed, resulting in hyperphosphataemia and hypocalcaemia. These abnormalities directly increase PTH levels, contributing to the development of secondary hyperparathyroidism (Fig. 117.1).

References

Almaden, Y., Canalejo, A., Ballesteros, E., *et al.* (2000). Effect of high extracellular P concentration on arachidonic acid production by parathyroid tissue in vitro. *J Am Soc Nephrol*, 11(9), 1712–18.

Ambuhl, P. M., Zajicek, H. K., Wang, H., *et al.* (1998). Regulation of renal P transport by acute and chronic metabolic acidosis in the rat. *Kidney Int*, 53(5), 1288–98.

Beck, L., Karaplis, A. C., Amizuka, N., *et al.* (1998). Targeted inactivation of Npt2 in mice leads to severe renal P wasting, hypercalciuria, and skeletal abnormalities. *Proc Natl Acad Sci U S A*, 95(9), 5372–7.

Ben-Dov, I. Z., Galitzer, H., Lavi-Moshayoff, V., *et al.* (2007). The parathyroid is a target organ for FGF23 in rats. *J Clin Invest*, 117(12), 4003–8.

Berndt, T., Craig, T. A., Bowe, A. E., *et al.* (2003). Secreted frizzled-related protein 4 is a potent tumor-derived phosphaturic agent. *J Clin Invest*, 112(5), 785–94.

Bianda, T., Hussain, M. A., Glatz, Y., *et al.* (1997). Effects of short-term insulin-like growth factor-I or growth hormone treatment on bone turnover, renal P reabsorption and 1,25 dihydroxyvitamin D3 production in healthy man. *J Intern Med*, 241(2), 143–50.

Blaine, J., Weinman, E. J., and Cunningham, R. (2011). The regulation of renal P transport. *Adv Chronic Kidney Dis*, 18(2), 77–84.

Borowitz, S. M. and Granrud, G. S. (1992). Glucocorticoids inhibit intestinal P absorption in developing rabbits. *J Nutr*, 122(6), 1273–9.

Cai, Q., Hodgson, S. F., Kao, P. C., *et al.* (1994). Brief report: inhibition of renal P transport by a tumor product in a patient with oncogenic osteomalacia. *N Engl J Med*, 330(23), 1645–9.

Canaff, L. and Hendy, G. N. (2002). Human Ca-sensing receptor gene. Vitamin D response elements in promoters P1 and P2 confer transcriptional responsiveness to 1,25-dihydroxyvitamin D. *J Biol Chem*, 277(33), 30337–50.

Collins, M. T., Lindsay, J. R., Jain, A., *et al.* (2005). Fibroblast growth factor-23 is regulated by 1alpha,25-dihydroxyvitamin D. *J Bone Miner Res*, 20(11), 1944–50.

Cozzolino, M., Lu, Y., Sato, T., *et al.* (2005). A critical role for enhanced TGF-alpha and EGFR expression in the initiation of parathyroid hyperplasia in experimental kidney disease. *Am J Physiol Renal Physiol*, 289(5), F1096–102.

Craver, L., Marco, M. P., Martínez, I., *et al.* (2007). Mineral metabolism parameters throughout chronic kidney disease stages 1-5—achievement of K/DOQI target ranges. *Nephrol Dial Transplant*, 22(4), 1171–6.

Ferrari, S.L., Bonjour, J. P., and R. Rizzoli, R. (2005). Fibroblast growth factor-23 relationship to dietary P and renal P handling in healthy young men. *J Clin Endocrinol Metab*, 90(3), 1519–24.

Hines, E.R., Kolek, O. I., Jones, M. D., *et al.* (2004). 1,25-dihydroxyvitamin D3 down-regulation of PHEX gene expression is mediated by apparent repression of a 110 kDa transfactor that binds to a polyadenine element in the promoter. *J Biol Chem*, 279(45), 46406–14.

Hoenderop, J. G., van Leeuwen, J. P., van der Eerden, B. C., *et al.* (2003). Renal Ca^{2+} wasting, hyperabsorption, and reduced bone thickness in mice lacking TRPV5. *J Clin Invest*, 112(12), 1906–14.

Ishiguro, M., Yamamoto, H., Masuda, M., *et al.* (2010). Thyroid hormones regulate P homoeostasis through transcriptional control of the renal type IIa sodium-dependent P co-transporter (Npt2a) gene. *Biochem J*, 427(1), 161–9.

Jonsson, K. B., Zahradnik, R., Larsson, T., *et al.* (2003). Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. *N Engl J Med*, 348(17), 1656–63.

Krajisnik, T., Björklund, P., Marsell, R., *et al.* (2007). Fibroblast growth factor-23 regulates parathyroid hormone and 1alpha-hydroxylase expression in cultured bovine parathyroid cells. *J Endocrinol*, 195(1), 125–31.

Kumar, R. (2000). Tumor-induced osteomalacia and the regulation of P homeostasis. *Bone*, 27(3), 333–8.

Kurnik, B. R. and Hruska, K. A. (1985). Mechanism of stimulation of renal P transport by 1,25-dihydroxycholecalciferol. *Biochim Biophys Acta*, 817(1), 42–50.

Kuro-o, M. (2006). Klotho as a regulator of fibroblast growth factor signaling and P/Ca metabolism. *Curr Opin Nephrol Hypertens*, 15(4), 437–41.

Kuro-o, M., Matsumura, Y., Aizawa, H., *et al.* (1997). Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature*, 390(6655), 45–51.

Kurosu, H., Ogawa, Y., Miyoshi, M., *et al.* (2006). Regulation of fibroblast growth factor-23 signaling by klotho. *J Biol Chem*, 281(10), 6120–3.

Laron, Z., Crawford, J. D., and Klein, R. (1957). Phosphaturic effect of cortisone in normal and parathyroidectomized rats. *Proc Soc Exp Biol Med*, 96(3), 649–51.

Liu, S. and Quarles, L. D. (2007). How fibroblast growth factor 23 works. *J Am Soc Nephrol*, 18(6), 1637–47.

Liu, S., Tang, W., Zhou, J., *et al.* (2006). Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. *J Am Soc Nephrol*, 17(5), 1305–15.

Liu, S., Zhou, J., Tang, W., *et al.* (2006). Pathogenic role of Fgf23 in Hyp mice. *Am J Physiol Endocrinol Metab*, 291(1), E38–49.

Liu, S., Guo, R., Simpson, L. G., *et al.* (2003). Regulation of fibroblastic growth factor 23 expression but not degradation by PHEX. *J Biol Chem*, 278(39), 37419–26.

Lorenz-Depiereux, B., Bastepe, M., Benet-Pagès, A., *et al.* (2006). DMP1 mutations in autosomal recessive hypoPmia implicate a bone matrix protein in the regulation of P homeostasis. *Nat Genet*, 38(11), 1248–50.

Lowe, K. E., Maiyar, A. C., and Norman, A. W. (1992). Vitamin D-mediated gene expression. *Crit Rev Eukaryot Gene Expr*, 2(1), 65–109.

Marks, J., Debnam, E. S., and Unwin, R. J. (2010). P homeostasis and the renal-gastrointestinal axis. *Am J Physiol Renal Physiol*, 299(2), F285–96.

Marks, J., Churchill, L. J., Debnam, E. S., *et al.* (2008). Matrix extracellular phosphoglycoprotein inhibits P transport. *J Am Soc Nephrol*, 19(12), 2313–20.

Miyamoto, K., Ito, M., Kuwahata, M., *et al.* (2005). Inhibition of intestinal sodium-dependent inorganic P transport by fibroblast growth factor 23. *Ther Apher Dial*, 9(4), 331–5.

Nakai, K., Komaba, H., and Fukagawa, M. (2010). New insights into the role of fibroblast growth factor 23 in chronic kidney disease. *J Nephrol*, 23(6), 619–25.

Nishida, Y., Taketani, Y., Yamanaka-Okumura, H., *et al.* (2006). Acute effect of oral P loading on serum fibroblast growth factor 23 levels in healthy men. *Kidney Int*, 70(12), 2141–7.

Omdahl, J. L., Morris, H. A., and May, B. K. (2002). Hydroxylase enzymes of the vitamin D pathway: expression, function, and regulation. *Annu Rev Nutr*, 22, 139–66.

Ozono, K., Sone, T., and Pike, J. W. (1991). The genomic mechanism of action of 1,25-dihydroxyvitamin D3. *J Bone Miner Res*, 6(10), 1021–7.

Perwad, F., Azam, N., Zhang, M. Y., *et al.* (2005). Dietary and serum P regulate fibroblast growth factor 23 expression and 1,25-dihydroxyvitamin D metabolism in mice. *Endocrinology*, 146(12), 5358–64.

Prie, D., Urena Torres, P., and Friedlander, G. (2009). Latest findings in P homeostasis. *Kidney Int*, 75(9), 882–9.

Ramon, I., Kleynen, P., Body, J. J., *et al.* (2010). Fibroblast growth factor 23 and its role in P homeostasis. *Eur J Endocrinol*, 162(1), 1–10.

Ritter, C.S., Martin, D. R., Lu, Y., *et al.* (2002). Reversal of secondary hyperparathyroidism by P restriction restores parathyroid Ca-sensing receptor expression and function. *J Bone Miner Res*, 17(12), 2206–13.

Rowe, P. S., Kumagai, Y., Gutierrez, G., *et al.* (2004). MEPE has the properties of an osteoblastic phosphatonin and minhibin. *Bone*, 34(2), 303–19.

Sabbagh, Y., O'Brien, S. P., Song, W., *et al.* (2009). Intestinal npt2b plays a major role in P absorption and homeostasis. *J Am Soc Nephrol*, 20(11), 2348–58.

Saito, H., Maeda, A., Ohtomo, S., *et al.* (2005). Circulating FGF-23 is regulated by 1alpha,25-dihydroxyvitamin D3 and P in vivo. *J Biol Chem*, 280(4), 2543–9.

Segawa, H., Onitsuka, A., Furutani, J., *et al.* (2009). Npt2a and Npt2c in mice play distinct and synergistic roles in inorganic P metabolism and skeletal development. *Am J Physiol Renal Physiol*, 297(3), F671–8.

Segawa, H., Yamanaka, S., Ohno, Y., *et al.* (2007). Correlation between hyperPmia and type II Na-Pi cotransporter activity in klotho mice. *Am J Physiol Renal Physiol*, 292(2), F769–79.

Shimada, T., Hasegawa, H., Yamazaki, Y., *et al.* (2004a). FGF-23 is a potent regulator of vitamin D metabolism and P homeostasis. *J Bone Miner Res*, 19(3), 429–35.

Shimada, T., Kakitani, M., Yamazaki, Y., *et al.* (2004b). Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in P and vitamin D metabolism. *J Clin Invest*, 113(4), 561–8.

Shimada, T., Mizutani, S., Muto, T., *et al.* (2001). Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci U S A*, 98(11), 6500–5.

Stauber, A., Radanovic, T., Stange, G., *et al.* (2005). Regulation of intestinal P transport. II. Metabolic acidosis stimulates Na(+)-dependent P absorption and expression of the Na(+)-P(i) cotransporter NaPi-IIb in small intestine. *Am J Physiol Gastrointest Liver Physiol*, 288(3), G501–6.

Tenenhouse, H. S., Martel, J., Gauthier, C., *et al.* (2003). Differential effects of Npt2a gene ablation and X-linked Hyp mutation on renal expression of Npt2c. *Am J Physiol Renal Physiol*, 285(6), F1271–8.

Urakawa, I., Yamazaki, Y., Shimada, T., *et al.* (2006). Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*, 444(7120), 770–4.

Uribarri, J. (2007). P homeostasis in normal health and in chronic kidney disease patients with special emphasis on dietary P intake. *Semin Dial*, 20(4), 295–301.

Van Abel, M., Hoenderop, J. G., van der Kemp, A. W., *et al.* (2005). Coordinated control of renal Ca(2+) transport proteins by parathyroid hormone. *Kidney Int*, 68(4), 1708–21.

Van de Graaf, S. F., Hoenderop, J. G., and Bindels, R. J. (2006). Regulation of TRPV5 and TRPV6 by associated proteins. *Am J Physiol Renal Physiol*, 290(6), F1295–302.

Villa-Bellosta, R., Ravera, S., Sorribas, V., *et al.* (2009). The Na^+-Pi cotransporter PiT-2 (SLC20A2) is expressed in the apical membrane of rat renal proximal tubules and regulated by dietary Pi. *Am J Physiol Renal Physiol*, 296(4), F691–9.

White, K. E., Evans, W. E., O'Riordan, J. L. H., *et al.* (2000). Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. *Nat Genet*, 26(3), 345–8.

Xu, H., Uno, J. K., Inouye, M., *et al.* (2003). Regulation of intestinal NaPi-IIb cotransporter gene expression by estrogen. *Am J Physiol Gastrointest Liver Physiol*, 285(6), G1317–24.

Xu, H., Collins, J. F., Bai, L., *et al.* (2001). Regulation of the human sodium-P cotransporter NaP(i)-IIb gene promoter by epidermal growth factor. *Am J Physiol Cell Physiol*, 280(3), C628–36.

Yamashita, T., Yoshioka, M., and Itoh, N. (2000). Identification of a novel fibroblast growth factor, FGF-23, preferentially expressed in the ventrolateral thalamic nucleus of the brain. *Biochem Biophys Res Commun*, 277(2), 494–8.

Yang, D., Singh, R., Divieti, P., *et al.* (2007). Contributions of parathyroid hormone (PTH)/PTH-related peptide receptor signaling pathways to the anabolic effect of PTH on bone. *Bone*, 40(6), 1453–61.

CHAPTER 118

Management of chronic kidney disease-mineral and bone disorder

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Monitoring of biochemical markers of chronic kidney disease-mineral and bone disorder

Both the 2003 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for bone metabolism and disease and the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for chronic kidney disease-mineral and bone disorder (CKD-MBD) advocate monitoring the serum levels of calcium (Ca), phosphorus (P), 25-hydroxyvitamin D (25(OH)D), intact parathyroid hormone (PTH), and alkaline phosphatase (ALP) beginning with stage 3 CKD (National Kidney Foundation, 2003; Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009). Table 118.1 shows the recommended frequency of monitoring of these laboratory parameters.

These levels should be assessed more frequently in response to changes in therapeutic interventions that affect these levels. Targets for biochemical parameters are summarized in Table 118.2.

Phosphorus and calcium

P and Ca should be maintained within the normal laboratory range in CKD stages 3 and 4. Epidemiologic data suggest that higher serum P levels are associated with increased cardiovascular morbidity and mortality in both the general population and CKD populations. Studies in dialysis patients confirmed the association of P levels with mortality, although slight differences in the inflection point (the point at which P level becomes significantly associated with increased all-cause mortality) varied from 5.0 to 5.5 mg/dL (Block et al., 2004a), > 5.5 mg/dL (Noordzij et al., 2005), 6.0–7.0 mg/dL (Kalantar-Zadeh et al., 2006), and > 6.5 mg/dL (Tentori et al., 2008).

Observational studies in CKD patients showed an increased risk of all-cause mortality with Ca levels > 9.5 mg/dL. There is not much evidence of an association between low Ca levels and mortality (Block et al., 2004a; Tentori et al., 2008).

Parathyroid hormone

The KDOQI practice guidelines suggested that target intact PTH (second-generation PTH assay) in CKD stage 5D patients should be between 150 and 300 pg/mL, because the prevailing opinion at that time was that this range was associated with relatively normal bone turnover. This target range was based on findings derived from a second-generation assay that is no longer commercially available. In addition, there are data suggesting significant variability with PTH results among the different available assays. Observational studies found an increase in all-cause mortality with PTH levels > 400 pg/mL (Kalantar-Zadeh et al., 2006), > 480 pg/mL (Young et al., 2005), > 500 pg/mL (Kimata et al., 2005) or > 600 pg/mL (Block et al., 2004a). Based on the above considerations, the KDIGO guidelines have broadened the range for target-PTH to two to nine times the upper limit of normal.

Vitamin D

Serum levels of 25(OH)D have been shown to be the best indicator of vitamin D status. The current KDOQI guidelines recommend screening for vitamin D deficiency and repeating testing at intervals determined by the baseline values obtained (González et al., 2004; LaClair et al., 2005; Wolf et al., 2007; Mehrotra et al., 2008).

Alkaline phosphatase

The frequency of measurement of ALP is similar to that of PTH and can provide additional information on bone turnover. Elevated serum ALP has been found to be associated with higher risks of hospitalization and death in CKD and dialysis patients (Blayney et al., 2008; Kovesdy et al., 2010).

Management of chronic kidney disease-mineral and bone disorder

The principles of therapy for secondary hyperparathyroidism include control of hyperphosphataemia, correction of hypocalcaemia, use of vitamin D sterols, use of calcimimetics, and parathyroidectomy (Box 118.1).

Table 118.1 KDIGO guidelines for laboratory monitoring according to CKD stage

CKD stage	PTH and ALP	Ca	P	25(OH)D
3	Based on baseline level	Every 6–12 months	Every 6–12 months	Based on baseline level
4	Every 6–12 months	Every 6–12 months	Every 6–12 months	Based on baseline level
5 and 5D	Every 3–6 months	Every 1–3 months	Every 1–3 months	Based on baseline level

Table 118.2 KDOQI and KDIGO guidelines for laboratory target range

Parameter	KDOQI goal	KDIGO goal
PTH (pg/mL)	CKD 3: 35–70 CKD 4: 70–110 CKD 5: 150–300	2–9 × the upper normal limit
Ca (mg/dL)	CKD 3: in the normal range CKD 4: in the normal range CKD 5: 8.4–10.2	In the normal range
P (mg/dL)	CKD 3: 2.7–4.6 CKD 4: 2.7–4.6 CKD 5: 3.5–5.5	In the normal range Towards the normal range

Control of hyperphosphataemia

Hyperphosphataemia has been associated with increased cardiovascular morbidity and mortality, secondary hyperparathyroidism, and vascular calcification (Kestenbaum et al., 2005; Slinin et al., 2005; Foley et al., 2009). Control of hyperphosphataemia remains the cornerstone of effective treatment of secondary hyperparathyroidism. The treatment strategies used to lower serum P levels include dietary P restriction, use of P binders, and removal of P with dialysis.

Diet

Several studies looked at the effect of dietary P restriction on abnormalities of bone and mineral metabolism, progression of renal dysfunction, and mortality (Williams et al., 1991; Martinez et al., 1997; Lafage-Proust et al., 1999). Foods rich in protein are an important source of dietary P, thus dietary P restriction can be associated with a decrease in dietary protein intake, which can lead to protein-calorie malnutrition.

Box 118.1 Principles of therapy of secondary hyperparathyroidism

- Control of hyperphosphataemia:
  - Diet
  - P binders
  - P removal with dialysis
- Correction of hypocalcaemia (if present)
- Vitamin D sterols
- Calcimimetics
- Parathyroidectomy.

Phosphorus binders

Aluminium salts

Aluminium hydroxide, an effective P binder, was the binder of choice for many years. However, long-term use of this binder was found to be associated with cognitive disturbances, osteomalacia, refractory microcytic anaemia, and myopathy. There is no evidence to suggest that even low levels of exposure to aluminium are safe for chronic use (Parkinson et al., 1979; Wills and Savory, 1983; Salusky et al., 1991; Malluche, 2002).

Ca-based binders

Ca acetate and Ca carbonate are inexpensive and effective in controlling hyperphosphataemia. Ca citrate can enhance intestinal Ca and aluminium absorption; therefore, it is used infrequently as a P binder. Ca-based binders can be associated with the development of hypercalcaemia, especially when used in combination with a vitamin D analogue (Sheikh et al., 1989; Emmett et al., 1991; Navaneethan et al., 2009). Long-term use of Ca-based P binders may contribute to soft tissue and vascular calcification, as suggested by some studies (Chertow et al., 2002; Block et al., 2005). KDOQI guidelines recommend limiting daily elemental Ca intake from binders to < 1500 mg per day. Ca-based binders should be avoided in patients with hypercalcaemia, vascular calcifications, or persistently low plasma PTH levels.

Sevelamer

Sevelamer hydrochloride (Renagel®) and sevelamer carbonate (Renvela®) are non-aluminium, non-Ca polymers that bind P through ion exchange. Sevelamer hydrochloride dissociates in the acidic environment of the stomach and gastrointestinal tract, exchanging the chloride ions attached to its polymer backbone for P ions, resulting in a decrease in serum bicarbonate concentration. Sevelamer carbonate does not decrease serum bicarbonate levels, and it may be used for patients at risk for metabolic acidosis (Delmez et al., 2007). Reported drawbacks of this binder are gastrointestinal disturbances, high pill burden, and a relatively low affinity and selectivity for P (Suki et al., 2007). Sevelamer binds bile acids and decreases faecal bile acid excretion and lowers low-density lipoprotein cholesterol (Chertow et al., 1997). Some studies also showed beneficial effects of sevelamer on other biochemical parameters, including C-reactive protein, uric acid, fetuin-A, and fibroblast growth factor 23 (FGF23) (Yilmaz et al., 2012).

Lanthanum carbonate

Lanthanum carbonate is able to bind P across a wide pH range. Short-term trials have assessed the efficacy of lanthanum carbonate in decreasing serum P, PTH, and FGF23 levels (Finn et al., 2004; Albaaj and Hutchison, 2005; Chiang et al., 2005; Shigematsu et al., 2012). Concerns have been expressed about the long-term safety of this drug, as experimental data showed that lanthanum accumulates in tissues such as liver and brain, and accumulation in bone has also been found in human studies (Hutchison et al., 2009). However, no significant toxicity has been found todate.

Iron-based binders

Iron-containing P binders are new options in the treatment of hyperphosphataemia in CKD. Two molecules are most promising—sucroferric oxyhydroxide (PA21) and ferric citrate—and it appears that both products have similar efficiency with other P binders. has recently approved PA21for the treatment of hyperphosphataemia in patients with CKD receiving dialysis. This decision was based on the results of a phase 3 study involving > 1000 patients, demonstrating that PA21 controls hyperphosphataemia over the long term and has a lower pill burden than sevelamer carbonate (Floege et al., 2012). Ferric citrate has also received approval from the US Food and Drug Administration.

Combined magnesium- and Ca-based binders

Magnesium-containing P binders have been in use for many years and the interest upon them greatly increased lately, with the apparition of a new formulation: magnesium carbonate plus Ca acetate. The use of this combination was supported by a phase 3 non-inferiority trial, which confirmed head-to-head efficacy with sevelamer hydrochloride in haemodialysis patients. Furthermore, magnesium had an equally good tolerability profile and is relatively inexpensive, compared to sevelamer or lanthanum carbonate (de Francisco et al., 2010).

Comparative trials of different P binders

Effects of P binders on vascular calcifications

The results of the studies on progression of vascular calcification with sevelamer versus Ca-based P binders have been contradictory. Two randomized controlled trials—Treat-To-Goal (TTG) and Renagel in New Dialysis (RIND)—showed a significant increase in the progression of vascular calcification in the Ca-based binder groups (Chertow et al., 2002; Block et al., 2005). The Calcium Acetate Renagel Evaluation 2 (CARE-2) trial compared prevalent haemodialysis patients assigned to Ca acetate or sevelamer, with both groups receiving atorvastatin to lower cholesterol levels. Although there was a high dropout rate, no significant difference was observed in the progression of coronary artery calcification between the two groups. Similarly, the Phosphate Binder Impact on Bone Remodeling and Coronary Calcification (BRiC) study found no difference in the rate of progression of vascular calcification between these binders (Barreto et al., 2008; Qunibi et al., 2008).

Effects of P binders on bone histology

The BRiC study also compared the effects of sevelamer and Ca acetate on bone histology and showed no significant differences in the two arms in bone turnover, mineralization, and volume (de Francisco et al., 2010). A few small trials have compared the effects of lanthanum and Ca carbonate on bone histology. In one study there was an improvement in bone turnover and volume, but worsened mineralization in patients receiving lanthanum (Malluche et al., 2008). In another study, more of the patients who received Ca-based binders developed adynamic bone disease (Spasovski et al., 2006).

Effects of P binders on mortality

The RIND study showed an adjusted increased mortality in the Ca-based binder group (Block et al., 2007), whereas the Dialysis Clinical Outcomes Revisited (DCOR) study, which enrolled 2103 haemodialysis patients assigned to either sevelamer or Ca-based binders, found no difference in mortality between the two groups (Suki et al., 2007). A recent meta-analysis of 11 open-label trials, including 4622 patients with CKD, revealed a 22% decrease in all-cause mortality among patients assigned to non-calcium-based P binders, compared with those assigned to calcium-based P binders (Jamal et al., 2013).

Phosphorus removal with dialysis

The kinetics of P removal differs significantly from classic urea kinetics. There is a rapid decline in P level during the first phase of haemodialysis, as a result of P removal from the extracellular space, followed by a second phase, during which P removal continues at a lower rate, as a consequence of P shift from intracellular compartments to plasma compartment. A rebound of P occurs within a couple of hours after termination of dialysis, reaching about 80% of pre-dialysis values.

P removal during haemodialysis is influenced by different factors of dialysis prescription, such as blood and dialysate flow rates, dialyzer membrane surface area, and ultrafiltration volume. With conventional thrice-weekly haemodialysis (4 hours per session), P removal reaches 600–900 mg per session (1800–2700 mg per week). Conventional haemodiafiltration improves P removal to about 1170 mg per session (Hou et al., 1991; Ayus et al., 2005). With short daily, extended daily, or three times weekly nocturnal haemodialysis, P mass clearance is increased, potentially allowing complete discontinuation of P binder use (Ayus et al., 2005; Culleton et al., 2007; Chertow et al., 2010).

Peritoneal P clearance is influenced by different peritoneal dialysis modalities and peritoneal membrane permeability. Peritoneal P clearance appears to be correlated with creatinine clearance, but not with urea clearance. Weekly average P removal in patients on continuous ambulatory peritoneal dialysis (CAPD) has been reported to be around 70 mmol (2170 mg) with 4 × 2 L exchanges per day and 105 mmol (3250 mg) with 4 × 3 L exchanges per day (Messa et al., 1998). In high-transporter patients there is no difference in P clearance between CAPD and continuous cyclic peritoneal dialysis (CCPD), whereas in high-average, low-average, and low-transporter patients, the peritoneal P clearance is higher with CAPD than with CCPD (Badve et al., 2008).

Control of hypocalcaemia

Hypocalcaemia, if present, should be corrected, because it is a potent stimulus for PTH secretion. However, its effect on arterial calcification remains unclear.

Vitamin D sterols

The use of vitamin D sterols is effective in the treatment of secondary hyperparathyroidism, as calcitriol lowers PTH levels and improves

bone histology. There are six active vitamin D derivatives currently available: calcitriol, alfacalcidol, doxercalciferol, 22-oxacalcitriol, falecalcitriol, and paricalcitol. In the United States the available agents include calcitriol, paricalcitol, and doxercalciferol.

Calcitriol is the natural form of active vitamin D and was the first agent used for the treatment of hyperparathyroidism. Oral and intravenous therapies are similar with regard to both PTH suppression and side effects (Quarles et al., 1994).

The vitamin D analogue paricalcitol was introduced and developed aiming to obtain a more selective action on the parathyroid gland, while minimizing other effects of vitamin D sterols, such as hypercalcaemia and hyperphosphataemia. Sprague at al. compared the safety and effectiveness of intravenous paricalcitol and calcitriol in 263 haemodialysis patients and found that paricalcitol reduced PTH concentrations more rapidly and was associated with fewer episodes of hypercalcaemia and/or increased Ca × P product than calcitriol therapy (Sprague et al., 2003).

Doxercalciferol, a prohormone that can be activated by the liver into a vitamin D receptor agonist, appears to have the potential for lesser toxicity and has proven its efficacy in reducing PTH levels. Both oral and intravenous preparations are well tolerated and able to lower plasma PTH; however, hypercalcaemia seems to be less frequent with intravenous administration (Maung et al., 2001).

No head-to-head comparisons of different vitamin D analogues have evaluated patient-related outcomes.

Calcimimetics

Calcimimetics such as cinacalcet are positive allosteric modulators of the calcium-sensing receptor, sensitizing the parathyroid gland to extracellular Ca and thus leading to a decrease in circulating PTH levels (Nemeth et al., 2004). Several prospective randomized studies in dialysis patients with uncontrolled hyperparathyroidism have shown that the use of calcimimetics produces suppression of PTH, Ca, and P levels (Lindberg et al., 2003; Quarles et al., 2003; Block et al., 2004b; Moe et al., 2005). A prospective observational study found that cinacalcet treatment was associated with improved survival in haemodialysis patients (Block et al., 2010).

The ADVANCE trial was a prospective randomized controlled trial, designed to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular and cardiac valve calcification in 360 prevalent adult haemodialysis patients, and it showed that coronary artery calcifications and valvular calcifications were significantly lower in the cinacalcet plus low-dose vitamin D group than in the vitamin D sterol alone group (Raggi et al., 2011).

In the EVOLVE trial, 3883 haemodialysis patients with moderate-to-severe secondary hyperparathyroidism were assigned to receive either cinacalcet or placebo. All patients were eligible to receive conventional therapy, including P binders, vitamin D sterols, or both. Cinacalcet did not significantly reduce the risk of death or major cardiovascular events (EVOLVE Trial Investigators et al., 2012). The results of the trial need to be interpreted in the light of intention-to-treat analysis, which was complicated by the fact that almost 20% of patients in the placebo group began receiving commercial cinacalcet before the occurrence of a primary event. Using a lag sensoring analysis to try to account for this issue appears to suggest that mortality was significantly reduced in the cinacalcet group. Accordingly, these studies should be regarded as non-definitive rather than negative.

Parathyroidectomy

Why parathyroidectomy?

Surgical removal of hyperplastic parathyroid glands (parathyroidectomy (PTX)) represents an extreme therapy—perhaps in some parts of the world considered to be a 'last resort' intervention—for severe secondary hyperparathyroidism in renal patients. The intervention has many decades of 'historical practice', and it is potentially applicable to patients with CKD pre-dialysis, on dialysis, or after successful kidney transplantation.

As a general rule however, especially in the clinical setting of progressive deterioration of biochemical parameters, and clinical symptoms, care needs to be undertaken truly to establish that there will be more than merely 'biochemical' improvements in a patient's well-being, when undergoing a potential PTX. In other words, clinical symptomatology (including pruritus, joint and bone pain, and muscle weakness) is expected to improve. Longer-term poor control of hyperparathyroidism can accelerate vascular and other ectopic calcifications, contribute to hypertension and dyslipidaemia, and can also lead to bone fractures and tendon ruptures. In well-selected patients rapid biochemical (serum Ca, P, and PTH) and clinical (pruritus and bone pain) improvements can be achieved, almost invariably, immediately after surgery; however, long-term benefits are much less clearly established (Urena et al., 1989; Gagne et al., 1992; Coen et al., 2001; Mazzaferro et al., 2008), given the lack of randomized controlled trials comparing medical, surgical or no specific interventional therapy. Rarely, calcific uraemic arteriolopathy can be caused or accelerated by hyperparathyroidism and here too a judicious PTX can be most efficacious. However, it should be remembered that in the modern era, most cases of calciphylaxis are accompanied by low PTH and low bone turnover, which would be harmed, not helped by PTX.

PTX rates have fallen significantly in the modern era of calcimimetic therapy, but this intervention is far from being historically obsolete.

When might PTX be justified?

As schematically reported in Box 118.2, clinical and biochemical parameters are generally used to indicate PTX. In contemporary clinical practice it is accepted that, before PTX surgery, there will be evidence of resistance to medical therapy with active drugs like vitamin D and, where these can be afforded, calcimimetics. Unacceptably and chronically high serum levels of Ca and P, with or without therapy, are additional considerations (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Grou, 2009). PTX has been advocated also for calciphylaxis, accelerated cardiovascular calcifications, accelerated and/or severe bone mineral loss and spontaneous skeletal fractures, refractory anaemia due to bone marrow fibrosis, excessive pruritus, and severe skin lesions. In kidney transplantation, PTX is often indicated in case of persistent and uncontrolled threatening hypercalcaemia and high PTH (Rostaing et al., 1997; Evenepoel et al., 2004; Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009). However, it must be underlined that no precise biochemical value or clinical criteria can be considered as absolute. It is not presently known whether early surgery, before any medical therapy, would result in better clinical, biochemical and skeletal outcomes (and as there are no randomized controlled trials, we do

Box 118.2 Biochemical and clinical signs to evaluate when considering PTX

Biochemical

- Persistent (> 6 months) serum PTH > 800 pg/mL
- Uncontrolled hypercalcaemia and/or hyperphosphataemia
- High levels of bone biomarkers (bone-specific ALP, TRAP5b)
- < 30% reduction of serum PTH levels following aggressive intravenous or oral active vitamin D analogues treatment for 12 weeks in a symptomatic patient
- < 30% reduction of PTH after 12 weeks of treatment with maximal doses of calcimimetics (180 mg/day) in a symptomatic patient.

Clinical

- Severe pruritus, muscular and osteo-articular pain, bone demineralization, fractures, accelerated vascular calcifications, calciphylaxis, peripheral calcifying uraemic arteriolopathy, erythropoietin-resistant anaemia, unexplained cardiomyopathy, or heart failure
- Intolerance or allergy to calcimimetics at active doses
- Extreme parathyroid gland dimensions (volume > 500 mm^3, diameter > 1000 mm, or estimated weight > 500 mg)
- Parathyromatosis.

not have information about a plethora of relevant outcomes, from biochemical to clinical).

As a general rough rule, patients with raised and rising total or bone-specific ALP are those who often have bone, muscle and skin symptoms, and typically PTX is performed in patients with raised Ca × P product, raised PTH and raised ALP concentrations.

Imaging techniques that can be considered prior to surgery, and certainly should be considered seriously prior to re-operations, include neck ultrasound, neck and cervical magnetic resonance scanning, computed tomography scanning, and nuclear scintigraphy. Local factors, including discussion with the local surgical team, will determine the best investigative approach.

Box 118.3 Contraindications to PTX

- Contraindication to general anaesthesia
- Severe degenerative cervical arthropathy (e.g. beta-2-microglobulin amyloid), heightening the risk of cervical hyperextension during surgery
- Severe cervical tissue fibrosis (previous surgeries or ethanol injections, irradiation or tumoural invasion)
- Aluminium overload
- Intrathoracic parathyroid glands (only accessible by embolization or by thoracotomy)
- Adynamic bone disease on bone biopsy.

When might it be wrong to perform PTX?

In some patients clinical worsening can be predicted following PTX (Box 118.3). Intra-operative neck hyperextension may result in medullary spine compression in cases of degenerative cervical arthropathy. Aluminium-related bone disease is expected to worsen following PTX. Furthermore, in less than expert hands or with highly complex patients, there is the risk of neck tissue, recurrent laryngeal, or phrenic nerve lesions.

Different types of PTX.

Three types of surgical PTX have been mostly performed: total PTX without parathyroid tissue autograft in the forearm, total PTX with parathyroid tissue autograft in the forearm, and subtotal PTX (Ogg, 1967; Diaz-Buxo et al., 1981; Kaye, 1989; Gagne et al., 1992; Torres et al., 2002). The incidence of surgical complications, disease persistence and recurrent hyperparathyroidism in CKD patients appears to be comparable with all three types of surgery (Stanbury et al., 1960; Kaye, 1989; Gagne et al., 1992; Richards et al., 2006; Gasparri et al., 2009). Given the high risk of ectopic or supernumerary glands in renal patients (Tominaga et al., 2001; Richards et al., 2006; Gasparri et al., 2009), a careful and complete exploration of the cervical area with identification of all possible parathyroid glands is common and good practice. Scanning for metabolically active (high blood flow) parathyroid tissue may be of value and is certainly of value in re-operations. Further possible interventions include minimally invasive video-assisted PTX (MIVAP) (Hindie et al., 1999; Alesina et al., 2010), local destruction through intraglandular injection of ethanol, vitamin D, and/or calcimimetics (Giangrande et al., 1985; Tanaka et al., 2005; Barbaros et al., 2009), or through the use of laser (Tanaka et al., 2006) or high-intensity focused ultrasound (HIFU) (Hansler et al., 2002; Adda et al., 2006; Carrafiello et al., 2006). The results obtained with these methods are still inconclusive (once again, no good evidence base exists, so careful thought is needed about locally available medical and surgical options).

Some centres offer intraoperative serum PTH concentration sampling; this helps to confirm the 'completeness' of PTX, but is cumbersome and expensive to organize, except in specialist centres.

Selective venous sampling of 'mediastinal' vein serum PTH concentrations can also sometimes help to confirm the presence of active parathyroid tissue in the chest in the challenging situation of ectopic parathyroid gland tissue.

Outcomes predicted for PTX in terms of mortality, biochemical control, and fractures.

For all types of PTX, improvements in mineral parameters, clinical symptoms (pruritus, bone and muscular pain, quality of life), bone mass, and even morbidity and mortality have been described (Gagne et al., 1992; Richards et al., 2006; Kovatcheva et al., 2012). However, while serum Ca and P drop significantly in > 95% of patients (Urena et al., 1989; Gagne et al., 1992; Coen et al., 2001), PTH levels may only rarely fall within the recommended target ranges (EVOLVE Trial Investigators et al., 2012). Moreover, as for survival rate, the available studies indicating possible advantages are observational and may suffer significant biases, not allowing firm conclusions to be drawn about survival advantage (Kestenbaum et al., 2004; Rudser et al., 2012).

Are there possible subpopulations which might benefit more from PTX than from calcimimetics?

Hypothetically, the typical dialysis patient who might benefit more from PTX would be a young patient (< 50 years), on the waiting list for kidney transplantation, high (> 800 pg/mL) or increasing PTH despite medical management (resistance established as described in the KDIGO recommendations) (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009), high Ca and P levels, developing cardiovascular calcifications, and having large parathyroid glands on ultrasounds examination (> 500 mm^3). Predictably, this would avoid long-term medical management with its possible side effects, and, in the case of calcimimetics, considerable medical costs.

In cases where surgery is especially risky or patients are extremely unkeen to undergo surgery, then medical therapy (calcimimetics to lower serum PTH and Ca concentrations) is preferable, as long as it is followed by compliance and responsiveness in terms of biochemistry and clinical symptomatology. Medical therapy is usually much slower to effect symptomatic or biochemical improvement compared to PTX (taking months, not days to weeks).

References

Adda, G., Scillitani, A., Epaminonda, P., *et al.* (2006). Ultrasound-guided laser thermal ablation for parathyroid adenomas: analysis of three cases with a three-year follow-up. *Hormone Res*, 65, 231–4.

Albaaj, F. and Hutchison, A. J. (2005). Lanthanum carbonate (Fosrenol): a novel agent for the treatment of hyperphosphataemia in renal failure and dialysis patients. *Int J Clin Pract*, 59(9), 1091–6.

Alesina, P. F., Hinrichs, J., Kribben, A., *et al.* (2010). Minimally invasive video-assisted parathyroidectomy (MIVAP) for secondary hyperparathyroidism: report of initial experience. *Am J Surg*, 199, 851–5.

Ayus, J. C., Mizani, M. R., Achinger, S. G., *et al.* (2005). Effects of short daily versus conventional hemodialysis on left ventricular hypertrophy and inflammatory markers: a prospective, controlled study. *J Am Soc Nephrol*, 16(9), 2778–88.

Badve, S. V., Zimmerman, D. L., Knoll, G. A., *et al.* (2008). Peritoneal P clearance is influenced by peritoneal dialysis modality, independent of peritoneal transport characteristics. *Clin J Am Soc Nephrol*, 3(6), 1711–17.

Barbaros, U., Erbil, Y., Yildirim, A., *et al.* (2009). Minimally invasive video-assisted subtotal parathyroidectomy with thymectomy for secondary hyperparathyroidism. *Langenbecks Arch Surg*, 394, 451–5.

Barreto, D. V., Barreto, F. de C., de Carvalho, A. B., *et al.* (2008). P binder impact on bone remodeling and coronary calcification—results from the BRiC study. *Nephron Clin Pract*, 110(4), c273–83.

Blayney, M. J., Pisoni, R. L., Bragg-Gresham, J. L., *et al.* (2008). High alkaline phosphatase levels in hemodialysis patients are associated with higher risk of hospitalization and death. *Kidney Int*, 74(5), 655–63.

Block, G. A., Klassen, P. S., Lazarus, J. M., *et al.* (2004a). Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*, 15(8), 2208–18.

Block, G. A., Martin, K. J., de Francisco, A. L., *et al.* (2004b). Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med*, 350(15), 1516–25.

Block, G. A., Raggi, P., Bellasi, A., *et al.* (2007). Mortality effect of coronary calcification and P binder choice in incident hemodialysis patients. *Kidney Int*, 71(5), 438–41.

Block, G. A., Spiegel, D. M., Ehrlich, J., *et al.* (2005). Effects of sevelamer and Ca on coronary artery calcification in patients new to hemodialysis. *Kidney Int*, 68(4), 1815–24.

Block, G. A., Zaun D, Smits G, *et al.* (2010). Cinacalcet hydrochloride treatment significantly improves all-cause and cardiovascular survival in a large cohort of hemodialysis patients. *Kidney Int*, 78(6), 578–89.

Carrafiello, G., Lagana, D., Mangini, M., *et al.* (2006). Treatment of secondary hyperparathyroidism with ultrasonographically guided percutaneous radiofrequency thermoablation. *Surg Laparosc Endosc Percutan Tech*, 16, 112–16.

Chertow, G. M., Burke, S. K., Lazarus, J. M., *et al.* (1997). Poly[allylamine hydrochloride] (RenaGel): a noncalcemic P binder for the treatment of hyperphosphatemic in chronic renal failure. *Am J Kidney Dis*, 29(1), 66–71.

Chertow, G. M., Burke, S. K., and Raggi, P. (2002). Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int*, 62(1), 245–52.

Chertow, G. M., Levin, N. W., Beck, G. J., *et al.* (2010). In-center hemodialysis six times per week versus three times per week. *N Engl J Med*, 363(24), 2287–300.

Chiang, S. S., Chen, J. B., and Yang, W. C. (2005). Lanthanum carbonate (Fosrenol) efficacy and tolerability in the treatment of hyperphosphatemic patients with end-stage renal disease. *Clin Nephrol*, 63(6), 461–70.

Coen, G., Calabria, S., Bellinghieri, G., *et al.* (2001). Parathyroidectomy in chronic renal failure: short- and long-term results on parathyroid function, blood pressure and anemia. *Nephron*, 88, 149–55.

Culleton, B. F., Walsh, M., Klarenbach, S. W., *et al.* (2007). Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. *JAMA*, 298(11), 1291–9.

De Francisco, A. L., Leidig, M., Covic, A. C., *et al.* (2010). Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability. *Nephrol Dial Transplant*. 25(11), 3707–17.

Delmez, J., Block, G., Robertson, J., *et al.* (2007). A randomized, double-blind, crossover design study of sevelamer hydrochloride and sevelamer carbonate in patients on hemodialysis. *Clin Nephrol*, 68(6), 386–91.

Diaz-Buxo, J. A., Geissinger, W. T., Walker, P. J., *et al.* (1981). Total parathyroidectomy and autotransplantation. *Clin Nephrol*, 16, 276–82.

Emmett, M., Sirmon, M. D., Kirkpatrick, W. G., *et al.* (1991). Ca acetate control of serum P in hemodialysis patients. *Am J Kidney Dis*, 17(5), 544–50.

Evenepoel, P., Claes, K., Kuypers, D., *et al.* (2004). Natural history of parathyroid function and calcium metabolism after kidney transplantation: a single-centre study. *Nephrol Dial Transplant*, 19, 1281–7.

EVOLVE Trial Investigators, Chertow, G. M., Block, G. A., *et al.* (2012). Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med*, 367(26), 2482–94.

Finn, W. F., Joy, M. S., and G. Hladik, G. (2004). Efficacy and safety of lanthanum carbonate for reduction of serum P in patients with chronic renal failure receiving hemodialysis. *Clin Nephrol*, 62(3), 193–201.

Floege, J., Ketteler, M., Rastogi, A., et al. (2012). *Efficacy and Safety of an Iron-Based Phosphate Binder, PA21, in Hyperphosphatemic CKD Patients on Dialysis*. Poster SA-PO1103 at ASN Congress 2012, San Diego, CA.

Foley, R. N., Collins, A. J., Herzog, C. A., *et al.* (2009). Serum P levels associate with coronary atherosclerosis in young adults. *J Am Soc Nephrol*, 20(2), 397–404.

Gagne, E. R., Urena, P., Leite-Silva, S., *et al.* (1992). Short- and long-term efficacy of total parathyroidectomy with immediate autografting compared with subtotal parathyroidectomy in hemodialysis patients. *J Am Soc Nephrol*, 3, 1008–17.

Gasparri, G., Camandona, M., Bertoldo, U., *et al.* (2009). The usefulness of preoperative dual-phase 99mTc MIBI-scintigraphy and IO-PTH assay in the treatment of secondary and tertiary hyperparathyroidism. *Ann Surg*, 250, 868–71.

Giangrande, A., Cantu, P., Solbiati, L., *et al.* (1985). Ultrasonically guided fine-needle alcohol injection as an adjunct to medical treatment in secondary hyperparathyroidism. *Proc Eur Dial Transplant Assoc*, 21, 895–901.

González, E. A., Sachdeva, A., Oliver, D. A., *et al.* (2004). Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. *Am J Nephrol*, 24(5), 503–10.

Hansler, J., Harsch, I. A., Strobel, D., *et al.* (2002). [Treatment of a solitary adenoma of the parathyroid gland with ultrasound-guided percutaneous radio-frequency-tissue-ablation (RFTA)]. *Ultraschall Med*, 23, 202–6.

Hindie, E., Urena, P., Jeanguillaume, C., *et al.* (1999). Preoperative imaging of parathyroid glands with technetium-99m-labelled sestamibi and iodine-123 subtraction scanning in secondary hyperparathyroidism. *Lancet*, 353, 2200–4.

Hou, S. H., Zhao, J., Ellman, C. F., *et al.* (1991). Ca and P fluxes during hemodialysis with low Ca dialysate. *Am J Kidney Dis*, 18(2), 217–24.

Hutchison, A. J., Barnett, M. E., Krause, R., *et al.* (2009). Lanthanum carbonate treatment, for up to 6 years, is not associated with adverse effects on the liver in patients with chronic kidney disease Stage 5 receiving hemodialysis. *Clin Nephrol*, 71(3), 286–95.

Jamal, S. A., Vandermeer, B., Raggi, P., *et al.* (2013). Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. *Lancet*, 382(9900), 1268–77.

Kalantar-Zadeh, K., Kuwae, N., Regidor, D. L., *et al.* (2006). Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int*, 70(4), 771–80.

Kaye, M. (1989). Parathyroidectomy in end-stage renal disease. *J Lab Clin Med*, 114, 334–5.

Kestenbaum, B., Andress, D. L., Schwartz, S. M., *et al.* (2004). Survival following parathyroidectomy among United States dialysis patients. *Kidney Int*, 66, 2010–16.

Kestenbaum, B., Sampson, J. N., Rudser, K. D., *et al.* (2005). Serum P levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol*, 16(2), 520–8.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009). KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*, 113, S1–130.

Kimata, N., Akiba, T., Pisoni, R. L., *et al.* (2005). Mineral metabolism and haemoglobin concentration among haemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*, 20(5), 927–35.

Kovatcheva, R. D., Vlahov, J. D., Stoinov, J. I., *et al.* (2012). High-intensity focussed ultrasound (HIFU) treatment in uraemic secondary hyperparathyroidism. *Nephrol Dial Transplant*, 27, 76–80.

Kovesdy, C. P., Ureche, V., Lu, J. L., *et al.* (2010). Outcome predictability of serum alkaline phosphatase in men with pre-dialysis CKD. *Nephrol Dial Transplant*, 25(9), 3003–11.

LaClair, R. E., Hellman, R. N., Karp, S. L., *et al.* (2005). Prevalence of calcidiol deficiency in CKD: a cross-sectional study across latitudes in the United States. *Am J Kidney Dis*, 45(6), 1026–33.

Lafage-Proust, M. H., Combe, C., Barthe, N., *et al.* (1999). Bone mass and dynamic parathyroid function according to bone histology in nondialyzed uremic patients after long-term protein and P restriction. *J Clin Endocrinol Metab*, 84(2), 512–19.

Lindberg, J. S., Moe, S. M., Goodman, W. G., *et al.* (2003). The calcimimetic AMG 073 reduces parathyroid hormone and Ca x P in secondary hyperparathyroidism. *Kidney Int*, 63(1), 248–54.

Malluche, H. H. (2002). Aluminium and bone disease in chronic renal failure. *Nephrol Dial Transplant*, 17 Suppl 2, 21–4.

Malluche, H.H., Siami, G. A., Swanepoel, C., *et al.* (2008). Improvements in renal osteodystrophy in patients treated with lanthanum carbonate for two years. *Clin Nephrol*, 70(4), 284–95.

Martinez, I., Saracho, R., Montenegro, J., *et al.* (1997). The importance of dietary Ca and phosphorous in the secondary hyperparathyroidism of patients with early renal failure. *Am J Kidney Dis*, 29(4), 496–502.

Maung, H. M., Elangovan, L., Frazão, J. M., *et al.* (2001). Efficacy and side effects of intermittent intravenous and oral doxercalciferol (1alpha-hydroxyvitamin D(2)) in dialysis patients with secondary hyperparathyroidism: a sequential comparison. *Am J Kidney Dis*, 37(3), 532–43.

Mazzaferro, S., Pasquali, M., Farcomeni, A., *et al.* (2008). Parathyroidectomy as a therapeutic tool for targeting the recommended NKF-K/DOQI ranges for serum calcium, phosphate and parathyroid hormone in dialysis patients. *Nephrol Dial Transplant*, 23, 2319–23.

Mehrotra, R., Kermah, D., Budoff, M., *et al.* (2008). Hypovitaminosis D in chronic kidney disease. Clin *J Am Soc Nephrol*, 3(4), 1144–51.

Messa, P., Gropuzzo, M., Cleva, M., *et al.* (1998). Behaviour of P removal with different dialysis schedules. *Nephrol Dial Transplant*, 13 Suppl 6, 43–8.

Minutolo, R., Bellizzi, V., Cioffi, M., *et al.* (2002). Postdialytic rebound of serum P: pathogenetic and clinical insights. *J Am Soc Nephrol*, 13(4), 1046–54.

Moe, S. M., Chertow, G. M., Coburn, J. W., *et al.* (2005). Achieving NKF-K/DOQI bone metabolism and disease treatment goals with cinacalcet HCl. *Kidney Int*, 67(2), 760–71.

National Kidney Foundation (2003). K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*, 42(4 Suppl 3), S1–201.

Navaneethan, S. D., Palmer, S. C., Craig, J. C., *et al.* (2009). Benefits and harms of P binders in CKD: a systematic review of randomized controlled trials. *Am J Kidney Dis*, 54(4), 619–37.

Nemeth, E. F., Heaton, W. H., Miller, M., *et al.* (2004). Pharmacodynamics of the type II calcimimetic compound cinacalcet HCl. *J Pharmacol Exp Ther*, 308(2), 627–35.

Noordzij, M., Korevaar, J. C., Boeschoten, E. W., *et al.* (2005). The Kidney Disease Outcomes Quality Initiative (K/DOQI) Guideline for Bone Metabolism and Disease in CKD: association with mortality in dialysis patients. *Am J Kidney Dis*, 46(5), 925–32.

Ogg, C. S. (1967). Total parathyroidectomy in treatment of secondary (renal) hyperparathyroidism. *Br Med J*, 4, 331–4.

Parkinson, I. S., Ward, M. K., Feest, T. G., *et al.* (1979). Fracturing dialysis osteodystrophy and dialysis encephalopathy. An epidemiological survey. *Lancet*, 1(8113), 406–9.

Quarles, L. D., Sherrard, D. J., Adler, S., *et al.* (2003). The calcimimetic AMG 073 as a potential treatment for secondary hyperparathyroidism of end-stage renal disease. *J Am Soc Nephrol*, 14(3), 575–83.

Quarles, L. D., Yohay, D. A., Carroll, B. A., *et al.* (1994). Prospective trial of pulse oral versus intravenous calcitriol treatment of hyperparathyroidism in ESRD. *Kidney Int*, 45(6), 1710–21.

Qunibi, W., Moustafa, M., Muenz, L. R., *et al.* (2008). A 1-year randomized trial of Ca acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Ca Acetate Renagel Evaluation-2 (CARE-2) study. *Am J Kidney Dis*, 51(6), 952–65.

Raggi, P., Chertow, G. M., Torres, P. U., *et al.* (2011). The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transplant*, 26(4), 1327–39.

Richards, M. L., Wormuth, J., Bingener, J., *et al.* (2006). Parathyroidectomy in secondary hyperparathyroidism: is there an optimal operative management? *Surgery*, 139, 174–80.

Rostaing, L., Moreau-Gaudry, X., Baron, E., *et al.* (1997). Changes in blood pressure and renal function after subtotal parathyroidectomy in renal transplant patients presenting persistent hypercalcemic hyperparathyroidism. *Transplant Proc*, 29, 204–6.

Rudser, K. D., de Boer, I. H., Dooley, A., *et al.* (2007). Fracture risk after parathyroidectomy among chronic hemodialysis patients. *J Am Soc Nephrol*, 18, 2401–7.

Salusky, I. B., Foley, J., Nelson, P., *et al.* (1991). Aluminum accumulation during treatment with aluminum hydroxide and dialysis in children and young adults with chronic renal disease. *N Engl J Med*, 324(8), 527–31.

Sheikh, M. S., Maguire, J. A., Emmett, M., *et al.* (1989). Reduction of dietary P absorption by P binders. A theoretical, in vitro, and in vivo study. *J Clin Invest*, 83(1), 66–73.

Shigematsu, T., Negi, S., Ishida, M., *et al.* (2012). Combined therapy with lanthanum carbonate and Ca carbonate for hyperphosphatemic decreases serum FGF-23 level independently of Ca and PTH (COLC Study). *Nephrol Dial Transplant*, 27(3), 1050–4.

Slinin, Y., Foley, R. N., and Collins, A. J. (2005). Ca, P, parathyroid hormone, and cardiovascular disease in hemodialysis patients: the USRDS waves 1, 3, and 4 study. *J Am Soc Nephrol*, 16(6), 1788–93.

Spasovski, G.B., Sikole, A., Gelev, S., *et al.* (2006). Evolution of bone and plasma concentration of lanthanum in dialysis patients before, during 1 year of treatment with lanthanum carbonate and after 2 years of follow-up. *Nephrol Dial Transplant*, 21(8), 2217–24.

Sprague, S. M., Llach, F., Amdahl, M., *et al.* (2003). Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. *Kidney Int*, 63(4), 1483–90.

Stanbury, S. W., Lumb, G. A., and Nicholson, W. F. (1960). Elective subtotal parathyroidectomy for renal hyperparathyroidism. *Lancet*, 1, 793–9.

Suki, W. N., Zabaneh, R., Cangiano, J. L., *et al.* (2007). Effects of sevelamer and Ca-based P binders on mortality in hemodialysis patients. *Kidney Int*, 72(9), 1130–7.

Tanaka, M., Itoh, K., Matsushita, K., *et al.* (2005). Efficacy of percutaneous ethanol injection therapy for secondary hyperparathyroidism in patients on hemodialysis as evaluated by parathyroid hormone levels according to K/DOQI guidelines. *Ther Apher Dial*, 9, 48–52.

Tanaka, M., Itoh, K., Matsushita, K., *et al.* (2006). Combination therapy of intravenous maxacalcitol and percutaneous ethanol injection therapy lowers serum parathyroid hormone level and calcium x phosphorus product in secondary hyperparathyroidism. *Nephron Clin Pract*, 102, c1–7.

Tentori, F., Blayney, M. J., Albert, J. M., *et al.* (2008). Mortality risk for dialysis patients with different levels of serum Ca, P, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*, 52(3), 519–30.

Tominaga, Y., Uchida, K., Haba, T., *et al.* (2001). More than 1,000 cases of total parathyroidectomy with forearm autograft for renal hyperparathyroidism. *Am J Kidney Dis*, 38, S168–71.

Torres, A., Lorenzo, V., and Salido, E. (2002). Calcium metabolism and skeletal problems after transplantation. *J Am Soc Nephrol*, 13, 551–8.

Urena, P., Basile, C., Grateau, G., *et al.* (1989). Short-term effects of parathyroidectomy on plasma biochemistry in chronic uremia. *Kidney Int*, 36, 120–6.

Williams, P. S., Stevens, M. E., Fass, G., *et al.* (1991). Failure of dietary protein and P restriction to retard the rate of progression of chronic renal failure: a prospective, randomized, controlled trial. *QJM*, 81(294), 837–55.

Wills, M. R. and Savory, J. (1983). Aluminium poisoning: dialysis encephalopathy, osteomalacia, and anaemia. *Lancet*, 2(8340), 29–34.

Wolf, M., Shah, A., Gutierrez, O., *et al.* (2007). Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int*, 72(8), 1004–13.

Yilmaz, M. I., Sonmez, A., Saglam, M., *et al.* (2012). Comparison of Ca acetate and sevelamer on vascular function and fibroblast growth factor 23 in CKD patients: a randomized clinical trial. *Am J Kidney Dis*, 59(2), 177–85.

Young, E. W., Albert, J. M., Satayathum, S., *et al.* (2005). Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. *Kidney Int*, 67(3), 1179–87.

CHAPTER 119

Fibroblast growth factor 23, Klotho, and phosphorus metabolism in chronic kidney disease

Orlando M. Gutiérrez

Introduction

Phosphorus (P) is an essential micronutrient involved in a number of critical biological processes including bone metabolism, energy transfer, and intracellular signalling. Systemic P homeostasis is tightly regulated through a dynamic balance between dietary P absorption, urinary P excretion, and exchanges with bone, soft tissue, and intracellular stores. For over seven decades, parathyroid hormone (PTH) was considered the primary hormonal regulator of P balance via its modulation of vitamin D synthesis, bone resorption, and renal P handling. However, the more recent discovery and characterization of several new P-regulating hormones (collectively termed 'phosphatonins'(Cai et al., 1994)) has revolutionized our understanding of P metabolism and clarified much of the pathophysiology underlying disturbances in P homeostasis in health and chronic kidney disease (CKD). Fibroblast growth factor 23 (FGF23) and Klotho in particular appear to play central roles in regulating mineral metabolism. Disturbances in the expression of FGF23 and Klotho are strongly linked to the genesis and progression of altered bone and mineral metabolism in CKD. Moreover, abnormal concentrations of FGF23 and Klotho have been implicated in the pathogenesis of cardiovascular disease, kidney disease progression, and death in CKD patients. The focus of this chapter will be to review the role of FGF23 and Klotho in P and vitamin D homeostasis, their link to disturbances in P and vitamin D metabolism in kidney disease, and their potential role in mediating adverse outcomes in CKD.

Physiological actions of FGF23 and Klotho in health and in chronic kidney disease

FGF23

FGF23 was initially discovered as the causative factor for several rare forms of osteomalacia/rickets that are either inherited (X-linked hypophosphataemic rickets (XLH), autosomal dominant hypophosphataemic rickets (ADHR)) or acquired (tumour-induced osteomalacia (TIO)). All are characterized by hypophosphataemia due to urinary P wasting and low or inappropriately normal circulating 1,25 dihydroxyvitamin D ($1,25(OH)_2D$) concentrations (Jonsson et al., 2003; Quarles, 2003). Collaborative efforts to uncover the genetic basis for ADHR culminated in the discovery that mutations in the gene encoding FGF23 were strongly associated with ADHR (ADHR Consortium, 2000). Mechanistic studies later showed that these mutations resulted in the synthesis and secretion of an FGF23 peptide that was resistant to proteolytic cleavage, allowing for the accumulation of excess quantities of biologically active FGF23 in the circulation of ADHR patients (White et al., 2001; Bai et al., 2003). Studies subsequently showed that circulating concentrations of FGF23 were also markedly elevated in patients with XLH and TIO (Shimada et al., 2001; Jonsson et al., 2003), explaining the striking phenotypic similarities between these syndromes. Further, overexpression of *fgf23* in animal models recapitulated the biochemical and metabolic derangements characteristic of these conditions (Shimada et al., 2001, 2004; Bai et al., 2003), indicating that excess FGF23 is the primary causative factor underlying these disorders. In parallel, studies showed that genetic mutations that result in decreased FGF23 bioactivity led to severe ectopic calcification due to excess serum P and $1,25(OH)_2D$ concentrations (Chefetz et al., 2005; Ichikawa et al., 2005; Larsson et al., 2005a, 2005b; Kato et al., 2006), highlighting the critical role of FGF23 in regulating P and vitamin D metabolism.

The *FGF23* gene encodes a protein of 251 amino acids and is most highly expressed in osteocytes and osteoblasts (Quarles, 2008). The N-terminal domain of FGF23 contains the FGF homology domain, whereas the C-terminal domain contains the unique 71-amino acid sequence that distinguishes it from the other known members of the FGF family. Interestingly, FGF23 belongs to a subfamily of FGFs (known as the FGF19 subfamily) that lack several amino acid residues in their C-terminal domain, allowing them to be more soluble in circulation, due to their low binding affinity to heparin, and thus able to exert systemic actions in contrast to other FGFs (such as FGF1 and FGF2) that primarily exert paracrine/autocrine effects (Quarles, 2012). Binding of FGF23 to its cognate receptor is mediated by Klotho, a transmembrane protein

that is most highly expressed in the kidney and parathyroid glands (discussed in greater detail below) (Urakawa et al., 2006).

Role of FGF23 in P and vitamin D metabolism

Although primarily secreted by bone cells, the main sites of action of FGF23 are the kidneys and parathyroid glands (Fig. 119.1). In the kidneys, FGF23 stimulates the endocytosis of Na-P cotransporters (NPT2a and NPT2c) from the apical membrane of renal proximal tubular cells, resulting in diminished reabsorption of inorganic P filtered at the glomerulus (Saito et al., 2003). In addition, FGF23 inhibits the synthesis of renal 25(OH)D-1α-hydroxylase (Bowe et al., 2001; Yamashita et al., 2002; Saito et al., 2003; Liu et al., 2006), the enzyme required to convert 25(OH)D to its more active metabolite, $1,25(OH)_2D$, and upregulates the activity of 24-hydroxylase (Inoue et al., 2005), the enzyme that represents the major catabolic pathway for both 25(OH)D and $1,25(OH)_2D$. In the parathyroid glands, FGF23 directly inhibits the synthesis and secretion of PTH (Ben-Dov et al., 2007; Krajisnik et al., 2007), perhaps representing a secondary, indirect mechanism for inhibiting $1,25(OH)_2D$ synthesis. Furthermore, in contrast to its inhibitory effect on 25(OH)D-1α-hydroxylase in the kidney, Krajisnik et al. showed that FGF23 stimulated the expression of 25(OH)D-1α-hydroxylase in bovine parathyroid gland tissue (Krajisnik et al., 2007). Although the reasons for this finding were unclear, the authors speculated that this may lead to increased local $1,25(OH)_2D$ concentrations in parathyroid tissue, perhaps as an additional inhibitor of PTH synthesis. Collectively, these actions appear to serve the main purpose of maintaining P homeostasis in states of P excess, by enhancing urinary P excretion and diminishing intestinal P absorption by reducing the stimulatory effect of $1,25(OH)_2D$ on Na-P cotransporters (NPT2b) in gut epithelial cells (Katai et al., 1999; Marks et al., 2010).

Consistent with these actions, the primary systemic regulators of FGF23 secretion are $1,25(OH)_2D$, dietary P intake and, potentially, PTH (Ferrari et al., 2005; Ito et al., 2005; Perwad et al., 2005; Saito et al., 2005; Antoniucci et al., 2006; Burnett et al., 2006; Liu et al., 2006; Lavi-Moshayoff et al., 2010). $1,25(OH)_2D$ directly stimulates FGF23 expression by binding to a vitamin D response element in the promoter region of *fgf23* (Liu et al., 2006). Increased dietary P

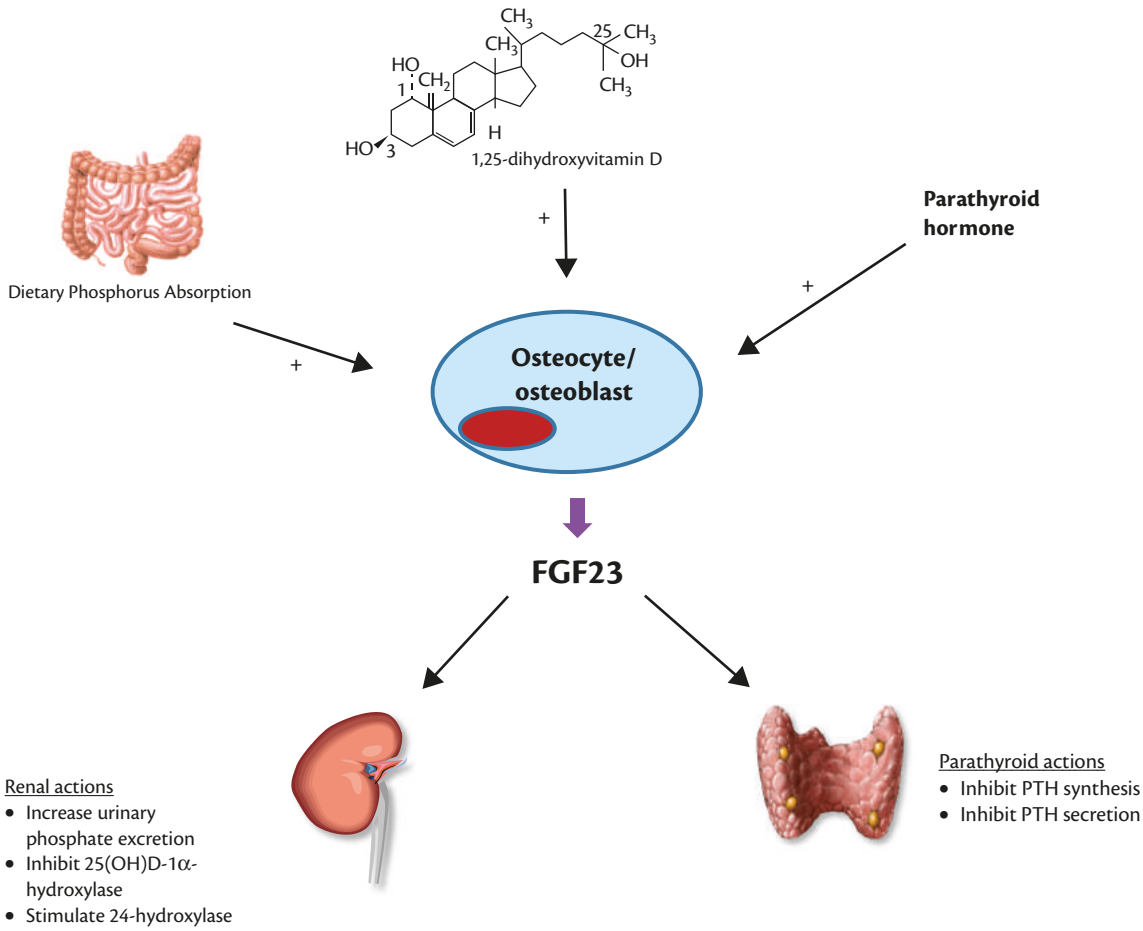

Fig. 119.1 Regulation and action of fibroblast growth factor 23 (FGF23). Osteoblasts and osteocytes are the primary cells that synthesize and secrete FGF23. There are three primary systemic stimuli of FGF23 secretion—increased dietary phosphorus absorption, increased 1,25-dihydroxyvitamin D concentrations, and increased parathyroid hormone concentrations. FGF23 acts primarily in the kidneys and parathyroid glands. In the kidneys, FGF23 augments urinary phosphate excretion by downregulating sodium-phosphate cotransporters in renal proximal tubular cells. In addition, FGF23 inhibits the synthesis of 25-hydoxyvitamin D-1α-hydroxylase and upregulates 24-hydroxylase, both of which serve to decrease circulating 1,25-dihydroxyvitamin D concentrations. In the parathyroid glands, FGF23 inhibits both the synthesis and secretion of parathyroid hormone. Together, these actions appear to serve the primary purpose of maintaining phosphorus homeostasis in states of phosphorus excess (like chronic kidney disease) by enhancing urinary phosphate excretion and decreasing intestinal phosphorus absorption via lower 1,25-dihydroxyvitamin D concentrations.

intake also stimulates the secretion of FGF23 (Ferrari et al., 2005; Antoniucci et al., 2006; Burnett et al., 2006), though the mechanisms involved in the regulation of FGF23 secretion by dietary P remain unclear. Interestingly, *in vitro* and *in vivo* studies have failed to convincingly show that inorganic P can directly stimulate FGF23 secretion itself, suggesting that FGF23 may regulate net P balance instead of serum P per se. The effects of PTH on FGF23 are more controversial. Whereas studies have shown that PTH indirectly stimulates FGF23 by increasing systemic $1,25(OH)_2D$ concentrations (Burnett-Bowie et al., 2009; Sridharan et al., 2010; Wesseling-Perry et al., 2010; Lopez et al., 2011), the data suggesting that PTH directly stimulates FGF23 are less consistent, with some (Lavi-Moshayoff et al., 2010; Lopez et al., 2011), but not all studies (Liu et al., 2006; Samadfam et al., 2009; Saji et al., 2010), showing that PTH augments the expression of *fgf23* in bone cells. Further studies will need to clarify whether PTH directly regulates FGF23 or not. If so, it would support the notion that PTH and FGF23 exist in a classic negative feedback loop, whereby higher PTH concentrations directly induce the expression of FGF23 in order to inhibit both PTH and 25(OH) D-1α-hydroxylase and thus serve as a physiological brake towards further PTH-induced stimulation of $1,25(OH)_2D$ synthesis.

Systemic calcium (Ca) and iron also appear to regulate FGF23. Several groups have shown that Ca deficiency strongly inhibits the synthesis of FGF23 (Rodriguez-Ortiz et al., 2012; Quinn et al., 2013), likely as an adaptive mechanism to increase $1,25(OH)_2D$ concentrations and promote dietary Ca absorption. In line with these findings, dietary P loading failed to stimulate FGF23 secretion in hypocalcaemic animals until the Ca deficiency had been reversed (Rodriguez-Ortiz et al., 2012; Quinn et al., 2013), suggesting that P-induced stimulation of FGF23 secretion is at least partly dependent on the concurrent Ca economy. In addition, iron has been shown to regulate FGF23, potentially by altering cleavage of the FGF23 peptide (Farrow et al., 2011; Imel et al., 2011; Braithwaite et al., 2012; Wolf et al., 2013).

Several studies suggest that FGF23 may also have important effects on bone mineralization, independent of its effects on systemic P and vitamin D metabolism. Inactivating mutations in the genes that encode DMP1, PHEX, ANK1, and ENPP1—all local bone-derived factors that regulate bone mineralization—result in increased FGF23 expression (Sitara et al., 2004; Feng et al., 2006; Lorenz-Depiereux et al., 2006; Levy-Litan et al., 2010; Lorenz-Depiereux et al., 2010; Chen et al., 2011; Quarles, 2012), suggesting that FGF23 may play a role in regulating bone mineralization. Further, overexpression of FGF23 in rat calvaria cells suppressed osteoblast differentiation and matrix mineralization independently of inorganic P (Wang et al., 2008). A subsequent study demonstrated a similar inhibitory effect of excess FGF23 on matrix mineralization in an osteoblast-like cell line (Shalhoub et al., 2011). In contrast, complete absence of FGF23 was associated with impaired skeletal mineralization despite elevated circulating levels of P and vitamin D (Shimada et al., 2004; Sitara et al., 2004). Together, these results suggest that either over- or underexpression of FGF23 impairs bone mineralization via dysregulation of osteoblast function.

Role of FGF23 in altered P and vitamin D metabolism in CKD

FGF23 concentrations increase early in the course of CKD—perhaps as early as an estimated glomerular filtration rate (eGFR) of 90 mL/min/1.73 m^2 (Ix et al., 2010)—and progressively rise as kidney function declines, such that by the time that patients reach end-stage renal disease, FGF23 concentrations can be up to 1000-fold above the normal range (Larsson et al., 2003; Gutierrez et al., 2008). The increase in FGF23 in early CKD appears to be an appropriate physiological response to maintain normal P balance in the face of declining nephron mass, by increasing urinary P excretion and decreasing gut P absorption via decreased $1,25(OH)_2D$ concentrations (Gutierrez et al., 2005). The importance of this response for maintaining P balance in CKD is supported by several observations. Hasegawa et al. examined the impact of lowering FGF23 concentrations on P homeostasis in CKD by injecting anti-FGF23 antibody in rats with experimentally-induced kidney disease (Hasegawa et al., 2010). Anti-FGF23 antibodies markedly lowered serum FGF23 concentrations in these animals, resulting in decreased urinary fractional excretion of P and higher $1,25(OH)_2D$ concentrations. As a consequence, serum P concentrations significantly increased, despite concurrently elevated PTH concentrations. These data strongly suggest that increased FGF23 concentrations are essential for mitigating hyperphosphataemia in CKD—even in the face of concomitant hyperparathyroidism—by enhancing urinary P excretion and, perhaps more importantly, limiting intestinal absorption of P via lower $1,25(OH)_2D$ concentrations. Consistent with these observations, studies have shown that restriction of dietary P absorption decreased, and in some cases normalized, blood FGF23 concentrations in animals or humans with CKD (Koiwa et al., 2005; Nagano et al., 2006; Oliveira et al., 2010; Gonzalez-Parra et al., 2011; Moe et al., 2011; Shigematsu et al., 2012), supporting the concept that elevations in circulating FGF23 are essential adaptive changes for maintaining P homeostasis in the face of unrestricted dietary P intake in kidney failure.

In line with the critical role of FGF23 in maintaining P balance in kidney injury, experimental and human data suggest that increases in FGF23 are among the earliest biochemical manifestations of disturbed P metabolism in CKD—chronologically preceding increases in PTH and serum P and decreases in serum Ca and $1,25(OH)_2D$ concentrations. Hasegawa et al. showed that, following the induction of kidney injury in rats, FGF23 was the first analyte to increase in the serum, followed in sequential order by a decrease in $1,25(OH)_2D$ concentrations and then an increase in PTH concentrations (Hasegawa et al., 2010). Given the powerful inhibitory effect of FGF23 on $1,25(OH)_2D$ synthesis, these data suggest that increases in blood FGF23 concentrations may be the sentinel hormonal disturbance in P metabolism that initiates or accelerates the fall in $1,25(OH)_2D$ concentrations in early-stage kidney failure, a key factor underlying the development of secondary hyperparathyroidism in CKD. In line with this, Isakova et al. analysed the prevalence of abnormal concentrations of P, Ca, PTH, and FGF23 across narrow categories of eGFR in a cross-sectional sample of 3519 patients with CKD (Isakova et al., 2011a). These investigators found that the prevalence of excess FGF23 was substantially higher than the other cardinal manifestations of disordered mineral metabolism (i.e. hyperparathyroidism, hypocalcaemia, and hyperphosphataemia) in the earliest stages of kidney disease. Moreover, using restricted cubic splines, these investigators showed that circulating FGF23 concentrations started to increase prior to any of the other indices of mineral metabolism, first occurring around an eGFR cut-point of 60 mL/min/1.73 m^2.

When taken together, these data suggest that FGF23 may be the earliest 'bellwether' of disturbances in P metabolism in kidney disease and thus, an important potential target for retarding the progression of disordered mineral metabolism in CKD patients. Since dietary P intake is among the strongest systemic physiological stimuli of FGF23, this would support much earlier restriction of dietary P absorption (either through decreased intake or increased use of oral phosphorus binders) than is currently recommended in clinical practice guidelines. Moreover, since nutritional and activated forms of vitamin D strongly stimulate FGF23 secretion (Wesseling-Perry et al., 2011; Burnett-Bowie et al., 2012)—perhaps 'fuelling' the fire of FGF23 excess—this may also suggest that the use of these therapeutics may need to be used in conjunction with dietary P restriction, or be curtailed in favour of dietary P restriction in early CKD.

FGF23 and adverse outcomes in CKD

Beyond its critical role in regulating P and vitamin D metabolism, FGF23 may also have an important role in cardiovascular morbidity and mortality in CKD. Studies have shown that higher FGF23 concentrations were independently associated with higher risk of kidney disease progression, cardiovascular disease events, and death in chronic haemodialysis patients and in patients with CKD not yet requiring haemodialysis (Fliser et al., 2007; Gutierrez et al., 2008; Jean et al., 2009; Seiler et al., 2010; Isakova et al., 2011b; Kendrick et al., 2011; Scialla et al., 2013a). In addition, higher FGF23 concentrations were associated with higher risk of cardiovascular disease events and death in individuals with mostly preserved kidney function (Parker et al., 2010; Ix et al., 2012).

While the mechanisms underlying these associations remain unclear, growing evidence suggests that FGF23 may directly mediate cardiovascular disease. A number of groups have shown that higher FGF23 concentrations were independently associated with higher left ventricular mass (Gutierrez et al., 2009; Mirza et al., 2009c; Faul et al., 2011), and higher prevalence of left ventricular hypertrophy, endothelial dysfunction, and vascular calcification, even in individuals with preserved kidney function (Gutierrez et al., 2009; Mirza et al., 2009a, 2009b, 2009c; Kanbay et al., 2010; Faul et al., 2011). Further, lowering FGF23 concentrations was associated with improved endothelial function in patients with CKD (Yilmaz et al., 2012). Importantly, however, other studies have shown that FGF23 either does not induce or in fact protects against vascular calcification, suggesting that the link between FGF23 and vascular disease is not mediated via dystrophic calcification (Lim et al., 2012; Scialla et al., 2013b; Zhu et al., 2013). In contrast, FGF23 was shown to directly induce hypertrophy of rat neonatal cardiomyocytes via FGFR-dependent activation of the calcineurin-NFAT signalling pathway *in vitro*, and induced LVH after intra-myocardial or intravenous injection of FGF23 in mice *in vivo*, revealing a direct stimulatory effect of FGF23 on myocardial hypertrophy (Faul et al., 2011). Another study showed that FGF23 promoted LVH via alterations in intracellular concentrations of calcium in cardiomyocytes, revealing another potential pathway by which FGF23 may induce cardiac hypertrophy (Touchberry et al., 2013). Together, these data suggest that elevated FGF23 concentrations may induce or accelerate cardiovascular disease in CKD and thus, may be a promising target of intervention for ameliorating cardiovascular outcomes in CKD patients.

Klotho

Klotho is a key regulator of mineral metabolism, glucose homeostasis, and endothelial function. Klotho exists in two forms, a transmembrane form and a circulating form, each with distinct functions. The transmembrane form serves as the critical co-factor required for FGF23 signal transduction in the kidney and the parathyroid glands (Kurosu et al., 2006; Urakawa et al., 2006). The secreted form has systemic effects modulating P and Ca metabolism (Chang et al., 2005; Imura et al., 2007; Alexander et al., 2009; Hu et al., 2010a), insulin sensitivity (Utsugi et al., 2000; Anour et al., 2012), and endothelial function (Saito et al., 1998; Nagai et al., 2000). Collectively, these actions appear to contribute to the 'anti-ageing' properties of Klotho (Kurosu et al., 2005), with potential implications for developing novel therapies to retard the development of age-related diseases.

The discovery of Klotho was a fortuitous accident. In an attempt to develop a transgenic mouse model overexpressing the rabbit type-I sodium-proton exchanger, an exogenous transgene was accidentally inserted within the promoter region of what was later discovered to be the *klotho* gene (Kuro-o et al., 1997). Mice with this insertional mutation developed a phenotype strongly resembling human ageing, characterized by growth retardation, inactivity, osteoporosis, arteriosclerosis, dystrophic calcification, and skin atrophy, among other age-related phenomena (Kuro-o et al., 1997). In addition, affected mice exhibited increased serum concentrations of Ca and P and hypoglycaemia (Kuro-o et al., 1997). Subsequent cloning of the *klotho* gene revealed that it encoded a 1012-amino acid long peptide with a single transmembrane domain and an extracellular domain with two internal repeats (KL1 and KL2) that exhibit β-glucosidase activity (Matsumura et al., 1998). In addition to the membrane-bound form, Klotho also has a circulating form that is derived either from alternative RNA splicing or cleavage of the extracellular domain by various proteases (Matsumura et al., 1998; Shiraki-Iida et al., 1998; Imura et al., 2004; Chen et al., 2007; Bloch et al., 2009). Both the transmembrane and secreted forms of Klotho appear to be expressed primarily in the brain, the kidney, and the parathyroid glands (Kuro-o et al., 1997; Li et al., 2004), with lower-grade expression detected in a variety of other tissues.

Role of Klotho in P, Ca, and vitamin D metabolism

Both the transmembrane and secreted forms of Klotho have important and sometimes overlapping roles in the regulation of mineral metabolism (Fig. 119.2). The transmembrane form of Klotho serves as the critical co-factor necessary for FGF23 to bind to its cognate receptor with high-enough affinity to effect signal transduction. Urakawa et al. demonstrated that Klotho does so by converting FGF receptor 1 (FGFR1, isoform IIIc) from a general canonical receptor for FGFs into a specific receptor for FGF23, allowing for high-affinity binding of FGF23 to FGFR and subsequent activation of the early growth-responsive 1 (Egr-1) signalling pathway (Urakawa et al., 2006). Klotho also appears to form binary complexes with FGFR3c and FGFR4, substantially increasing their affinity for FGF23 (Kurosu et al., 2006). The critical importance of these actions to FGF23 signal transduction is evidenced by *klotho* knockout mice that develop severe hyperphosphataemia, hypercalcaemia, and inappropriately elevated $1,25(OH)_2D$ concentrations, despite markedly elevated FGF23 concentrations (Nakatani et al., 2009), suggesting functional inhibition of FGF23 activity. In

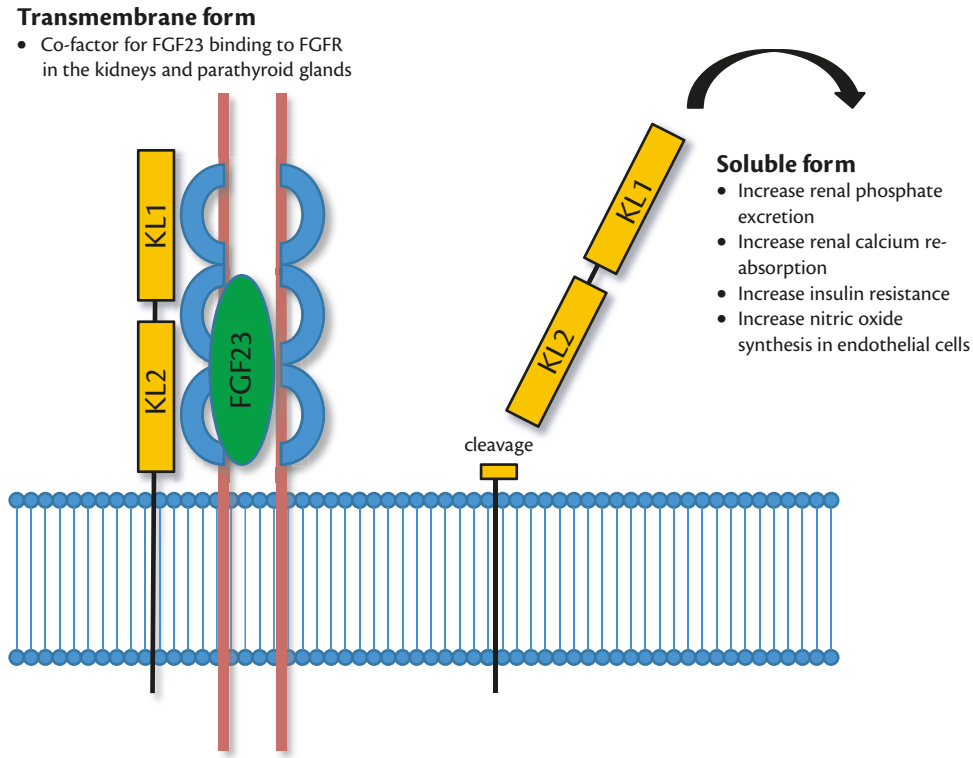

Fig. 119.2 Transmembrane and soluble forms of Klotho and their actions. Klotho has two forms, a transmembrane form and a secreted form derived from alternative RNA splicing or cleavage of the extracellular domain by various proteases. The transmembrane form serves as the critical co-factor needed for FGF23 to bind to FGF receptors in the kidneys and the parathyroid glands. The soluble form has a number of actions including increasing urinary phosphate excretion via an FGF23-independent mechanism, enhancing renal distal tubule calcium reabsorption, increasing insulin sensitivity, and increasing nitric oxide synthesis in endothelial cells. The cleavage of Klotho is stimulated by a number of factors including insulin and peroxisome proliferator-activated receptor gamma.

addition to these actions, the localized tissue expression of transmembrane Klotho appears to provide tissue specificity for the actions of FGF23, despite the nearly ubiquitous expression of FGFRs throughout the body. Indeed, *klotho* is primarily expressed in the kidney and parathyroid glands (Kuro-o et al., 1997; Li et al., 2004), the two main sites of FGF23 action.

The secreted form of Klotho also has independent phosphaturic effects. Circulating Klotho directly induces phosphaturia by enhancing the endocytosis of Na-P cotransporters in proximal tubule cells via deglycosylation of N-linked glycans of NPT2a (Hu et al., 2010a). Thus, in addition to regulating P by acting as a co-factor for FGF23, Klotho also appears to directly modulate renal P handling.

Klotho regulates systemic Ca homeostasis via two main actions (Chang et al., 2005; Imura et al., 2007; Cha et al., 2008; Alexander et al., 2009). Klotho increases the density of transient receptor potential cation channel, subfamily V, member 5 (TRPV5), on the apical aspect of distal nephron cells (Chang et al., 2005). TRPV5 is the primary channel responsible for transcellular Ca absorption in the kidney. By removing the terminal sialic acid residues on TRPV5 via a putative sialidase activity, Klotho prevents the endocytosis of the channel, increasing its cell-surface abundance in distal nephron cells and thus, the reabsorption of filtered Ca from the tubule lumen (Cha et al., 2008). The importance of these actions for renal Ca handling is supported by *klotho* knock-out mice that show evidence of renal Ca wasting, likely due to decreased TRPV5 channel density in distal nephron tubules (Alexander et al., 2009; Asai et al., 2012). In addition to these actions, Klotho has also been shown to increase the activity of Na-K ATPase in the kidney and parathyroid glands, thereby augmenting transcellular Ca reabsorption by promoting a greater Na gradient in distal nephron tubular cells and by potentiating PTH secretion in response to hypocalcaemia (Imura et al., 2007; Razzaque, 2008).

Role of Klotho in altered P and vitamin D metabolism in CKD

Disturbances in Klotho expression may play an important role in the development of altered mineral metabolism in CKD. Renal *klotho* expression was shown to be downregulated in a 5/6th nephrectomy animal model of CKD and in animals with experimentally induced acute kidney injury (Aizawa et al., 1998; Sugiura et al., 2005; Hu et al., 2010b). In an ischaemia-reperfusion model of acute kidney injury, plasma and urine levels of Klotho decreased after the induction of kidney injury in rats and then returned to baseline levels with recovery of kidney function, suggesting that decreased expression of Klotho in response to kidney injury may be reversible (Hu et al., 2010b). Similarly, renal *klotho* expression was substantially decreased in nephrectomy specimens from CKD patients as compared to otherwise healthy controls (Koh et al., 2001), and Klotho concentrations in the urine of patients with acute kidney injury and CKD were found to be significantly lower than in healthy volunteers (Hu et al., 2010b; Hu et al., 2011). Although the reasons for the decreased expression of Klotho in kidney disease

are currently unclear, one study implicated epigenetic DNA hypermethylation of *klotho* by uraemic toxins as a potential mechanism (Sun et al., 2012).

The finding of decreased Klotho expression in kidney failure has led to the hypothesis that kidney disease may be a state of relative 'Klotho deficiency,' potentially leading to FGF23 resistance in the kidney and the parathyroid glands. Several observations support this view. A number of groups have shown that the expression of *klotho* and the Klotho–FGFR complex were reduced in parathyroid glands from uraemic animals and CKD patients as compared to non-uraemic controls (Canalejo et al., 2010; Galitzer et al., 2010; Komaba et al., 2010; Kumata et al., 2010; Krajisnik et al., 2010). Further, overexpression of Klotho in an animal model of CKD resulted in decreased serum PTH concentrations than in wild-type animals with moderate CKD (Hu et al., 2011). Since transmembrane Klotho serves as the critical co-factor needed for FGF23 to bind to FGFR in the parathyroid glands and thereby inhibit PTH synthesis, these findings suggest that decreased Klotho expression in CKD may partly explain the diminished ability of FGF23 to inhibit PTH synthesis in uraemic parathyroid glands as compared to parathyroid glands from non-uraemic controls (Canalejo et al., 2010; Galitzer et al., 2010). Notably, however, other groups have shown that Klotho expression in parathyroid glands from uraemic animals or CKD patients was preserved or higher than in non-uraemic controls (Hofman-Bang et al., 2010; Ohkido et al., 2010), underscoring the complexity of these relationships. Nevertheless, if decreased Klotho expression in uraemic parathyroid glands can be definitively confirmed, this would suggest that relative Klotho deficiency may abrogate the inhibitory effect of elevated FGF23 concentrations on PTH synthesis and thus, represent a novel mechanism for secondary hyperparathyroidism in CKD.

Decreased Klotho expression in the kidneys may similarly inhibit the phosphaturic effects of FGF23 in renal proximal tubule cells. In support of this possibility is a study showing that overexpression of Klotho in animals with experimentally-induced CKD resulted in higher urinary P excretion and lower serum P concentrations than wild-type animals with moderate CKD (Hu et al., 2011). Whether this was due to an improved ability of FGF23 to induce signal transduction in the kidney or a direct phosphaturic effect of circulating Klotho was unclear. If the former, it would support the concept that higher FGF23 concentrations in CKD may be due, in part, to end-organ resistance at the level of the kidney, an intriguing hypothesis that requires confirmation in future studies.

In addition to its effects on FGFR binding, decreased Klotho expression may also affect FGF23 concentrations through direct regulation of FGF23 synthesis. Smith et al. showed that mice overexpressing Klotho developed markedly increased circulating FGF23 concentrations via stimulation of FGF23 synthesis at the level of the bone (Smith et al., 2012). In light of these findings, and in contrast to current prevailing views that decreases in Klotho expression in CKD are 'maladaptive', it is possible that decreased Klotho expression may represent an appropriate response to lower circulating FGF23 concentrations by reducing Klotho-induced simulation of FGF23 synthesis in CKD.

Beyond its effects on mineral metabolism, there is growing evidence that Klotho may also have important renoprotective properties. Hu et al. and Sugiura et al. demonstrated that overexpression of Klotho or administration of recombinant Klotho in animals protected them against renal ischaemic injury (Sugiura et al., 2005, 2010; Hu et al., 2010b), whereas decreased Klotho expression exacerbated kidney injury after unilateral ureteral obstruction (Sugiura et al., 2012). In addition, overexpression of Klotho or administration of Klotho protein was shown to protect the kidneys from injury due to angiotensin II infusion (Mitani et al., 2002), chronic hypertension (Wang and Sun, 2009), uninephrectomy with or without contralateral ischaemia-reperfusion (Hu et al., 2011; Nagasu et al., 2011), unilateral ureteral obstruction (Doi et al., 2011), and immune complex-mediated glomerulonephritis (Haruna et al., 2007), supporting a potential role for Klotho as a renoprotective factor.

Role of Klotho in endothelial function and insulin sensitivity

Even before its role in regulating mineral metabolism was first recognized, Klotho was shown to have important actions modulating endothelial function and insulin sensitivity. Circulating Klotho increases nitric oxide (NO) synthesis in endothelial cells, which is critical for maintaining vascular reactivity (Saito et al., 1998; Nagai et al., 2000). The importance of this action was demonstrated in Klotho-deficient mice which exhibited markedly reduced vasodilation in response to acetylcholine challenge as compared to wild-type controls (Saito et al., 1998). Importantly, parabiosis between wild-type and heterozygous *klotho* mice restored endothelial function in the Klotho-deficient animals, confirming the critical role of circulating Klotho in maintaining endothelial health (Saito et al., 1998). Furthermore, adenovirus-mediated Klotho gene delivery in an animal model of accelerated atherogenesis improved vascular endothelial dysfunction, increased NO production, and reduced elevated blood pressure (Saito et al., 2000), and overexpression of Klotho protected endothelial cell health via both antioxidative and antiapoptotic effects (Ikushima et al., 2006; Rakugi et al., 2007). In addition, overexpression of Klotho decreased vascular calcification in an animal model of CKD, in part by inhibiting P-induced osteogenic changes in vascular smooth muscle cells (Hu et al., 2011), whereas Klotho knockdown promoted vascular calcification by potentiating FGF23 anticalficic effects (Lim et al., 2012), further supporting a key role of Klotho in protecting cardiovascular health.

The finding that Klotho-deficient mice developed hypoglycaemia despite very low circulating insulin concentrations led to the recognition that Klotho also has important sensitizing effects on insulin action (Kuro-o et al., 1997; Utsugi et al., 2000; Anour et al., 2012). This was confirmed by Klotho-overexpressing transgenic mice that demonstrated resistance to both insulin and insulin growth factor 1 (IGF-1) via direct inhibition of the action of these hormones (Kurosu et al., 2005). Furthermore, insulin stimulates the shedding of Klotho into the circulation (Chen et al., 2007), and peroxisome proliferator-activator receptor gamma (PPAR-γ) upregulates Klotho expression (Zhang et al., 2008), suggesting important counter-regulatory relationships between Klotho and these key mediators of systemic glucose homeostasis. Whether these actions contribute to the anti-ageing properties of Klotho is possible (Kurosu et al., 2005), but requires further investigation.

Summary

The discovery and characterization of FGF23 and Klotho have revolutionized our understanding of P and vitamin D metabolism, and clarified much of the mechanisms underlying disorders in mineral

metabolism in CKD. Disturbances in the expression of both FGF23 and Klotho occur very early in the course of kidney disease, suggesting that both hormones may show promise as novel biomarkers of early kidney disease. In addition, growing evidence that these hormones have direct and indirect effects on cardiovascular health above and beyond their effects on mineral metabolism suggests that therapies targeted at normalizing FGF23 and Klotho concentrations may help improve markedly poor outcomes in patients with CKD. Further studies aimed at clarifying pathophysiological mechanisms by which FGF23 and Klotho contribute to bone and cardiovascular disease may help accelerate the development of these hormones as potential tools for guiding the clinical management of disordered mineral metabolism in CKD.

References

ADHR Consortium (2000). Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. *Nat Genet*, 26, 345–8.

Aizawa, H., Saito, Y., Nakamura, T., *et al.* (1998). Downregulation of the Klotho gene in the kidney under sustained circulatory stress in rats. *Biochem Biophys Res Commun*, 249, 865–71.

Alexander, R. T., Woudenberg-Vrenken, T. E., Buurman, J., *et al.* (2009). Klotho prevents renal calcium loss. *J Am Soc Nephrol*, 20, 2371–9.

Anour, R., Andrukhova, O., Ritter, E., *et al.* (2012). Klotho lacks a vitamin D independent physiological role in glucose homeostasis, bone turnover, and steady-state PTH secretion in vivo. *PLoS One*, 7, e31376.

Antoniucci, D. M., Yamashita, T., and Portale, A. A. (2006). Dietary phosphorus regulates serum fibroblast growth factor-23 concentrations in healthy men. *J Clin Endocrinol Metab*, 91, 3144–9.

Asai, O., Nakatani, K., Tanaka, T., *et al.* (2012). Decreased renal alpha-Klotho expression in early diabetic nephropathy in humans and mice and its possible role in urinary calcium excretion. *Kidney Int*, 81, 539–47.

Bai, X. Y., Miao, D., Goltzman, D., *et al.* (2003). The autosomal dominant hypophosphatemic rickets R176Q mutation in fibroblast growth factor 23 resists proteolytic cleavage and enhances in vivo biological potency. *J Biol Chem*, 278, 9843–9.

Ben-Dov, I. Z., Galitzer, H., Lavi-Moshayoff, V., *et al.* (2007). The parathyroid is a target organ for FGF23 in rats. *J Clin Invest*, 117, 4003–8.

Bloch, L., Sineshchekova, O., Reichenbach, D., *et al.* (2009). Klotho is a substrate for alpha-, beta- and gamma-secretase. *FEBS Lett*, 583, 3221–4.

Bowe, A. E., Finnegan, R., Jan De Beur, S. M., *et al.* (2001). FGF-23 inhibits renal tubular phosphate transport and is a PHEX substrate. *Biochem Biophys Res Commun*, 284, 977–81.

Braithwaite, V., Jarjou, L. M., Goldberg, G. R., *et al.* (2012). Iron status and fibroblast growth factor-23 in Gambian children. *Bone*, 50, 1351–6.

Burnett-Bowie, S. A., Leder, B. Z., Henao, M. P., *et al.* (2012). Randomized trial assessing the effects of ergocalciferol administration on circulating FGF23. *Clin J Am Soc Nephrol*, 7(4), 624–31.

Burnett-Bowie, S. M., Henao, M. P., Dere, M. E., *et al.* (2009). Effects of hPTH(1-34) infusion on circulating serum phosphate, 1,25-dihydroxyvitamin D, and FGF23 levels in healthy men. *J Bone Miner Res*, 24, 1681–5.

Burnett, S. M., Gunawardene, S. C., Bringhurst, F. R., *et al.* (2006). Regulation of C-terminal and intact FGF-23 by dietary phosphate in men and women. *J Bone Miner Res*, 21, 1187–96.

Cai, Q., Hodgson, S. F., Kao, P. C., *et al.* (1994). Brief report: inhibition of renal phosphate transport by a tumor product in a patient with oncogenic osteomalacia. *N Engl J Med*, 330, 1645–9.

Canalejo, R., Canalejo, A., Martinez-Moreno, J. M., *et al.* (2010). FGF23 fails to inhibit uremic parathyroid glands. *J Am Soc Nephrol*, 21, 1125–35.

Cha, S. K., Ortega, B., Kurosu, H., *et al.* (2008). Removal of sialic acid involving Klotho causes cell-surface retention of TRPV5 channel via binding to galectin-1. *Proc Natl Acad Sci U S A*, 105, 9805–10.

Chang, Q., Hoefs, S., Van Der Kemp, A. W., *et al.* (2005). The beta-glucuronidase klotho hydrolyzes and activates the TRPV5 channel. *Science*, 310, 490–3.

Chefetz, I., Heller, R., Galli-Tsinopoulou, A., *et al.* (2005). A novel homozygous missense mutation in FGF23 causes familial tumoral calcinosis associated with disseminated visceral calcification. *Hum Genet*, 118, 261–6.

Chen, C. D., Podvin, S., Gillespie, E., *et al.* (2007). Insulin stimulates the cleavage and release of the extracellular domain of Klotho by ADAM10 and ADAM17. *Proc Natl Acad Sci U S A*, 104, 19796–801.

Chen, I. P., Wang, L., Jiang, X., *et al.* (2011). A Phe377del mutation in ANK leads to impaired osteoblastogenesis and osteoclastogenesis in a mouse model for craniometaphyseal dysplasia (CMD). *Hum Mol Genet*, 20, 948–61.

Doi, S., Zou, Y., Togao, O., *et al.* (2011). Klotho inhibits transforming growth factor-beta1 (TGF-beta1) signaling and suppresses renal fibrosis and cancer metastasis in mice. *J Biol Chem*, 286, 8655–65.

Farrow, E. G., Yu, X., Summers, L. J., *et al.* (2011). Iron deficiency drives an autosomal dominant hypophosphatemic rickets (ADHR) phenotype in fibroblast growth factor-23 (Fgf23) knock-in mice. *Proc Natl Acad Sci U S A*, 108, E1146–55.

Faul, C., Amaral, A. P., Oskouei, B., *et al.* (2011). FGF23 induces left ventricular hypertrophy. *J Clin Invest*, 121, 4393–408.

Feng, J. Q., Ward, L. M., Liu, S., *et al.* (2006). Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. *Nat Genet*, 38, 1310–5.

Ferrari, S. L., Bonjour, J. P., and Rizzoli, R. (2005). Fibroblast growth factor-23 relationship to dietary phosphate and renal phosphate handling in healthy young men. *J Clin Endocrinol Metab*, 90, 1519–24.

Fliser, D., Kollerits, B., Neyer, U., *et al.* (2007). Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. *J Am Soc Nephrol*, 18, 2600–8.

Galitzer, H., Ben-Dov, I. Z., Silver, J., *et al.* (2010). Parathyroid cell resistance to fibroblast growth factor 23 in secondary hyperparathyroidism of chronic kidney disease. *Kidney Int*, 77, 211–18.

Gonzalez-Parra, E., Gonzalez-Casaus, M. L., Galan, A., *et al.* (2011). Lanthanum carbonate reduces FGF23 in chronic kidney disease Stage 3 patients. *Nephrol Dial Transplant*, 26, 2567–71.

Gutierrez, O., Isakova, T., Rhee, E., *et al.* (2005). Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. *J Am Soc Nephrol*, 16, 2205–15.

Gutierrez, O. M., Januzzi, J. L., Isakova, T., *et al.* (2009). Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. *Circulation*, 119, 2545–52.

Gutierrez, O. M., Mannstadt, M., Isakova, T., *et al.* (2008). Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med*, 359, 584–92.

Haruna, Y., Kashihara, N., Satoh, M., *et al.* (2007). Amelioration of progressive renal injury by genetic manipulation of Klotho gene. *Proc Natl Acad Sci U S A*, 104, 2331–6.

Hasegawa, H., Nagano, N., Urakawa, I., *et al.* (2010). Direct evidence for a causative role of FGF23 in the abnormal renal phosphate handling and vitamin D metabolism in rats with early-stage chronic kidney disease. *Kidney Int*, 78, 975–80.

Hofman-Bang, J., Martuseviciene, G., Santini, M. A., *et al.* (2010). Increased parathyroid expression of klotho in uremic rats. *Kidney Int*, 78, 1119–27.

Hu, M. C., Shi, M., Zhang, J., *et al.* (2010a). Klotho: a novel phosphaturic substance acting as an autocrine enzyme in the renal proximal tubule. *FASEB J*, 24, 3438–50.

Hu, M. C., Shi, M., Zhang, J., *et al.* (2011). Klotho deficiency causes vascular calcification in chronic kidney disease. *J Am Soc Nephrol*, 22, 124–36.

Hu, M. C., Shi, M., Zhang, J., *et al.* (2010b). Klotho deficiency is an early biomarker of renal ischemia-reperfusion injury and its replacement is protective. *Kidney Int*, 78, 1240–51.

Ichikawa, S., Lyles, K. W., and Econs, M. J. (2005). A novel GALNT3 mutation in a pseudoautosomal dominant form of tumoral

calcinosis: evidence that the disorder is autosomal recessive. *J Clin Endocrinol Metab*, 90, 2420–3.
Ikushima, M., Rakugi, H., Ishikawa, K., *et al.* (2006). Anti-apoptotic and anti-senescence effects of Klotho on vascular endothelial cells. *Biochem Biophys Res Commun*, 339, 827–32.
Imel, E. A., Peacock, M., Gray, A. K., *et al.* (2011). Iron modifies plasma FGF23 differently in autosomal dominant hypophosphatemic rickets and healthy humans. *J Clin Endocrinol Metab*, 96, 3541–9.
Imura, A., Iwano, A., Tohyama, O., *et al.* (2004). Secreted Klotho protein in sera and CSF: implication for post-translational cleavage in release of Klotho protein from cell membrane. *FEBS Lett*, 565, 143–7.
Imura, A., Tsuji, Y., Murata, M., *et al.* (2007). alpha-Klotho as a regulator of calcium homeostasis. *Science*, 316, 1615–18.
Inoue, Y., Segawa, H., Kaneko, I., *et al.* (2005). Role of the vitamin D receptor in FGF23 action on phosphate metabolism. *Biochem J*, 390, 325–31.
Isakova, T., Wahl, P., Vargas, G. S., *et al.* (2011a). Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int*, 79, 1370–8.
Isakova, T., Xie, H., Yang, W., *et al.* (2011b). Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *JAMA*, 305, 2432–9.
Ito, M., Sakai, Y., Furumoto, M., *et al.* (2005). Vitamin D and phosphate regulate fibroblast growth factor-23 in K-562 cells. *Am J Physiol Endocrinol Metab*, 288, E1101–9.
Ix, J. H., Katz, R., Kestenbaum, B. R., *et al.* (2012). Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals: CHS (Cardiovascular Health Study). *J Am Coll Cardiol*, 60, 200–7.
Ix, J. H., Shlipak, M. G., Wassel, C. L., *et al.* (2010). Fibroblast growth factor-23 and early decrements in kidney function: the Heart and Soul Study. *Nephrol Dial Transplant*, 25, 993–7.
Jean, G., Terrat, J. C., Vanel, T., *et al.* (2009). High levels of serum fibroblast growth factor (FGF)-23 are associated with increased mortality in long haemodialysis patients. *Nephrol Dial Transplant*, 24, 2792–6.
Jonsson, K. B., Zahradnik, R., Larsson, T., *et al.* (2003). Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. *N Engl J Med*, 348, 1656–63.
Kanbay, M., Nicoleta, M., Selcoki, Y., *et al.* (2010). Fibroblast growth factor 23 and fetuin A are independent predictors for the coronary artery disease extent in mild chronic kidney disease. Clin *J Am Soc Nephrol*, 5, 1780–6.
Katai, K., Miyamoto, K., Kishida, S., *et al.* (1999). Regulation of intestinal Na+-dependent phosphate co-transporters by a low-phosphate diet and 1,25-dihydroxyvitamin D3. *Biochem J*, 343 Pt 3, 705–12.
Kato, K., Jeanneau, C., Tarp, M. A., *et al.* (2006). Polypeptide GalNAc-transferase T3 and familial tumoral calcinosis. Secretion of fibroblast growth factor 23 requires O-glycosylation. *J Biol Chem*, 281, 18370–7.
Kendrick, J., Cheung, A. K., Kaufman, J. S., *et al.* (2011). FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. *J Am Soc Nephrol*, 22, 1913–22.
Koh, N., Fujimori, T., Nishiguchi, S., *et al.* (2001). Severely reduced production of klotho in human chronic renal failure kidney. *Biochem Biophys Res Commun*, 280, 1015–20.
Koiwa, F., Kazama, J. J., Tokumoto, A., *et al.* (2005). Sevelamer hydrochloride and calcium bicarbonate reduce serum fibroblast growth factor 23 levels in dialysis patients. *Ther Apher Dial*, 9, 336–9.
Komaba, H., Goto, S., Fujii, H., *et al.* (2010). Depressed expression of Klotho and FGF receptor 1 in hyperplastic parathyroid glands from uremic patients. *Kidney Int*, 77, 232–8.
Krajisnik, T., Bjorklund, P., Marsell, R., *et al.* (2007). Fibroblast growth factor-23 regulates parathyroid hormone and 1alpha-hydroxylase expression in cultured bovine parathyroid cells. *J Endocrinol*, 195, 125–31.
Krajisnik, T., Olauson, H., Mirza, M. A., *et al.* (2010). Parathyroid Klotho and FGF-receptor 1 expression decline with renal function in hyperparathyroid patients with chronic kidney disease and kidney transplant recipients. *Kidney Int*, 78, 1024–32.
Kumata, C., Mizobuchi, M., Ogata, H., *et al.* (2010). Involvement of alpha-klotho and fibroblast growth factor receptor in the development of secondary hyperparathyroidism. *Am J Nephrol*, 31, 230–8.
Kuro-O, M., Matsumura, Y., Aizawa, H., *et al.* (1997). Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature*, 390, 45–51.
Kurosu, H., Ogawa, Y., Miyoshi, M., *et al.* (2006). Regulation of fibroblast growth factor-23 signaling by klotho. *J Biol Chem*, 281, 6120–3.
Kurosu, H., Yamamoto, M., Clark, J. D., *et al.* (2005). Suppression of aging in mice by the hormone Klotho. *Science*, 309, 1829–33.
Larsson, T., Davis, S. I., Garringer, H. J., *et al.* (2005a). Fibroblast growth factor-23 mutants causing familial tumoral calcinosis are differentially processed. *Endocrinology*, 146, 3883–91.
Larsson, T., Nisbeth, U., Ljunggren, O., *et al.* (2003). Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. *Kidney Int*, 64, 2272–9.
Larsson, T., Yu, X., Davis, S. I., *et al.* (2005b). A novel recessive mutation in fibroblast growth factor-23 causes familial tumoral calcinosis. *J Clin Endocrinol Metab*, 90, 2424–7.
Lavi-Moshayoff, V., Wasserman, G., Meir, T., *et al.* (2010). PTH increases FGF23 gene expression and mediates the high-FGF23 levels of experimental kidney failure: a bone parathyroid feedback loop. *Am J Physiol Renal Physiol*, 299, F882–9.
Levy-Litan, V., Hershkovitz, E., Avizov, L., *et al.* (2010). Autosomal-recessive hypophosphatemic rickets is associated with an inactivation mutation in the ENPP1 gene. *Am J Hum Genet*, 86, 273–8.
Li, S. A., Watanabe, M., Yamada, H., *et al.* (2004). Immunohistochemical localization of Klotho protein in brain, kidney, and reproductive organs of mice. *Cell Struct Funct*, 29, 91–9.
Lim, K., Lu, T. S., Molostvov, G., *et al.* (2012). Vascular Klotho deficiency potentiates the development of human artery calcification and mediates resistance to fibroblast growth factor 23. *Circulation*, 125, 2243–55.
Liu, S., Tang, W., Zhou, J., *et al.* (2006). Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. *J Am Soc Nephrol*, 17, 1305–15.
Lopez, I., Rodriguez-Ortiz, M. E., Almaden, Y., *et al.* (2011). Direct and indirect effects of parathyroid hormone on circulating levels of fibroblast growth factor 23 in vivo. *Kidney Int*, 80, 475–82.
Lorenz-Depiereux, B., Bastepe, M., Benet-Pages, A., *et al.* (2006). DMP1 mutations in autosomal recessive hypophosphatemia implicate a bone matrix protein in the regulation of phosphate homeostasis. *Nat Genet*, 38, 1248–50.
Lorenz-Depiereux, B., Schnabel, D., Tiosano, D., *et al.* (2010). Loss-of-function ENPP1 mutations cause both generalized arterial calcification of infancy and autosomal-recessive hypophosphatemic rickets. *Am J Hum Genet*, 86, 267–72.
Marks, J., Debnam, E. S., and Unwin, R. J. (2010). Phosphate homeostasis and the renal-gastrointestinal axis. *Am J Physiol Renal Physiol*, 299, F285–96.
Matsumura, Y., Aizawa, H., Shiraki-Iida, T., *et al.* (1998). Identification of the human klotho gene and its two transcripts encoding membrane and secreted klotho protein. *Biochem Biophys Res Commun*, 242, 626–30.
Mirza, M. A., Hansen, T., Johansson, L., *et al.* (2009a). Relationship between circulating FGF23 and total body atherosclerosis in the community. *Nephrol Dial Transplant*, 24, 3125–31.
Mirza, M. A., Larsson, A., Lind, L., *et al.* (2009b). Circulating fibroblast growth factor-23 is associated with vascular dysfunction in the community. *Atherosclerosis*, 205, 385–90.
Mirza, M. A., Larsson, A., Melhus, H., *et al.* (2009c). Serum intact FGF23 associate with left ventricular mass, hypertrophy and geometry in an elderly population. *Atherosclerosis*, 207, 546–51.
Mitani, H., Ishizaka, N., Aizawa, T., *et al.* (2002). In vivo klotho gene transfer ameliorates angiotensin II-induced renal damage. *Hypertension*, 39, 838–43.

Moe, S. M., Zidehsarai, M. P., Chambers, M. A., *et al.* (2011). Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. Clin *J Am Soc Nephrol*, 6, 257–64.

Nagai, R., Saito, Y., Ohyama, Y., *et al.* (2000). Endothelial dysfunction in the klotho mouse and downregulation of klotho gene expression in various animal models of vascular and metabolic diseases. *Cell Mol Life Sci*, 57, 738–46.

Nagano, N., Miyata, S., Abe, M., *et al.* (2006). Effect of manipulating serum phosphorus with phosphate binder on circulating PTH and FGF23 in renal failure rats. *Kidney Int*, 69, 531–7.

Nagasu, H., Satoh, M., Kuwabara, A., *et al.* (2011). Overexpression of klotho protein modulates uninephrectomy-induced compensatory renal hypertrophy by suppressing IGF-I signals. *Biochem Biophys Res Commun*, 407, 39–43.

Nakatani, T., Ohnishi, M., and Razzaque, M. S. (2009). Inactivation of klotho function induces hyperphosphatemia even in presence of high serum fibroblast growth factor 23 levels in a genetically engineered hypophosphatemic (Hyp) mouse model. *FASEB J*, 23, 3702–11.

Ohkido, I., Yokoyama, K., Imura, A., *et al.* (2010). Persistent alpha-Klotho (a-Kl) expression in the parathyroid glands of patients with secondary hyperparathyroidism. *Nephrol Dial Transplant*, 25, 1007–8.

Oliveira, R. B., Cancela, A. L., Graciolli, F. G., *et al.* (2010). Early control of PTH and FGF23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy? Clin *J Am Soc Nephrol*, 5, 286–91.

Parker, B. D., Schurgers, L. J., Brandenburg, V. M., *et al.* (2010). The associations of fibroblast growth factor 23 and uncarboxylated matrix Gla protein with mortality in coronary artery disease: the Heart and Soul Study. *Ann Intern Med*, 152, 640–8.

Perwad, F., Azam, N., Zhang, M. Y., *et al.* (2005). Dietary and serum phosphorus regulate fibroblast growth factor 23 expression and 1,25-dihydroxyvitamin D metabolism in mice. *Endocrinology*, 146, 5358–64.

Quarles, L. D. (2003). FGF23, PHEX, and MEPE regulation of phosphate homeostasis and skeletal mineralization. *Am J Physiol Endocrinol Metab*, 285, E1–9.

Quarles, L. D. (2008). Endocrine functions of bone in mineral metabolism regulation. *J Clin Invest*, 118, 3820–8.

Quarles, L. D. (2012). Skeletal secretion of FGF-23 regulates phosphate and vitamin D metabolism. *Nat Rev Endocrinol*, 8(5), 276–86.

Quinn, S. J., Thomsen, A. R., Pang, J. L., *et al.* (2013). Interactions between calcium and phosphorus in the regulation of the production of fibroblast growth factor 23 in vivo. *Am J Physiol Endocrinol Metab*, 304, E310–20.

Rakugi, H., Matsukawa, N., Ishikawa, K., *et al.* (2007). Anti-oxidative effect of Klotho on endothelial cells through cAMP activation. *Endocrine*, 31, 82–7.

Razzaque, M. S. (2008). Klotho and Na^+,K^+-ATPase activity: solving the calcium metabolism dilemma? *Nephrol Dial Transplant*, 23, 459–61.

Rodriguez-Ortiz, M. E., Lopez, I., Munoz-Castaneda, J. R., *et al.* (2012). Calcium deficiency reduces circulating levels of FGF23. *J Am Soc Nephrol*, 23, 1190–7.

Saito, H., Kusano, K., Kinosaki, M., *et al.* (2003). Human fibroblast growth factor-23 mutants suppress Na+-dependent phosphate co-transport activity and 1alpha,25-dihydroxyvitamin D3 production. *J Biol Chem*, 278, 2206–11.

Saito, H., Maeda, A., Ohtomo, S., *et al.* (2005). Circulating FGF-23 is regulated by 1alpha,25-dihydroxyvitamin D3 and phosphorus in vivo. *J Biol Chem*, 280, 2543–9.

Saito, Y., Nakamura, T., Ohyama, Y., *et al.* (2000). In vivo klotho gene delivery protects against endothelial dysfunction in multiple risk factor syndrome. *Biochem Biophys Res Commun*, 276, 767–72.

Saito, Y., Yamagishi, T., Nakamura, T., *et al.* (1998). Klotho protein protects against endothelial dysfunction. *Biochem Biophys Res Commun*, 248, 324–9.

Saji, F., Shigematsu, T., Sakaguchi, T., *et al.* (2010). Fibroblast growth factor 23 production in bone is directly regulated by 1{alpha},25-dihydroxyvitamin D, but not PTH. *Am J Physiol Renal Physiol*, 299, F1212–17.

Samadfam, R., Richard, C., Nguyen-Yamamoto, L., *et al.* (2009). Bone formation regulates circulating concentrations of fibroblast growth factor 23. *Endocrinology*, 150, 4835–45.

Scialla, J. J., Astor, B. C., Isakova, T., *et al.* (2013a). Mineral metabolites and CKD progression in African Americans. *J Am Soc Nephrol*, 24, 125–35.

Scialla, J. J., Lau, W. L., Reilly, M. P., *et al.* (2013b). Fibroblast growth factor 23 is not associated with and does not induce arterial calcification. *Kidney Int*, 83, 1159–68.

Seiler, S., Reichart, B., Roth, D., *et al.* (2010). FGF-23 and future cardiovascular events in patients with chronic kidney disease before initiation of dialysis treatment. *Nephrol Dial Transplant*, 25(12), 3983–9.

Shalhoub, V., Ward, S. C., Sun, B., *et al.* (2011). Fibroblast growth factor 23 (FGF23) and alpha-klotho stimulate osteoblastic MC3T3.E1 cell proliferation and inhibit mineralization. *Calcif Tissue Int*, 89, 140–50.

Shigematsu, T., Negi, S., and COLC Research Group (2012). Combined therapy with lanthanum carbonate and calcium carbonate for hyperphosphatemia decreases serum FGF-23 level independently of calcium and PTH (COLC Study). *Nephrol Dial Transplant*, 27(3), 1050–4.

Shimada, T., Kakitani, M., Yamazaki, Y., *et al.* (2004). Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. *J Clin Invest*, 113, 561–8.

Shimada, T., Mizutani, S., Muto, T., *et al.* (2001). Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci U S A*, 98, 6500–5.

Shiraki-Iida, T., Aizawa, H., Matsumura, Y., *et al.* (1998). Structure of the mouse klotho gene and its two transcripts encoding membrane and secreted protein. *FEBS Lett*, 424, 6–10.

Sitara, D., Razzaque, M. S., Hesse, M., *et al.* (2004). Homozygous ablation of fibroblast growth factor-23 results in hyperphosphatemia and impaired skeletogenesis, and reverses hypophosphatemia in Phex-deficient mice. *Matrix Biol*, 23, 421–32.

Smith, R. C., O'bryan, L. M., Farrow, E. G., *et al.* (2012). Circulating alphaKlotho influences phosphate handling by controlling FGF23 production. *J Clin Invest*, 122, 4710–5.

Sridharan, M., Cheung, J., Moore, A. E., *et al.* (2010). Circulating fibroblast growth factor-23 increases following intermittent parathyroid hormone (1-34) in postmenopausal osteoporosis: association with biomarker of bone formation. *Calcif Tissue Int*, 87, 398–405.

Sugiura, H., Yoshida, T., Mitobe, M., *et al.* (2010). Klotho reduces apoptosis in experimental ischaemic acute kidney injury via HSP-70. *Nephrol Dial Transplant*, 25, 60–8.

Sugiura, H., Yoshida, T., Shiohira, S., *et al.* (2012). Reduced Klotho expression level in kidney aggravates renal interstitial fibrosis. *Am J Physiol Renal Physiol*, 302(10), F1252–64.

Sugiura, H., Yoshida, T., Tsuchiya, K., *et al.* (2005). Klotho reduces apoptosis in experimental ischaemic acute renal failure. *Nephrol Dial Transplant*, 20, 2636–45.

Sun, C. Y., Chang, S. C., and Wu, M. S. (2012). Suppression of Klotho expression by protein-bound uremic toxins is associated with increased DNA methyltransferase expression and DNA hypermethylation. *Kidney Int*, 81, 640–50.

Touchberry, C. D., Green, T. M., Tchikrizov, V., *et al.* (2013). FGF23 is a novel regulator of intracellular calcium and cardiac contractility in addition to cardiac hypertrophy. *Am J Physiol Endocrinol Metab*, 304, E863–73.

Urakawa, I., Yamazaki, Y., Shimada, T., *et al.* (2006). Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*, 444, 770–4.

Utsugi, T., Ohno, T., Ohyama, Y., *et al.* (2000). Decreased insulin production and increased insulin sensitivity in the klotho mutant mouse, a novel animal model for human aging. *Metabolism*, 49, 1118–23.

Wang, H., Yoshiko, Y., Yamamoto, R., *et al.* (2008). Overexpression of fibroblast growth factor 23 suppresses osteoblast differentiation and matrix mineralization in vitro. *J Bone Miner Res*, 23, 939–48.

Wang, Y. and Sun, Z. (2009). Klotho gene delivery prevents the progression of spontaneous hypertension and renal damage. *Hypertension*, 54, 810–7.

Wesseling-Perry, K., Harkins, G. C., Wang, H. J., *et al.* (2010). The calcemic response to continuous parathyroid hormone (PTH)(1-34) infusion in

end-stage kidney disease varies according to bone turnover: a potential role for PTH(7-84). *J Clin Endocrinol Metab*, 95, 2772–80.

Wesseling-Perry, K., Pereira, R. C., Sahney, S., *et al.* (2011). Calcitriol and doxercalciferol are equivalent in controlling bone turnover, suppressing parathyroid hormone, and increasing fibroblast growth factor-23 in secondary hyperparathyroidism. *Kidney Int*, 79, 112–9.

White, K. E., Carn, G., Lorenz-Depiereux, B., *et al.* (2001). Autosomal-dominant hypophosphatemic rickets (ADHR) mutations stabilize FGF-23. *Kidney Int*, 60, 2079–86.

Wolf, M., Koch, T. A., and Bregman, D. B. (2013). Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. *J Bone Miner Res*, 28, 1793–803.

Yamashita, T., Konishi, M., Miyake, A., *et al.* (2002). Fibroblast growth factor (FGF)-23 inhibits renal phosphate reabsorption by activation of the mitogen-activated protein kinase pathway. *J Biol Chem*, 277, 28265–70.

Yilmaz, M. I., Sonmez, A., Saglam, M., *et al.* (2012). Comparison of Calcium Acetate and Sevelamer on Vascular Function and Fibroblast Growth Factor 23 in CKD Patients: A Randomized Clinical Trial. *Am J Kidney Dis*, 59, 177–85.

Zhang, H., Li, Y., Fan, Y., *et al.* (2008). Klotho is a target gene of PPAR-gamma. *Kidney Int*, 74, 732–9.

Zhu, D., Mackenzie, N. C., Millan, J. L., *et al.* (2013). A protective role for FGF-23 in local defence against disrupted arterial wall integrity? *Mol Cell Endocrinol*, 372, 1–11.

CHAPTER 120

Vascular calcification

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Introduction

Chronic kidney disease (CKD) is a very prevalent condition, affecting approximately 10% of the global population (Chronic Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease Working Group, 2013). It is well known that cardiovascular (CV) disease is a common complication in CKD and patients with advanced stages of CKD are more likely to die from CV disease than from kidney failure (Keith et al., 2004). In fact, some authors suggest that an inverse linear relationship exists between glomerular filtration rate (GFR) estimated with the Modification of Diet in Renal Disease (MDRD) formula (Levey et al., 1999), on one hand, and mortality and CV events, on the other hand (Go et al., 2004). This finding comes from the observation that CKD patients are not only exposed to traditional CV risk factors, but also to non-traditional risk factors, including mineral metabolism disturbances, anaemia, inflammation, and oxidative stress. This relationship is due in part to the presence of excess vascular calcification (VC), particularly in the form of extensive coronary artery calcification (CAC), a frequent complication of CKD patients which can be observed even in very young dialysis patients (Sigrist et al., 2007). Furthermore, the KDIGO guidelines published in August 2009 suggest that stage 3–5D CKD patients with vascular/valvular calcifications may be considered to be at the highest CV risk (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009).

VC is a frequent, threatening complication, particularly in the scenario of CKD, and investigators have demonstrated that the extent and histopathological aspect of VC are predictors of subsequent vascular mortality (London et al., 2003). It is associated with fragmentation and reduction of elastic fibres in the arterial wall, vascular stiffening, and, hence, increased cardiac afterload (Wexler et al., 1996). From a morphologic point of view, there are at least two types of pathologic calcium (Ca) phosphate deposition in the arterial wall—namely, intima calcification (mostly associated with atherosclerotic plaques) and media calcification (associated with stiffening of the vasculature, resulting in significantly adverse CV outcomes) (Amann, 2008).

The main question which arises is about what drives the development and maintenance, or progression, of such abnormal calcification, and currently there are several hypotheses for explaining this complex process. Currently, the nephrology community agrees with the fact that not only Ca salts (e.g. from Ca-containing oral phosphate binders) can promote VC, and this comes from the observation that some CKD patients exposed to little elemental Ca are not spared from developing VC. This and the complex physiopathology suggest that probably many additional clinical factors are also associated with VC in the population with CKD. Although research efforts in the past decade have greatly improved our knowledge of the multiple factors and mechanisms involved in VC in patients with kidney disease, many questions remain unanswered.

Epidemiology

VC is highly prevalent in patients with CKD, cases of rare calcification syndromes being first reported 100 or more years ago (Bryant and Hale White, 1901). Although the case reports dating from 1855 to 1945 (Mulligan, 1947) were typically a consequence of severe hypercalcaemia, the analysis of subsequent studies suggested that factors other than Ca intake and abnormalities of mineral metabolism may promote the risk of VC.

Given that VC has been found in up to 70% of patients entering dialysis treatment (Block et al., 2005) and up to 92% of patients with long dialysis vintage (Blacher et al., 2001; Raggi et al., 2002; Goldsmith et al., 2004), the process leading to VC development appears as a 'continuum' with increasing proportion of calcified patients from earlier stages of CKD to end-stage renal disease (ESRD) (Russo et al., 2007). Among CKD stages 3–5 (not dialysed) patients, published information showed that 47–83% had CV calcifications. This is thought to be related to the increasing age, the high prevalence of diabetes mellitus, the dialysis vintage, and the use of Ca-containing phosphate (P)-binders or the elevated P levels. Regarding age, VCs are present even in children on dialysis therapy, with a prevalence of almost 20% in one study (Shroff et al., 2007; Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009). In young adults receiving dialysis treatment (age ranges 20–30 years in one study, 19–39 years in a second study) with childhood-onset CKD, VC prevalence was 87.5% and 92%, respectively (Goodman et al., 2000; Oh et al., 2002; Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009). Furthermore, prevalent haemodialysis (HD) patients had a higher likelihood of having detectable VC scores than incident ones, and the data are similar in peritoneal dialysis (PD) patients (Gallieni et al., 2012). Although studies of VC in kidney transplant recipients are few and small and have short follow-up, it seems that VC progression is substantial in prevalent patients (Marechal et al., 2012).

The progression of VC has been reported to vary from 50% to 60% in ESRD patients (Goodman et al., 2000; Chertow et al., 2002, 2004; Mehrotra et al., 2005) and from 20% to 36% in subjects with normal renal function (Budoff and Raggi, 2001; Gradaus et al.,

2001; Ketteler et al., 2003; Russo et al., 2004). Calcification scores nearly double in young adults on dialysis therapy for a mean of 20 months (Goodman et al., 2000) and increase by 14% and 25% after 26 and 52 weeks, respectively, in a cohort of strictly controlled patients on dialysis (Chertow et al., 2002). However, the increase in the prevalence of VC over decades is also related to the better screening and imaging diagnostic techniques.

Pathophysiological mechanisms of vascular calcification

Although VC was viewed initially as a passive phenomenon, secondary to a simple precipitation of Ca and P in the vessel wall, the real mechanism is an active one and is not completely understood. It appears to be a cell-mediated, dynamic and actively regulated process that closely resembles the formation of normal bone tissue (Giachelli et al., 2001; Shanahan et al., 2005; Moe et al., 2007; Schoppet et al., 2008; Massy and Drüek, 2012).The arterial remodelling in CKD patients, including fibroelastic intimal thickening, calcification of elastic lamellae, or more collagen deposition with relatively less elastic fibre content, involves several bone-associated proteins, including osteocalcin (OC), osteopontin, and osteoprotegerin (OPG), and many bone morphogenetic proteins, which are expressed in calcified arterial lesions and are associated with VC. The vascular smooth muscle cells (VSMCs) play an important role in this process. In CKD patients, VSMCs can suffer phenotypic transformation: loss of inhibitor function, development of a calcifiable extracellular matrix, and induction of apoptosis and vesicle release. These phenotypic changes are accompanied by osteogenic or chondrogenic differentiation of VSMCs and may lead to a calcified smooth muscle, in a process similar to bone formation. In other words, this pattern of VC is actually an ectopic ossification. Moreover, uraemia induces differentiation of VSMCs into an osteoblast-like phenotype and also inhibits the differentiation of monocyte-macrophages into osteoclasts.

Recent data indicate that the starting point of VC in uraemia seems to be the formation of nanocrystals; these could directly stimulate calcification and vascular cell differentiation (Verberckmoes et al., 2007). The chemical analysis of the composition of VC described hydroxyapatite as the sole mineral phase of uraemic arterial calcifications. More recently, using synchrotron radiation analysis, Verberckmoes et al. found amorphous calcium phosphate precipitate apatite in the aortic wall from rodent models of uraemic-induced VC and also whitlockite, a magnesium-substituted tricalcium phosphate or calcium magnesium orthophosphate ($(Ca,Mg)_3(PO_4)_2$), in animals treated with calcitriol (Verberckmoes et al., 2007). In a freshly detailed investigation of the composition of the iliac arteries in 30 dialysis patients, Schlieper et al. showed the co-localization of hydroxyapatite and whitlockite, confirming that this type of calcium phosphate crystals is also found in the vascular space (Schlieper et al., 2010). Additionally, calcification inhibitors fetuin-A, osteopontin, and matrix Gla protein (MGP) were also found in close association with VC.

Determinants of vascular calcification

The risk factors associated with VC can be differentiated in two groups: (1) the traditional ones, such as age, hypertension, diabetes, and dyslipidaemia; and (2) 'non-traditional' ones, including Ca and P metabolism abnormalities, extreme parathyroid hormone (PTH) serum levels, excess administration of Ca salts, inflammation, malnutrition, and oxidative stress (see Table 120.1 and Fig. 120.1).

Table 120.1 Determinants of vascular calcifications

Promoters of VC	Inhibitors of VC
Phosphate and calcium	Fetuin-A
Parathyroid hormone	Matrix Gla protein
Vitamin D	Osteoprotegerin
FGF23	Vitamin K
Indoxyl sulphate	Pyrophosphate
Inflammation	
Oxidative stress	

VC seems to be the result of the dysregulation of the equilibrium between calcification promoters and inhibitors.

Promoters of vascular calcification

Phosphate and calcium metabolism

The altered P and Ca metabolism seems to be one of the most important contributors to the development and progression of VC (Covic et al., 2010). There is strong evidence that VC is closely associated with serum levels of Ca, P, and Ca × P product. Two possible mechanisms have been proposed to explain this relationship: a passive one, the direct Ca-P precipitation in the vasculature, and an active one, that induces the expression of bone-associated genes in VSMCs, which acquire the phenotype of bone-forming (osteoblast-like) cells. Recent studies indicate that elevated P has a major role in promoting osteogenic/chondrogenic differentiation of VSMCs, apoptosis, matrix vesicle release, and matrix remodelling, whereas elevated Ca has a predominant role in promoting VSMC apoptosis and vesicle release (Shanahan et al., 2011).

Importantly, studies *in vitro* and in animal models show that the initiation of VC requires an increased uptake of Ca and P by the VSMCs. Extracellular P is transported into the cell through a type III sodium-dependent P cotransporter (Pit-1); the influx of P induces the upregulation of osteogenic/chondrogenic gene expression (Runt-related transcription factor 2 (Runx2), osteoblast-specific

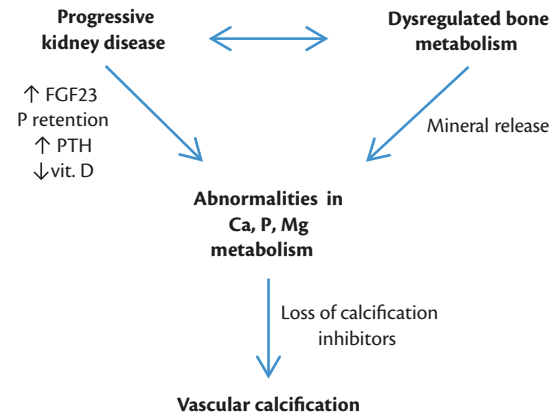

Fig. 120.1 Mechanisms of vascular calcification in CKD patients.

transcription factor Osterix (Osx), alkaline phosphatase (ALP), and osteopontin), and simultaneous downregulation of smooth muscle (SM) lineage gene expression (SMα actin and SM22α) (Shanahan et al., 2011). Ultrastructurally, the osteogenic/chondrogenic phenotype of VSMCs is characterized by the appearance of matrix vesicles containing apatite and calcifying collagen fibrils on the surface of VSMCs; these vesicles most likely act as early nucleation sites for calcification. The blockade of Pit-1 impairs mineralization and prevents induction of core binding factor 1 (Cbfa1) (a transcriptional activator of osteoblastic differentiation)/Runx2 and osteoclast expression in VSMCs, even under high extracellular P concentrations. Moreover, elevated serum P also stimulates VSMC apoptosis, through downregulation of growth arrest-specific gene 6 (Shanahan et al., 2011).

In bovine and mice models, it was recently demonstrated that elevated P levels induced the production of mitochondrial superoxide ($O_2^{\cdot-}$) and activated nuclear factor kappa B (NF-κB) to promote VC (Shanahan et al., 2011). The mitochondrial reactive oxygen species (ROS) have an important contribution in inducing autophagy, a process with an essential role in maintaining chondrocyte and osteoblast/osteocyte survival and terminal differentiation. In a recent study, Dai et al. showed in a dietary adenine-induced rat model of chronic renal failure that P increases ROS levels and potentiates autophagy in cultured VSMCs and aortic walls; this process was mediated by the sodium-dependent P cotransporter Pit1 (Dai et al., 2013). The inhibition of autophagy significantly aggravated P-induced Ca deposition; the possible mechanism seems to be related to the matrix vesicle release rather than cell apoptosis. Likewise, the administration of valproic acid, a pharmacological inducer of autophagy, significantly ameliorated the increased calcification.

The role of Ca in promoting VC is complex. First of all, the elevated Ca serum levels act additively, inducing the expression of Pit-1 and increasing the influx of P into the VSMC. Furthermore, Ca is essential for VSMC contractility and is tightly regulated by the Ca-sensing receptor (CaSR), as well as by voltage-gated Ca channels that mediate extracellular Ca uptake (Covic et al., 2010). The CaSR is capable of sensing changes in extracellular Ca concentrations and regulate vascular myogenic tone. When VSMCs are exposed to high extracellular Ca *in vitro*, the expression of CaSR is downregulated. The expression of this Ca receptor is also downregulated in CKD patients with VC. The ablation of Ca receptor increases VSMC calcification. Moreover, the treatment with calcimimetics could, at least theoretically, ameliorate calcification. Until now, the most plausible explanation for this protective effect in the presence of a functional Ca receptor seems to be its role in regulating the expression of MGP, a key inhibitor of VC.

Moreover, when VSMCs undergo osteogenic/chondrogenic differentiation, VSMCs downregulate voltage-activated L-type Ca channel expression (that mediate extracellular Ca uptake) and ryanodine expression (that mediates sarcoplasmic reticulum intracellular Ca release). These changes in both intracellular and extracellular Ca pools are likely to impact dramatically on VSMCs, promoting VC (Shanahan et al., 2011). Furthermore, the treatment with Ca channel blockers, which block the inward movement of Ca by binding to the L-type Ca channels, may slow the progression of calcification in hypertensive patients with or without renal failure.

If P appears to have the most important contribution in osteogenic differentiation of VSMCs, elevated Ca alone does not seem to mediate this phenotypic transition. Elevated Ca is involved in VSMC apoptosis, in VSMC matrix vesicle release, and in vesicle calcification. The ability of Ca to promote matrix vesicle calcification seems to be related to the changes in annexin content, phospholipid composition, and matrix metalloproteinase (MMP)-9 activation (Chen et al., 2008). In normal condition, the calcification inhibitors (fetuin-A and MGP) will pass into the vesicles and will ameliorate the matrix vesicle calcification; however, in CKD patients, both fetuin-A levels and MGP levels are reduced. Additionally, Ca has been shown to upregulate MGP production in a number of studies, potentially as an adaptive response designed to inhibit calcification.

Nevertheless, a recent study showed a high prevalence (83%) of radiological VC in HD patients, even in those with good control of P and Ca levels, suggesting that these factors are not the only ones involved in the pathogenesis of VC (Levin et al., 2007).

Parathyroid hormone

The progression of CKD is associated with disorders of the mineral metabolism (hyperphosphataemia and hypocalcaemia), leading to development of secondary hyperparathyroidism, characterized by increased PTH and parathyroid gland hyperplasia. High PTH levels are responsible for the enhanced number and activity of osteoclasts, being a major contributor to increased bone resorption in CKD (National Kidney Foundation, 2003). As this process increases in severity, mesenchymal cells are activated and differentiate into fibroblast-like cells, which form fibrous tissue, and fibrosis develops in the marrow space (Covic et al., 2010). High PTH levels could cause VC even in the presence of low Ca or normal P levels or preserved renal function. *In vivo* studies demonstrated that that continuous high PTH levels per se were capable of inducing VC development in rats, although the precise mechanism is unclear. It seems that this could be a direct effect of PTH on VSMCs, or an indirect one, increasing the Ca or the P load.

Vitamin D

The implication of vitamin D in VC is extremely complex. Although vitamin D determines an increase in serum Ca and P and indirectly promotes VC, new evidence suggests an important role for vitamin D in VSMC function and physiology.

VSMCs possess 25(OH) D-1-hydroxylase and vitamin D receptor (VDR). The calcitriol effects on VSMCs are contrasting. At high doses, it promotes VSMC osteoblast-like phenotype and calcification by increasing the receptor activator of NF-κB ligand (RANKL)/OPG ratio, together with upregulation of proteins regulating mineralization and Ca transport. At low doses, calcitriol suppresses VSMC proliferation, mediating the inhibition of endothelial growth factor (EGF), which is implicated in cell proliferation (Shanahan et al., 2011). In uraemic mice, low doses of both calcitriol and paricalcitol have been shown to be protective against aortic calcification. In these circumstances, Zittermann et al. postulated a biphasic dose–response curve between vitamin D and VC, with adverse effects associated with very high and very low vitamin D levels (Zittermann et al., 2007).

Negative effects associated with vitamin D excess include hyperphosphataemia, hypercalcaemia, increased MMP levels, medial calcification, arterial stiffness, and left ventricular hypertrophy. Increased levels of proinflammatory cytokines, increased MMP levels, and a decrease in factors protective of endothelial cells are all associated with vitamin D deficiency (Drüeke and and Massy, 2012). Vitamin D deficiency might be also associated

with blood levels of inflammatory factors, including tumour necrosis factor alpha (TNF-α) and interleukin (IL)-10 or IL-1β (Evans et al., 2006). The association between proinflammatory factors and VC was reported in general and in CKD populations. Moreover, these cytokines are inversely related with fetuin-A, an inhibitor of VC.

In a recent *in vitro* experiment, using human VSMCs, Aoshima et al. demonstrated the role of vitamin D sterols in reducing VSMC mineralization induced by exposure to high P and TNF-α (Aoshima et al., 2012). The mechanism are multiple: first, vitamin D downregulates the expression of Cbfa1/Runx2 and osteocalcin, the genes involved in the transformation of VSMCs into osteoblatic-like cells; second, vitamin D sterols reduce the expression of MMP-2, which degrades elastin in the vessel wall and is a major contributor to VC.

Fibroblast growth factor 23

Fibroblast growth factor 23 (FGF23) is involved in the regulation of P and of vitamin D metabolites. The level of FGF23 rises in CKD from early stages and causes renal P loss by inhibiting the Na-P cotransporter type IIa (NPT2a) in the renal proximal tubule (Juppner et al., 2010). It also suppresses the renal expression of CYP27B1, resulting in the impairment of $1,25(OH)_2D$ synthesis (Chanakul et al., 2013). FGF23 binds to its receptor via alpha-Klotho, a pleiotropic transmembrane protein expressed in the kidney.

The relationship between FGF23 and VC is uncertain. Some human and animal studies showed that reduced FGF23 or Klotho activities are closely associated with VC, but others reported no independent association between them. Small sample sizes, differential approaches to adjust for confounding, imaging of different arterial beds, and lack of prospective data limit the conclusions that can be drawn from these studies.

The possible mechanism is not well understood. Through maintaining a normal serum P in the early stages of CKD, FGF23 indirectly contributes to decreased VC. On the other hand, FGF23 can reduce calcification by inhibiting vitamin D activity. Moreover, it has been speculated that FGF23 may directly inhibit VC (Memon et al., 2008).

Indoxyl sulphate

Indoxyl sulphate (IS), a protein-bound uraemic toxin, results from dietary tryptophan. Normally the kidneys excrete IS via proximal tubular secretion but, because of impaired renal function, IS accumulates in CKD patients. Additionally, IS cannot be removed efficiently by conventional HD because of its high affinity for albumin. Several studies have proposed that IS may play a role in VC. Yamamoto et al. showed for the first time that IS can stimulate the proliferation of rat VSMC in vitro (Yamamoto et al., 2006). It also promotes aortic calcification and aortic wall thickening in hypertensive rats; IS increases the expression of osteoblast-specific proteins, such as osteopontin, Cbfa1, ALP, and OC and promotes osteoblastic transdifferentiation of VSMC (Adijiang et al., 2008). More notably, IS promotes cell senescence with increased expression of SA-β-gal, p53, p21, p16, and Rb in the cells embedded in the calcification area in hypertensive rats (Kuilman et al., 2010). IS also stimulates the generation of ROS such as superoxide by upregulating NADPH oxidase Nox4, with an important role in the transdifferentiation of human aortic VSMC into cells with a more osteoblastic phenotype (Dou et al., 2007).

Leptin

Adipose tissue is an active endocrine organ, producing a variety of bioactive substances named adipocytokines, including hormones and cytokines like adiponectine, leptin, IL-6, and TNF-α. Leptin in particular can accelerate the atherosclerotic process and VC in obese, diabetic, and renal populations (Bueno de Oliveira et al., 2013). Leptin levels in CKD patients rise progressively with declining GFR and are higher in dialysis patients. Leptin levels were significantly correlated with inflammatory markers (IL-6 and C-reactive protein) and VC and its consequences: athero- and arteriosclerosis. A positive correlation between circulating levels of leptins and CAC was found in general and diabetic populations (Zeadin et al., 2009). The possible proatherogenic effects of leptin include induction of endothelial cell dysfunction, stimulation of inflammatory processes, increased levels of oxidative stress, increased bone morphogenic protein 2 (BMP2) production, and increased migration and proliferation of VSMCs (Serrano et al., 2011). Recent data from Chavez et al. revealed that this migration and proliferation in response to leptin is determined by upregulation of thrombospondin 1 expression, through a JAK2/ERK/JNK-dependent mechanism this response is inhibited by a TSP-1 blocking antibody (Chavez et al., 2012). Additionally, leptin could induce calcification via its hypothalamic receptors, generating an increased sympathetic activity and consecutively, osteoblast β-adrenergic receptors stimulation.

Recent studies showed that leptin is able to increase VC *in vitro* and in mice; these calcifying vascular cells had a 5- to 10-fold increase in ALP activity, a marker of osteogenic differentiation of osteoblastic cells, when treated with leptin.

Inhibitors of vascular calcification

Extracellular calcium regulatory proteins: fetuin-A and MGP

Fetuin-A is mostly synthesized in the liver and is a reverse acute-phase reactant. Fetuin-A is an extracellular Ca-regulatory protein acting as a potent inhibitor of Ca-P precipitation, binding to both Ca and P in the serum and forming small 'calciparticles' removed through the reticuloendothelial system. Moreover, fetuin-A inhibits calcification by binding hydroxyapatite structures and VSMC apoptosis by perturbing death-signalling pathways: it is internalized by VSMCs and concentrated in intracellular vesicles and it is secreted via vesicle release from apoptotic and viable VSMC (Reynolds et al., 2005); the presence of fetuin-A in vesicles abrogates their ability to nucleate basic Ca-P; in addition, fetuin-A enhances phagocytosis of vesicles by VSMC. These observations provide evidence that the uptake of the serum protein fetuin-A by VSMCs is a key event in the inhibition of vesicle-mediated VSMC calcification. *In vitro*, fetuin-A antagonizes the antiproliferative action of TGF-β1 and blocks osteogenesis and deposition of Ca-containing matrix in dexamethosone-treated rat bone marrow cells.

Serum fetuin-A levels decline only late on during the course of progression of patients with CKD. Ketteler et al. showed that CKD patients with lower serum fetuin-A levels have increased mortality due to CV events, suggesting that fetuin-A is involved in preventing the accelerated extraskeletal calcification (Ketteler et al., 2003). Westenfeld et al. showed in a mouse model that fetuin-A deficiency, CKD, and high-P diet act synergistically in the pathogenesis of extraosseous calcification, but fetuin-A knockout mice developed the most severe vascular and other tissue calcification (Westenfeld

et al., 2009). A reduction in fetuin-A levels is associated with both all-cause and cardiovascular mortality in HD and PD (Hermans et al., 2007).

MGP, a small ubiquitous matrix protein, is produced by VSMCs and acts in the vascular wall. To achieve full biological activity, MPG needs to be activated by gamma-glutamate carboxylation or serine phosphorylation. The first of these depends on vitamin K and establishes its role as a calcification inhibitor. Studies have demonstrated that MGP inhibits calcification of cartilage and blood vessels (O'Young et al., 2011). The mechanism is not well established. MGP, or more precisely, the MPG-fetuin complex, inhibits the Ca crystal formation and Ca-P precipitation; alternatively, MPG binds and inactivates BMP 2, inhibiting VSMC differentiation to the osteoblast-like phenotype (Boström et al., 2001). MGP also appears to be an important factor in ensuring correct differentiation of VSMC. In CKD patients, increased amounts of MGP are found at sites of medial calcification; but recently it was reported that these arteries exhibit a poor MPG carboxylation status and a high amount of uncarboxylated MPG (Krueger et al., 2009). However, this conclusion is based exclusively on immunohistochemistry, which can be influenced by non-specific binding and variable exposure of epitopes, particularly if MGP is bound to hydroxyapatite. Also, immunohistochemistry cannot distinguish between intact MGP and fragments. The role of the deficiency of carboxylated MPG in VC in the CKD population remains to be establishing in future studies.

Osteoprotegerin

OPG is a member of the TNF-related family and forms a system with RANK and the ligand of this receptor (RANKL). This system may play a role in bone–VC imbalance and could be a marker of VC extent and progression.

OPG is involved in maintaining the critical balance between bone formation (osteoblasts) and bone resorption (osteoclasts). RANKL expressed on osteoblastic cells binds to RANK on the surface of osteoclasts; the RANKL–RANK interactions initiate intracellular signalling cascades required for osteoclast differentiation and activity. OPG acts as a soluble decoy receptor competing for RANKL, preventing RANK–RANKL interactions and osteoclast differentiation and bone resorption.

Animal studies showed that OPG-deficient mice develop both severe osteoporosis and VC; additionally, another studies demonstrated that OPG is integrated in atherosclerotic plaques. It is uncertain if OPG is only a marker for atherosclerosis or if is an active constituent in the atherosclerotic process. Animal studies showed different results: Sandberg et al. (2005) found that the inactivation of OPG inhibits atherosclerotic plaque progression, while Morony et al. treated atherogenic diet-fed mice with OPG or vehicle for 5 months and found that OPG injections significantly reduced the calcified lesion area without affecting atherosclerotic lesion size or number, vascular cytokines, or plasma cholesterol levels, supporting a role for OPG as an inhibitor of calcification and a marker, rather than a mediator, of atherosclerosis (Morony et al., 2008).

In the general population and in high-risk patients with diabetes, heart failure, or acute coronary syndrome, elevated levels of OPG have been reported, suggesting that an increase in OPG levels may represent a compensatory self-defensive mechanism against factors promoting VC, atherosclerosis, and other forms of vascular damage (Venuraju et al., 2010). Moreover, these elevated plasma levels of OPG are associated with increased mortality in these high-risk categories (Omland et al., 2008).

In CKD patients, levels of OPG are generally elevated and inversely related to kidney function, with a subsequent decrease of OPG levels after renal transplantation (Kazama et al., 2002). These levels of OPG correlate with the degree of VC. In one study, Morena et al. found that in CKD patients CAC is strongly associated with plasma OPG; values of OPG > 757.7 pg/mL were predictive of the presence of CAC in these patients (Morena et al., 2009).

Data from several small cohort studies showed that elevated OPG levels predict CV and all-cause mortality in CKD patients. Sigrist et al. (2009) showed in a cohort of 134 subjects (60 HD, 28 PD, and 46 CKD stage 4) that OPG was associated with increased odds of death. Nishiura et al. (2009) showed the same results in 99 new HD patients. The high OPG group at baseline showed a higher prevalence of CV morbidity and mortality compared with the low OPG group after 41 months of follow-up. The same interesting data are reported for renal transplantation. In a relatively small cohort of 173 renal transplantation recipients, Hjelmesaeth et al. (2006) showed that high OPG levels at baseline was associated with all-cause mortality and CV death. Svensson et al. (2012) demonstrated an association between elevated levels of OPG graft loss, CV events, cardiac mortality, and all-cause mortality in 1889 renal transplant recipients.

Vitamin K

Vitamin K_1 is the primary form of vitamin K found in the diet and the major form of vitamin K found in the liver and tissues. Vitamin K_2 is a generic name for the family of menaquinones; between them, menaquinone-4 (MK-4) is the major form found in the vessels. Vitamin K_1 is converted to MK-4 in the pancreas, testes, and in the vessels.

Vitamin K plays an important role in the carboxylation of MGP and OC (McCabe et al., 2013). Vitamin K is a cofactor for the carboxylase enzyme that is responsible for the formation of Gla residues that confer Ca-binding properties to MGP. High dietary vitamin K (K_1 or MK-4) increases the carboxylation of MGP (K_1); the dietary deficiency of vitamin K determines low tissue vitamin K levels and an increase in the level of inactive uncarboxylated MGP that is not able to oppose VC. On the contrary, increasing vitamin K via the diet increases tissue vitamin K levels, and increases levels of active carboxylated MGP which acts locally inhibiting VC.

Pyrophosphate

Pyrophosphate (PPi) is a potent inhibitor of medial VC, through its ability to inhibit hydroxyapatite formation (Lomashvili et al., 2004). PPi is produced by arterial smooth muscle; it is synthetized from extracellular ATP by the ectoenzyme nucleotide pyrophosphatase/phosphodiesterase-1 (NPP1), and lack of this enzyme leads to massive arterial calcification in mice and humans (Prosdocimo et al., 2010). Another potential source could be transport out of cells through the putative transporter ANK. The homozygous mice for a mutation in ANK develop aortic calcification on a high-P diet; but it is important to note that transport of PPi has never been directly demonstrated in cultured cells or in tissues.

PPi level is controlled by hydrolysis via a tissue-non-specific alkaline phosphatase (TNAP), which hydrolyses PPi and generates orthophosphate, the major determinant of hydroxyapatite formation. The TNAP inhibitors prevent only 50% of PPi hydrolysis,

suggesting that additional, but as yet unknown enzymes are also involved.

In HD patients, plasma PPi is deficient; these lower circulating levels of PPi in HD patients are not understood, but could result from higher hydrolysis (an increase in TNAP activity and PPi hydrolysis was demonstrated in uraemic rats), and from dialytic clearance (PPi is removed during the HD session) (Lomashvili et al., 2008). The precise role of PPi in VC in CKD patients is unknown because of the complexity in measuring PPi and the unsure correlation between circulating levels and levels in the vascular wall.

Recently, O'Neill et al. published the first study that compares the circulating PPi levels and VC in 115 patients with CKD stages 4 and 5 (O'Neill et al., 2010). They found that both baseline calcification and change in calcification were independently and inversely associated with plasma PPi, consistent with an inhibitory effect of PPi.

Genetic pathways of vascular calcification

VC has a high heritable component, studies in animal models suggesting that genetic factors are important in the tendency to calcify. In contrast, there is a paucity of evidence concerning the role of genetic factors in the pathogenesis of VC in humans without renal failure. One large investigation concluded that, after adjusting for multiple risk factors, 42% of the residual variation in CAC quantity in patients with coronary disease was attributable to genetic factors. The genetic susceptibility to VC was attributed to the mutations in the ecto-NPP1 enzyme or to gene polymorphisms such as the *ACE* gene insertion/deletion and *TNF* gene polymorphism. Similar studies have not been performed in patients with renal dysfunction.

Methods for assessing vascular calcification

A number of non-invasive imaging techniques are available to investigate VC—plain X-rays to identify macroscopic calcifications of aorta and peripheral arteries; two-dimensional ultrasound for calcification of carotid arteries, femoral arteries, and aorta; echocardiography for assessment of valvular calcification; and of course, computed tomography (CT) technologies that constitute the gold standard for quantification of coronary artery and aorta calcification. All these methods have a series of advantages and limitations.

Computed tomography

Electron-beam computed tomography (EBCT) and newer multi-slice spiral CT (MSCT) are highly sensitive methods, assessing accurately and quantitatively CACs, valvular and aortic calcification, without contrast administration (Agatston et al., 1990). These CT technologies are considered equivalent in accuracy and reproducibility even if they operate on the basis of different imaging platforms. These methods could be successfully used to study prevalent calcifications, the progressive VC, and the impact of therapy on VC (Haydar et al., 2004). The most frequently used is the Agatston score. This score is calculated as the product of a calcified plaque area by its peak density (measured in Hounsfield units). The sum of all scores in each calcified lesion identified along the coronary tree constitutes the total score. The volume and mass score are more reproducible and appropriate for use with modern CT scanners than the Agatston score (Sharples et al., 2004).

However, there are conflicting results about the correlation between the severity of CAC measured by EBCT and subsequent clinical cardiac events in dialysis patients (Kauppila et al., 1997; Bellasi et al., 2006). This can be explained by the fact that an arterial calcification score generated by CT scanning is a composite of both medial and intimal calcification. This is a limitation of these CT-based imaging techniques, as they are unable to distinguish between the two predominant arterial calcification sites (Okuno et al., 2007); the medial calcification increases the burden of disease without causing luminal obstruction (Sharples et al., 2004).

To evaluate coronary VC, especially aortic calcification, EBCT, MSCT, or even conventional CT may be used. Measuring the proportion of aortic circumference showing calcification can generate an aortic calcification index (ACI). This method seems to be simple, relatively inexpensive, and useful for initial diagnosis of VC. Calcification of the aorta was associated with *de novo* CV events and increased arterial stiffness in CKD patients (Verbeke et al., 2011).

The most important limitation of these CT-based methods for VC assessment has already been mentioned—the incapacity to discriminate intimal from medial calcification; other additional limitations are (1) CT does not supply functional parameters of myocardial perfusion or function, (2) the radiation exposure, and (3) the expensive equipment and high costs of test.

Latero-abdominal plain radiography

This is a valuable and inexpensive tool for the detection of VC in CKD patients and is the only technique for the detection of VC included in the KDIGO guidelines for CVD in dialysis patients.

The method is semi-quantitative, possibly missing subtle changes in the evolution of VC. Kauppila et al. used lateral lumbar films to detect the presence of calcification in the abdominal aortic wall, in the region corresponding to the first through fourth lumbar vertebrae, and developed a score of 0–24 based on the number and extent of calcification (Kauppila et al., 1997). Bellasi et al. reported a good correlation of this score with CAC score measured by EBCT in 140 prevalent dialysis patients (Bellasi et al., 2012). In two observational studies of > 1500 dialysis patients, the Kauppila score was highly predictive of all-cause mortality and CV events. Compared with the lowest tertile of AAC, the risk of a non-fatal CV events or death was increased by a factor of 3.7 in patients with a score of 5–15 (middle tertile), and by a factor 8.6 in patients with scores of 16–24 (Raggi et al., 2002).

Although widely available, simple, and inexpensive, this method also has a lot of limitations and provides only a semi-quantitative assessment of VC. It is also operator dependent, the reproducibility is unknown, so it is unlikely to be used to asses progression and treatment-related changes, and although validated for dialysis patients, it is not validated for early stages of CKD. Despite that, it has been suggested that it may yield some information about the localization of calcification within the arterial wall (intima vs media). Linear, railroad calcifications that delineate the wall of the artery in an angiogram-like pattern are thought to be representative of medial calcification, whereas patchy calcifications are believed to be associated with intimal atherosclerosis (Simon et al., 2010).

Ultrasound-based methods

Ultrasound is a universally available and a semi-quantitative technique helpful to assess VC in superficial vessels, such as the femoral and carotid arteries. VC detected by ultrasound was associated with CV and all-cause mortality in dialysis patients (Leskinen et al., 2009).

This method has two significant limitations: it is unable to differentiate medial from intimal calcification, and data derived from ultrasound are qualitative and are unlikely to detect small changes, at least over the shorter term. Using transthoracic echocardiography the valvular calcification can be quantified. This seems to be very important given the fact that calcification of the cardiac valves and arterial wall are closely associated in HD (CKD-5) patients (Kato et al., 2003). Although less frequent than VC, calcification of the cardiac valves is found in CKD-5 patients with a prevalence several-fold higher than in the general population (Ekart et al., 2005).

Using high-resolution ultrasound transducers, the intima—media thickness, a surrogate marker of subclinical atherosclerosis, can also be measured. In one study, Leskinen et al. found that valvular calcification in CKD patients is associated with increased carotid intima–media thickness, carotid plaque, coronary artery disease, and peripheral arterial disease (Leskinen et al., 2009).

Consequences of vascular calcification

Atherosclerosis

In CKD patients, atherosclerosis is highly prevalent and amplified compared with matched non-renal populations. This cannot be explained simply by the large number of risk factors that are present in dialysis patients; it is now well known that even young adults who have had CKD since childhood express advanced coronary arterial sclerosis and calcification, which begins before the initiation of dialysis treatment and progresses rapidly after that. The coronary plaque morphology is different (Baber et al., 2012). Almost all patients express the type VII lesion, respectively calcified atherosclerotic plaque, with a larger lipid index with a higher prevalence of Ca, cholesterol crystals, and plaque disruption. The degree of coronary atherosclerosis is well linked to the coronary calcification. There is an association between the Agatston score and the prevalence of atherosclerotic disease in HD patients. CAC (evaluated by EBCT) has been directly correlated with the severity and number of atherosclerotic lesions in numerous studies (Raggi et al., 2002). Additionally, the absence of the calcified plaques was recently identified as a protective factor.

Chronic kidney disease—vascular calcification and stroke

CKD patients have an increased stroke risk (Townsend, 2008). Patients with CKD have a greater prevalence of traditional risk factors; additionally, CKD is associated with an increase in non-traditional risk factors such as hyperhomocysteinaemia, inflammation, asymmetric dimethylarginine, oxidative stress, anaemia, and thrombogenic factors such as left ventricular hypertrophy, endothelial dysfunction, and arterial stiffness. Patients with CKD and stroke had an increased prevalence of intracranial artery calcification, varying in different studies from 76.2% to 95% (Bugnicourt et al., 2009). Although highly prevalent, the intracranial artery calcification does not associate with ischaemic stroke.

Arteriosclerosis

Arteriosclerosis—arterial stiffness—and increased pulse wave velocity (PWV) are induced by VC. PWV measured in large elastic arteries could be another indirect method for quantification of the VC. A positive correlation between VC and arterial stiffness measured by PWV has been demonstrated in both early CKD and HD patients (Sigrist et al., 2007). Several possible mechanisms for the association between arterial stiffness and VC can be hypothesized. First, arterial calcification may induce arterial wall stiffness and increased PWV. A recent study in adult HD patients reported an association between 25- hydroxyvitamin D deficiency and arterial stiffness (Patange et al., 2012). Second, increased arterial stiffness may cause vessel wall damage and atherosclerosis (van Popele et al., 2001). Third, changes in the intrinsic properties of the arterial wall by arterial remodelling may contribute to both processes in CKD patients (Shanahan et al., 2011). VCs (evaluated by different methods) have been associated with increased arterial stiffness, in both pre-dialysis and dialysis patients. Guerin et al. showed a positive correlation between VC (semi-quantitative assessment based on a B-mode ultrasound-derived score calculated according to the number of arterial sites with calcifications) and increased stiffness of elastic type arteries such as aorta and common carotid artery (Guerin et al., 2000). Block et al. found a strong association between PWV and radiological measures of abdominal aorta calcification, and less strongly associated with thoracic aorta and CAC (Block et al., 2007). Adragao et al. found also an independent and direct association between the simple VC score, assessed in plain radiographs of hands and pelvis, and increased stiffness of muscle arteries such as radial, iliac, and femoral arteries (Adragao et al., 2009). Decreased arterial compliance may be the product of numerous contributing factors such as change in the collagen elastin ratio, atherosclerotic plaque, or the calcification of the intima or the media layer of the vessel wall. Moreover, CAC progression is associated with a simultaneous deterioration of the arterial compliance and cardiac repolarization.

Mortality

Matsuoka et al. followed 102 chronic HD patients and evaluated the impact of CAC on survival. After a 5-year follow-up, the cumulative survival was significantly lower in the high (score ≥ 200) than in the low (< 200) CAC group (84% and 68%) (Matsuoka et al., 2004). Similarly, Block et al. showed a higher mortality risk with a high CAC score (> 400) among 127 HD patients followed for nearly 5 years from the time of screening (Block et al., 2007). More recently, Shantouf et al. reported a high mortality risk in HD patients with both CAC score 101–400 and > 400, compared to a score of 0 (hazard ratio (HR) 8.5; 95% confidence interval (CI) 1.1–48.1; P = 0.02; and HR 13.3; 95% CI 1.3–65.1; P = 0.01, respectively). This association was independent of demographic characteristics, comorbidities, and other traditional and uraemic-related risk factors (Shantouf et al., 2010).

Coronary artery disease

As discussed earlier in this chapter, patients with CKD tend to accumulate a large burden of coronary artery calcium (CAC) with worsening renal function. The correlation between CAC score severity and coronary artery disease is only modest (Sharples et al., 2004) and the extent of CAC should not be used as an indication to perform invasive coronary angiography. However, in at least one study, CAC showed a good association with the presence of obstructive coronary artery disease especially when the score was > 400 (Rosário et al., 2010). A major limitation of invasive angiography in

CKD, like all other modalities requiring injection of iodinated contrast media, is the risk of inducting further deterioration of renal function with iodine contrast; this potential complication requires careful management of the patient in preparation of the test and following its completion (Kelly et al., 2008).

Bone

The link between VC and bone in dialysis patients is extremely complex. There are some studies which have demonstrated an inverse relationship between VC and low bone turnover assessed by histomorphometric markers (Toussaint et al., 2009). London et al. found an association between systemic arterial calcifications (aorta and the main peripheral arteries) and indexes of low bone turnover, but not trabecular volume (London et al., 2004). In contrast, Adragao et al. found an association between low bone volume and VC, but not with bone turnover (Adragao et al., 2009). Barreto et al. found a negative correlation between coronary calcifications and trabecular bone volume or its thickness (Barreto et al., 2008). The different arterial territories analysed and the relationships of the different bone changes (bone volume, osteoblast number, or tetracycline labelling), which do not necessarily reflect the same mechanisms, seem to explain these differences. In contrast, recent papers have not found any relation between VC and low bone turnover when multivariate analysis was performed.

The new modern concept sustains that it is not bone turnover itself which is related to VC, but bone resorption which is in excess compared to bone formation, which can occur at any rate of turnover. In agreement with this concept, Baretto et al. reported that the correction of the balance in bone turnover, either high or low, protects against the progression of VC (Barreto et al., 2008).

The link between VC and bone is more than a part of the ageing process; the similarities between bone development and mineralization and the process of VC resulting from the experimental studies seems to be the responsible mechanism. Additionally, data from clinical studies found several common risk factors for VC and osteoporosis, like diabetes, inflammation, oxidative stress, oestrogen, vitamin D or vitamin K deficiency, or dyslipidaemia.

On the other hand, in epidemiological studies in general and CKD populations, the progressive VC was associated with lower bone mass and increased incidence of new osteoporotic fractures. This finding was confirmed in animal studies, which showed an inverse relation between VC and bone mass. The analysis of areas of VC showed overexpression of the family of secreted frizzled-related proteins (SFRPs) and circulating wingless/int (Wnt) protein inhibitors. SFRPs are inhibitors of the Wnt pathway, which is actively involved in bone formation and VC.

Prevention and treatment

Lowering phosphate

P and Ca play central roles in the calcification process in CKD patients, justifying interventional trials aimed at reducing P level without increasing Ca intake by different molecules. One such compound is the non-absorbable agent sevelamer which contains neither Ca nor aluminium. This drug is a cationic polymer that binds P through ion exchange. Randomized controlled trials comparing sevelamer with Ca-containing P binders have been conducted with conflicting results on VC. The largest and best designed such clinical trial, which also evaluated progression of VC, was the 'Treat-to-Goal' study, conducted by Chertow et al. in 200 HD patients, comparing the effects of sevelamer to Ca acetate on coronary artery and thoracic aorta calcification assessed by electron beam tomography. After a follow-up period of 1 year, the median absolute Ca score of coronary arteries and thoracic aorta increased significantly in the Ca treatment group but not in the sevelamer group (Chertow et al., 2002). Furthermore, although serum P control was similar with both agents, Ca-based P binders were associated with a higher incidence of hypercalcaemia and an increased incidence of low PTH levels. A beneficial effect of sevelamer on CAC was also reported in another randomized controlled trial involving new HD patients with a follow-up of 18 months. The use of Ca-containing P binders conducted to more pronounced calcification in coronary arteries, measured by EBCT than did the use of sevelamer and this was particularly true in those with evidence of coronary calcification at baseline (Block et al., 2005). In a post hoc analysis of this, a survival advantage was depicted in patients treated with sevelamer, although a subpopulation of the study that did not show initial cardiac calcification remained free of calcification, despite receiving Ca-containing P binders (Block et al., 2007). The apparent survival benefit may also have been related to decreases in C-reactive protein, total cholesterol, and LDL cholesterol, also observed with greater frequency in association with sevelamer. Of interest, in a recent post hoc analysis of the RIND trial, the authors reported that another surrogate marker of cardiovascular risk—epicardial adipose tissue (EAT)—was a predictor of mortality. EAT is fat located below the parietal pericardium; it is capable of producing a large amount of inflammatory mediators and it is believed to promote atherosclerosis via paracrine effects (D'Marco et al., 2013). The volume of EAT correlated positively with CAC; the 5-year survival rate was 44. 6% (95% CI 21.1–65.7) and 71.2% (95% CI 45.95–86.25) in patients with EAT above or below the mean (129 ± 69.5 cc), respectively. Interestingly, in a retrospective analysis investigators linked EAT to the malnutrition-inflammation-arteriosclerosis syndrome, as well as increased arterial stiffness in CKD subjects (Turkmen et al., 2011; Turan et al., 2013). This suggests that markers such as CAC and EAT may be useful factors to consider for a better risk stratification of CKD patients.

In contrast, the Calcium Acetate Renagel Evaluation (CARE)-2 trial showed no difference in CAC progression between the Ca and sevelamer group (Chertow et al., 2004). The differences observed between these trials may be due, in part, to study limitations and the inclusion of a higher proportion of diabetic patients in the CARE-2 trial.

A growing number of alternative therapies are undergoing evaluation, including nicotinamide and polynuclear iron (III)-oxyhydroxide phosphate (PA21). Nicotinamide, a metabolite of nicotinic acid (niacin, vitamin B_3), inhibits the Na/Pi cotransport system in the gastrointestinal tract and kidneys and may be effective in lowering P levels in dialysis patients by reducing gastrointestinal tract phosphate absorption. However, data on the possible effect of nicotinamide on VC are missing (Cheng et al., 2012). PA21, a novel non-Ca P binder controls hyperphosphataemia over the long term and has a lower pill burden than sevelamer carbonate, according to a phase 3 study in in patients undergoing HD or PD. Furthermore, it appears that, at least in animal models, PA21 prevents the development of VC in uraemic rats (Floege et al., 2012). However, these promising results need to be confirmed in humans.

In conclusion, the small size of these studies and the conflicting results emphasize the need for large interventional trials looking at VC in addition to hard clinical endpoints.

Vitamin D receptor activators

Although vitamin D and its analogues are widely used to manage secondary hyperparathyroidism, there is some controversy as to whether active vitamin D compounds directly accelerate VC. This hypothesis is based on the fact that VSMCs possess 1a hydroxylase to transform 25-hydroxyvitamin D into the active form 1,25-dihydroxyvitamin D (Somjen et al., 2005) and also express the VDR (Wu-Wong et al., 2006). The vitamin D compounds may therefore induce VC through their calcaemic and phosphataemic actions. Oversuppression of PTH by vitamin D compounds leads to low-turnover bone disease, typically adynamic bone disease, which is associated with VC (London et al., 2004). Despite this, there is increasing evidence that the administration of native vitamin D to patients with low serum levels of vitamin D (which are very common in CKD) may be beneficial for survival.

In CKD patients, retrospective studies have shown a protective effect of 1a-hydroxyvitamin D_3 supplementation on VC (Ogawa et al., 2010). Vitamin D analogues were designed to suppress PTH with less calcaemic and phosphataemic actions, they sometimes induce hypercalcaemia and hyperphosphataemia. Despite encouraging experimental results in rodent models of CKD (Becker et al., 2011) and in historical cohorts of selective VDR activators (Teng et al., 2003), but these findings still need to be confirmed in randomized controlled trials. In this regard, the PRIMO (Paricalcitol Capsule Benefits in Renal Failure-Induced Cardiac Morbidity) study assigned CKD patients (stageS 3 and 4) to receive oral paricalcitol (2 micrograms/day) or placebo for 48 weeks, and did not show any difference in cardiac structure or function between the two groups of patients (Thadhani et al., 2012). Furthermore, episodes of hypercalcaemia were more frequent in the paricalcitol group.

Calcimimetics

Calcimimetic agents act on the CaSR in the parathyroid gland, and reduce PTH levels by increasing the sensitivity of the CaSR to Ca without affecting Ca intake (Nemeth and Bennett, 1998) and this should result in less hypercalcaemia and hence an inhibition of the calcification process. In this regard, a large randomized study (ADVANCE) to evaluate the effects of cinacalcet plus low-dose vitamin D versus flexible dosage of vitamin D alone on VC in 360 HD patients was conducted. No significant difference in CAC scores between the two groups was depicted, after a follow-up of 52 weeks. Only a relative reduction in aortic valve calcification was observed in the cinacalcet arm (Raggi et al., 2011). However, these results need to be considered with caution since nearly 40% of those assigned to treatment with cinacalcet and low doses of vitamin D sterols unexpectedly received weekly doses of vitamin D throughout the study that exceeded amounts specified in the protocol. In a post hoc analysis, protocol-adherent subjects given cinacalcet and low doses of vitamin D (CPA) as specified in the study protocol had a lower progression of CV calcification compared with control subjects in whom secondary hyperparathyroidism was treated with higher doses of vitamin D sterols alone (Urena-Torres et al., 2013).

Given these conflicting results, more trials are needed to definitely prove or disprove the usefulness of cinacalcet for treatment of VC.

Parathyroidectomy

In CKD patients with severe hyperparathyroidism who fail to respond to medical/pharmacological therapy, the 2009 CKD-mineral and bone disorder (MBD) KDIGO guideline recommends parathyroidectomy (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009). Even if this strategy generally results in a marked, sustained reduction in levels of serum PTH, no data are available on the effect of parathyroidectomy on mortality, fractures, or quality of life. It seems, however, that parathyroidectomy minimizes the progression of calcification by lowering the serum Ca and P concentrations but this is supported by few studies, such as the trial of Bleyer at al. which found that subtotal parathyroidectomy significantly decreased or stabilized VC (Bleyer et al., 2005).

Vitamin K_2

There is increasing evidence linking vitamin K deficiency to VC via a functional impairment of vitamin K-dependent calcification modulators, such as MGP (Krueger et al., 2009). Its activity is dependent upon vitamin K-dependent carboxylation, which is critical in mediating the activity of the protein to inhibit calcification locally (Krueger et al., 2009).

High dietary K_1 also determines an increase in the carboxylation of OC, but only in the presence of an increase in OC production, such as in CKD. Although both forms of vitamin K act are as cofactors, it is currently not known as to why conversion is necessary and whether there may be a separate role for MK-4.

In the general population, vitamin K contributes to bone health and reduces the incidence of clinical fractures. In the Rotterdam trial, low vitamin K intake was associated with a higher incidence of severe aortic calcification (Geleijnse et al., 2004). In a rodent model of CKD, vitamin K status was found to be critical in the predisposition of blood vessels to calcification. The high dietary vitamin K_1 intake attenuated the development of VC, whereas the treatment with therapeutic doses of warfarin markedly increased VC (McCabe et al., 2013).

Recent intervention studies in humans showed increased OC and MPG after vitamin K administration. In a pilot study of 53 CKD patients, Ketteler et al. demonstrated that the daily administration of vitamin K determines a significant increase of MPG and OC (Westenfeld et al., 2012). Moreover, Holden et al. showed that the long-term use of warfarin in HD patients was independently associated with the severity of aortic valve calcification (Holden et al., 2007).

In conclusion, increasing MGP activity in arterial vessels could constitute a valuable therapeutic and prophylactic target allowing reduced progression or development of VC.

Magnesium

The role of magnesium in the pathogenesis of VC has been a matter of some debate in recent years. It seems that magnesium is directly involved in the prevention of calcification because it is a natural biological Ca antagonist, magnesium prevents early calcium phosphate hydroxyapatite crystal growth. Additionally it serves as a cofactor and/or modulator of vitamin K, MGP or

Table 120.2 Observational studies regarding the use of magnesium in CKD patients

Authors (year)	Patients	Study design	Parameter	Assessment technique	P value
Spiegel et al. (2009)	7 (haemodialysis)	Prospective, follow-up over 18 months	Coronary artery calcification	Electron beam tomography	P = 0.0737
Turgut et al. (2008)	47 (haemodialysis)	Prospective, follow-up over 2 months	Intima–media thickness of the carotid artery	Ultrasound	P = 0.014
Ishimura et al. (2007)	390 (non-diabetic haemodialysis)	Prospective, single-blind follow-up over 4 months	Calcification of the hand arteries	Radiographic findings of the hands	P = 0. 036
Tzanakis et al. (2004)	93 (haemodialysis) and 182 age- and sex-matched healthy controls	Cross-sectional analysis	Carotids intima–media thickness	B-mode ultrasound	P = 0.001
Tzanakis et al. (1997)	56 (haemodialysis)	Retrospective analysis of 8 years	Mitral annular calcification	Doppler echocardiography	P = 0.008
Meema et al. (1987)	44 (continuous ambulatory peritoneal dialysis)	Prospective follow-up	Progression/regression of arterial calcification	Radiographic surveys	P < 0.001

pyrophosphatases, well-known inhibitors of VC (Zyryanov et al., 2002; Amizuka et al., 2005; Cunningham et al., 2012). Furthermore hypomagnesaemia promotes endothelial inflammation via oxidation of HDL cholesterol

Given the potential involvement of high serum magnesium in reducing VC as shown by various observational studies (see Table 120.2), some interventional studies have investigated the use of magnesium in CKD patients, though the level of evidence is low.

Data from a pilot study conducted over a period of 18 months showed that long-term administration of oral magnesium supplements to CKD patients on intermittent HD therapy might retard arterial calcification assessed by EBCT (Spiegel et al., 2007; Massy and Drüeke, 2012). In another larger randomized study in ESRD patients on HD, oral magnesium supplementation over a 2-month period led to a significant reduction in carotid intima–media thickness (Turgut et al., 2008; Massy and Drüeke, 2012). Although these results are promising, more randomized, double-blind controlled studies are needed to confirm the positive effect of magnesium supplementation in reducing VC.

Additional therapies

There are only a few studies that have evaluated additional agents to help retard or regress VC in patients with renal failure. Some interventions that have been evaluated include bisphosphonates (Nitta et al., 2004) which are non-hydrolysable PPi analogues (Rezg et al., 2011) and Ca-channel blockers like verapamil (Fleckenstein-Grun et al., 1995). The use of sodium thiosulfate to increase the functional ability of MGP to prevent VC is also being studied (Covic et al., 2010).

As expected, kidney transplantation seems also to ameliorate the progression of VC, as suggested in small non-randomized trials, but data are limited (Oschatz et al., 2006). In contrast, another study showed that there is significant progression of CAC (assessed by EBCT) in most subjects post-renal transplantation (Schankel et al., 2007).

References

Adijiang, A., Goto, S., Uramoto, S., *et al.* (2008). Indoxyl sulphate promotes aortic calcification with expression of osteoblast-specific proteins in hypertensive rats. *Nephrol Dial Transplant*, 23(6), 1892–901.

Adragao, T., Pires, A., Birne, R., *et al.* (2009). A plain X-ray vascular calcification score is associated with arterial stiffness and mortality in dialysis patients. *Nephrol Dial Transplant*, 24(3), 997–1002.

Agatston, A. S., Janowitz, W. R., Hildner, F. J., *et al.* (1990). Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*, 15(4), 827–32.

Amann, K. (2008). Media calcification and intima calcification are distinct entities in chronic kidney disease. *Clin J Am Soc Nephrol*, 3(6), 1599–605.

Amizuka, N., Li, M., and Maeda, T. (2005). [The interplay of magnesium and vitamin K2 on bone mineralization]. *Clin Calcium*, 15(7), 57–61.

Aoshima, Y., Mizobuchi, M., Ogata, H., *et al.* (2012). Vitamin D receptor activators inhibit vascular smooth muscle cell mineralization induced by phosphate and TNF-alpha. *Nephrol Dial Transplant*, 27(5), 1800–6.

Baber, U., Stone, G. W., Weisz, G., *et al.* (2012). Coronary plaque composition, morphology, and outcomes in patients with and without chronic kidney disease presenting with acute coronary syndromes. *JACC Cardiovasc Imaging*, 5(3 Suppl), S53–61.

Barreto, D. V., Barreto, F. de C., Carvalho, A. B., *et al.* (2008). Association of changes in bone remodeling and coronary calcification in hemodialysis patients: a prospective study. *Am J Kidney Dis*, 52(6), 1139–50.

Becker, L. E., Koleganova, N., Piecha, G., *et al.* (2011). Effect of paricalcitol and calcitriol on aortic wall remodeling in uninephrectomized ApoE knockout mice. *Am J Physiol Renal Physiol*, 300(3), F772–82.

Bellasi, A., Ferramosca, E., Muntner, P., *et al.* (2006). Correlation of simple imaging tests and coronary artery calcium measured by computed tomography in hemodialysis patients. *Kidney Int*, 70(9), 1623–8.

Bellasi, A., Ferramosca, E., Ratti, C., *et al.* (2012). Cardiac valve calcification is a marker of vascular disease in prevalent hemodialysis patients. *J Nephrol*, 25(2), 211–8.

Blacher, J., Guerin, A. P., Pannier, B., *et al.* (2001). Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension*, 38(4), 938–42.

Bleyer, A.J., Burkart, J., Piazza, M., *et al.* (2005). Changes in cardiovascular calcification after parathyroidectomy in patients with ESRD. *Am J Kidney Dis*, 46(3), 464–9.

Block, G. A., Raggi, P., Bellasi, A., *et al.* (2007). Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int*, 71(5), 438–41.

Block, G. A., Spiegel, D. M., Ehrlich, J., *et al.* (2005). Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int*, 68(4), 1815–24.

Boström, K., Tsao, D., Shen, S., *et al.* (2001). Matrix GLA protein modulates differentiation induced by bone morphogenetic protein-2 in C3H10T1/2 cells. *J Biol Chem*, 276(17), 14044–52.

Bryant, J. and Hale White, W. (1901). A case of calcification of the arteries and obliterative endarteritis, associated with hydronephrosis, in a child aged six months. *Guys Hosp Rep*, 40, 17.

Budoff, M. J. and Raggi, P. (2001). Coronary artery disease progression assessed by electron-beam computed tomography. *Am J Cardiol*, 88(2A), 46E–50E.

Bueno de Oliveira, R., Liabeuf, S., Okazaki, H., *et al.* (2013). The clinical impact of plasma leptin levels in a cohort of chronic kidney disease patients. *Clin Kidney J*, 63–70.

Bugnicourt, J. M., Chillon, J. M., Massy, Z. A., *et al.* (2009). High prevalence of intracranial artery calcification in stroke patients with CKD: a retrospective study. *Clin J Am Soc Nephrol*, 4(2), 284–90.

Chanakul, A., Zhang, M. Y., Louw, A., *et al.* (2013). FGF-23 regulates CYP27B1 transcription in the kidney and in extra-renal tissues. *PLoS One*, 8(9), e72816.

Chavez, R. J., Haney, R. M., Cuadra, R. H., *et al.* (2012). Upregulation of thrombospondin-1 expression by leptin in vascular smooth muscle cells via JAK2- and MAPK-dependent pathways. *Am J Physiol Cell Physiol*, 303(2), C179–91.

Chen, N. X., O'Neill, K. D., Chen, X., *et al.* (2008). Annexin-mediated matrix vesicle calcification in vascular smooth muscle cells. *J Bone Miner Res*, 23(11), 1798–805.

Cheng, S. C., Young, D. O., Huang, Y., *et al.* (2008). A randomized, double-blind, placebo-controlled trial of niacinamide for reduction of phosphorus in hemodialysis patients. *Clin J Am Soc Nephrol*, 3(4), 1131–8.

Chertow, G. M., Burke, S. K., Raggi, P., *et al.* (2002). Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int*, 62(1), 245–52.

Chertow, G. M., Raggi, P., Chasan-Taber, S., *et al.* (2004). Determinants of progressive vascular calcification in haemodialysis patients. *Nephrol Dial Transplant*, 19(6), 1489–96.

Covic, A., Kanbay, M., Voroneanu, L., *et al.* (2010). Vascular calcification in chronic kidney disease. *Clin Sci (Lond)*, 119(3), 111–21.

Cunningham, J., Rodríguez, M., and Piergiorgio Messa, P. (2012). Magnesium in chronic kidney disease stages 3 and 4 and in dialysis patients. *Clin Kidney J*, 5 Suppl 1, i39–51.

Dai, X. Y., Zhao, M. M., Cai, Y., *et al.* (2013). Phosphate-induced autophagy counteracts vascular calcification by reducing matrix vesicle release. *Kidney Int*, 83(6), 1042–51.

Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease Working Group (2013). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*, 3(1), 1–150.

D'Marco, L. G., Bellasi, A., Kim, S., *et al.* (2013). Epicardial adipose tissue predicts mortality in incident hemodialysis patients: a substudy of the Renagel in New Dialysis trial. *Nephrol Dial Transplant*, 28(10), 2586–95.

Dou, L., Jourde-Chiche, N., Faure, V., *et al.* (2007). The uremic solute indoxyl sulfate induces oxidative stress in endothelial cells. *J Thromb Haemost*, 5(6), 1302–8.

Drüeke, T. B. and Massy, Z. A. (2012). Role of vitamin D in vascular calcification: bad guy or good guy? *Nephrol Dial Transplant*, 27(5), 1704–7.

Ekart, R., Hojs, R., Hojs-Fabjan, T., *et al.* (2005). Predictive value of carotid intima media thickness in hemodialysis patients. *Artif Organs*, 29(8), 615–19.

Evans, K. N., Nguyen, L., Chan, J., *et al.* (2006). Effects of 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 on cytokine production by human decidual cells. *Biol Reprod*, 75(6), 816–22.

Fleckenstein-Grun, G., Thimm, F., Frey, M., *et al.* (1995). Progression and regression by verapamil of vitamin D3-induced calcific medial degeneration in coronary arteries of rats. *J Cardiovasc Pharmacol*, 26(2), 207–13.

Floege, J., Ketteler, M., Rastogi, A., et al. (2012). *Efficacy and Safety of an Iron-Based Phosphate Binder, PA21, in Hyperphosphatemic CKD Patients on Dialysis*. Poster SA-PO1103, ASN Congress 2012, San Diego, CA.

Gallieni, M., Caputo, F., Filippini, A., *et al.* (2012). Prevalence and progression of cardiovascular calcifications in peritoneal dialysis patients: a prospective study. *Bone*, 51(3), 332–7.

Geleijnse, J. M., Vermeer, C., Grobbee, D. E., *et al.* (2004). Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. *J Nutr*, 134(11), 3100–5.

Giachelli, C. M., Jono, S., Shioi, A., *et al.* (2001). Vascular calcification and inorganic phosphate. *Am J Kidney Dis*, 38(4 Suppl 1), S34–7.

Go, A. S., Chertow, G. M., Fan, D., *et al.* (2004). Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*, 351(13), 1296–305.

Goldsmith, D., Ritz, E., and Covic, A. (2004). Vascular calcification: a stiff challenge for the nephrologist: does preventing bone disease cause arterial disease? *Kidney Int*, 66(4), 1315–33.

Goodman, W. G., Goldin, J., Kuizon, B. D., *et al.* (2000). Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med*, 342(20), 1478–83.

Gradaus, F., Ivens, K., Peters, A. J., *et al.* (2001). Angiographic progression of coronary artery disease in patients with end-stage renal disease. *Nephrol Dial Transplant*, 16(6), 1198–202.

Guerin, A. P., London, G. M., Marchais, S. J., *et al.* (2000). Arterial stiffening and vascular calcifications in end-stage renal disease. *Nephrol Dial Transplant*, 15(7), 1014–21.

Haydar, A. A., Hujairi, N. M., Covic, A. A., *et al.* (2004). Coronary artery calcification is related to coronary atherosclerosis in chronic renal disease patients: a study comparing EBCT-generated coronary artery calcium scores and coronary angiography. *Nephrol Dial Transplant*, 19(9), 2307–12.

Hermans, M. M., Brandenburg, V., Ketteler, M., *et al.* (2007). Association of serum fetuin-A levels with mortality in dialysis patients. *Kidney Int*, 72(2), 202–7.

Hjelmesaeth, J., Ueland, T., Flyvbjerg, A., *et al.* (2006). Early posttransplant serum osteoprotegerin levels predict long-term (8-year) patient survival and cardiovascular death in renal transplant patients. *J Am Soc Nephrol*, 17(6), 1746–54.

Holden, R. M., Sanfilippo, A. S., Hopman, W. M., *et al.* (2007). Warfarin and aortic valve calcification in hemodialysis patients. *J Nephrol*, 20(4), 417–22.

Juppner, H., Wolf, M., and Salusky, I. B. (2010). FGF-23: More than a regulator of renal phosphate handling? *J Bone Miner Res*, 25(10), 2091–7.

Kato, A., Takita, T., Maruyama, Y., *et al.* (2003). Impact of carotid atherosclerosis on long-term mortality in chronic hemodialysis patients. *Kidney Int*, 64(4), 1472–9.

Kauppila, L. I., Polak, J. F., Cupples, L. A., *et al.* (1997). New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: a 25-year follow-up study. *Atherosclerosis*, 132(2), 245–50.

Kazama, J. J., Shigematsu, T., Yano, K., *et al.* (2002). Increased circulating levels of osteoclastogenesis inhibitory factor (osteoprotegerin) in patients with chronic renal failure. *Am J Kidney Dis*, 39(3), 525–32.

Keith, D. S., Nichols, G. A., Gullion, C. M., *et al.* (2004). Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med*, 164(6), 659–63.

Kelly, A., Dwamena, B., Cronin, P., *et al.* (2008). Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. *Ann Intern Med*, 148, 284–94.

Ketteler, M., Bongartz, P., Westenfeld, R., *et al.* (2003). Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. *Lancet*, 361(9360), 827–33.

Ketteler, M., Wanner, C., Metzger, T., *et al.* (2003). Deficiencies of calcium-regulatory proteins in dialysis patients: a novel concept of cardiovascular calcification in uremia. *Kidney Int Suppl*, 84, S84–7.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009). KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int* Suppl, 113, S1–130.

Krueger, T., Westenfeld, R., Ketteler, M., *et al.* (2009). Vitamin K deficiency in CKD patients: a modifiable risk factor for vascular calcification? *Kidney Int*, 76(1), 18–22.

Krueger, T., Westenfeld, R., Schurgers, L., *et al.* (2009). Coagulation meets calcification: the vitamin K system. *Int J Artif Organs*, 32(2), 67–74.

Kuilman, T., Michaloglou, C., Mooi, W. J., *et al.* (2010). The essence of senescence. *Genes Dev*, 24(22), 2463–79.

Leskinen, Y., Paana, T., Saha, H., *et al.* (2009). Valvular calcification and its relationship to atherosclerosis in chronic kidney disease. *J Heart Valve Dis*, 18(4), 429–38.

Levey, A. S., Bosch, J. P., Lewis, J. B., *et al.* (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*, 130(6), 461–70.

Levin, A., Bakris, G. L., Molitch, M., *et al.* (2007). Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int*, 71(1), 31–8.

Lomashvili, K. A., Cobbs, S., Hennigar, R. A., *et al.* (2004). Phosphate-induced vascular calcification: role of pyrophosphate and osteopontin. *J Am Soc Nephrol*, 15(6), 1392–401.

Lomashvili, K. A., Garg, P., Narisawa, S., *et al.* (2008). Upregulation of alkaline phosphatase and pyrophosphate hydrolysis: potential mechanism for uremic vascular calcification. *Kidney Int*, 73(9), 1024–30.

London, G. M., Guérin, A. P., Marchais, S. J., *et al.* (2003). Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant*, 18(9), 1731–40.

London, G. M., Marty, C., Marchais, S. J., *et al.* (2004). Arterial calcifications and bone histomorphometry in end-stage renal disease. *J Am Soc Nephrol*, 15(7), 1943–51.

Marechal, C., Coche, E., Goffin, E., *et al.* (2012). Progression of coronary artery calcification and thoracic aorta calcification in kidney transplant recipients. *Am J Kidney Dis*, 59(2), 258–69.

Massy, Z. A. and Drüeke, T. B. (2012). Magnesium and outcomes in patients with chronic kidney disease: focus on vascular calcification, atherosclerosis and survival. *Clin Kidney J*, 5(1), i52–i6.

Matsuoka, M., Iseki, K., Tamashiro, M., *et al.* (2004). Impact of high coronary artery calcification score (CACS) on survival in patients on chronic hemodialysis. *Clin Exp Nephrol*, 8(1), 54–8.

McCabe, K. M., Booth, S. L., Fu, X., *et al.* (2013). Dietary vitamin K and therapeutic warfarin alter the susceptibility to vascular calcification in experimental chronic kidney disease. *Kidney Int*, 83(5), 835–44.

Mehrotra, R., Budoff, M., Hokanson, J. E., *et al.* (2005). Progression of coronary artery calcification in diabetics with and without chronic kidney disease. *Kidney Int*, 68(3), 1258–66.

Memon, F., El-Abbadi, M., Nakatani, T., *et al.* (2008). Does Fgf23-klotho activity influence vascular and soft tissue calcification through regulating mineral ion metabolism? *Kidney Int*, 74(5), 566–70.

Moe, S. M., Drüeke, T., Lameire, N., *et al.* (2007). Chronic kidney disease-mineral-bone disorder: a new paradigm. *Adv Chronic Kidney Dis*, 14(1), 3–12.

Morena, M., Dupuy, A. M., Jaussent, I., *et al.* (2009). A cut-off value of plasma osteoprotegerin level may predict the presence of coronary artery calcifications in chronic kidney disease patients. *Nephrol Dial Transplant*, 24(11), 3389–97.

Morony, S., Tintut, Y., Zhang, Z., *et al.* (2008). Osteoprotegerin inhibits vascular calcification without affecting atherosclerosis in ldlr(-/-) mice. *Circulation*, 117(3), 411–20.

Mulligan, R. M. (1947). Metastatic calcification. *Arch Pathol (Chic)*, 43(2), 177–230.

National Kidney Foundation (2003). K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*, 42(4 Suppl 3), S1–201.

Nemeth, E. F. and Bennett, S.A. (1998). Tricking the parathyroid gland with novel calcimimetic agents. *Nephrol Dial Transplant*, 13(8), 1923–5.

Nishiura, R., Fujimoto, S., Sato, Y., *et al.* (2009). Elevated osteoprotegerin levels predict cardiovascular events in new hemodialysis patients. *Am J Nephrol*, 29(3), 257–63.

Nitta, K., Akiba, T., Suzuki, K., *et al.* (2004). Effects of cyclic intermittent etidronate therapy on coronary artery calcification in patients receiving long-term hemodialysis. *Am J Kidney Dis*, 44(4), 680–8.

O'Neill, W. C., Sigrist, M. K., and McIntyre, C. W. (2010). Plasma pyrophosphate and vascular calcification in chronic kidney disease. *Nephrol Dial Transplant*, 25(1), 187–91.

O'Young, J., Liao, Y., Xiao, Y., *et al.* (2011). Matrix Gla protein inhibits ectopic calcification by a direct interaction with hydroxyapatite crystals. *J Am Chem Soc*, 133(45), 18406–12.

Ogawa, T., Ishida, H., Akamatsu, M., *et al.* (2010). Relation of oral 1alpha-hydroxy vitamin D3 to the progression of aortic arch calcification in hemodialysis patients. *Heart Vessels*, 25(1), 1–6.

Oh, K. W., Nam, C. M., Jee, S. H., *et al.* (2002). Coronary artery calcification and dietary cholesterol intake in Korean men. *Acta Cardiol*, 57(1), 5–11.

Okuno, S., Ishimura, E., Kitatani, K., *et al.* (2007). Presence of abdominal aortic calcification is significantly associated with all-cause and cardiovascular mortality in maintenance hemodialysis patients. *Am J Kidney Dis*, 49(3), 417–25.

Omland, T., Ueland, T., Jansson, A. M., *et al.* (2008). Circulating osteoprotegerin levels and long-term prognosis in patients with acute coronary syndromes. *J Am Coll Cardiol*, 51(6), 627–33.

Oschatz, E., Benesch, T., Kodras, K., *et al.* (2006). Changes of coronary calcification after kidney transplantation. *Am J Kidney Dis*, 48(2), 307–13.

Patange, A. R., Valentini, R. P., Du, W., *et al.* (2012). Vitamin D deficiency and arterial wall stiffness in children with chronic kidney disease. *Pediatr Cardiol*, 33(1), 122–8.

Prosdocimo, D. A., Wyler, S. C., Romani, A. M., *et al.* (2010). Regulation of vascular smooth muscle cell calcification by extracellular pyrophosphate homeostasis: synergistic modulation by cyclic AMP and hyperphosphatemia. *Am J Physiol Cell Physiol*, 298(3), C702–13.

Raggi, P., Boulay, A., Chasan-Taber, S., *et al.* (2002). Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol*, 39(4), 695–701.

Raggi, P., Chertow, G. M., Torres, P. U., *et al.* (2011). The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transplant*, 26(4), 1327–39.

Reynolds, J. L., Skepper, J. N., McNair, R., *et al.* (2005). Multifunctional roles for serum protein fetuin-A in inhibition of human vascular smooth muscle cell calcification. *J Am Soc Nephrol*, 16(10), 2920–30.

Rezg, R., Barreto, F. C., Barreto, D. V., *et al.* (2011). Inhibitors of vascular calcification as potential therapeutic targets. *J Nephrol*, 24(4), 416–27.

Rosário, M., Lima, J. J., Parga, J. R., *et al.* (2010). Coronary calcium score as predictor of stenosis and events in pretransplant renal chronic failure. *Arq Bras Cardiol*, 94(2), 236–43.

Russo, D., Palmiero, G., De Blasio, A. P., *et al.* (2004). Coronary artery calcification in patients with CRF not undergoing dialysis. *Am J Kidney Dis*, 2004. 44(6), 1024–30.

Russo, D., Miranda, I., Ruocco, C., *et al.* (2007). Progression of coronary artery calcification in predialysis patients. *Am J Nephrol*, 27(2), 152–8.

Sandberg, W. J., Yndestad, A., Øie, E., *et al.* (2006). Enhanced T-cell expression of RANK ligand in acute coronary syndrome: possible role in plaque destabilization. *Arterioscler Thromb Vasc Biol*, 26(4), 857–63.

Schankel, K., Robinson, J., Bloom, R. D., *et al.* (2007). Determinants of coronary artery calcification progression in renal transplant recipients. *Am J Transplant*, 7(9), 2158–64.

Schlieper, G., Aretz, A., Verberckmoes, S. C., *et al.* (2010). Ultrastructural analysis of vascular calcifications in uremia. *J Am Soc Nephrol*, 21(4), 689–96.

Schoppet, M., Shroff, R. C., Hofbauer, L. C., *et al.* (2008). Exploring the biology of vascular calcification in chronic kidney disease: what's circulating? *Kidney Int*, 73(4), 384–90.

Serrano, C. V., Jr., Oranges, M., Brunaldi, V., *et al.* (2011). Skeletonized coronary arteries: pathophysiological and clinical aspects of vascular calcification. *Vasc Health Risk Manag*, 7, 143–51.

Shanahan, C. M. (2005). Mechanisms of vascular calcification in renal disease. *Clin Nephrol*, 63(2), 146–57.

Shanahan, C. M., Crouthamel, M. H., Kapustin, A., *et al.* (2011). Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. *Circ Res*, 109(6), 697–711.

Shantouf, R., Budoff, M. J., Ahmadi, N., *et al.* (2010). Total and individual coronary artery calcium scores as independent predictors of mortality in hemodialysis patients. *Am J Nephrol*, 31, 419–25.

Sharples, E., Pereira, D., Summers, S., *et al.* (2004). Coronary artery calcification measured with electron-beam computerized tomography correlates poorly with coronary artery angiography in dialysis patients. *Am J Kidney Dis*, 43(2), 313–19.

Shroff, R. C., Donald, A. E., Hiorns, M. P., *et al.* (2007). Mineral metabolism and vascular damage in children on dialysis. *J Am Soc Nephrol*, 18(11), 2996–3003.

Sigrist, M. K., Levin, A., Er, L., *et al.* (2009). Elevated osteoprotegerin is associated with all-cause mortality in CKD stage 4 and 5 patients in addition to vascular calcification. *Nephrol Dial Transplant*, 24(10), 3157–62.

Sigrist, M. K., Taal, M. W., Bungay, P., *et al.* (2007). Progressive vascular calcification over 2 years is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 chronic kidney disease. *Clin J Am Soc Nephrol*, 2(6), 1241–8.

Simon, A., Megnien, J. L., and Chironi, G. (2010). The value of carotid intima-media thickness for predicting cardiovascular risk. *Arterioscler Thromb Vasc Biol*, 30(2), 182–5.

Somjen, D., Weisman, Y., Kohen, F., *et al.* (2005). 25-hydroxyvitamin D3-1alpha-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. *Circulation*, 111(13), 1666–71.

Speer, M. Y. and Giachelli, C. M. (2004). Regulation of cardiovascular calcification. *Cardiovasc Pathol*, 13(2), 63–70.

Spiegel, D. M., Farmer, B., Smits, G., *et al.* (2007). Magnesium carbonate is an effective phosphate binder for chronic hemodialysis patients: a pilot study. *J Ren Nutr*, 17(6), 416–22.

Svensson, M., Dahle, D. O., Mjøen, G., *et al.* (2012). Osteoprotegerin as a predictor of renal and cardiovascular outcomes in renal transplant recipients: follow-up data from the ALERT study. *Nephrol Dial Transplant*, 27(6), 2571–5.

Teng, M., Wolf, M., Lowrie, E., *et al.* (2003). Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med*, 349(5), 446–56.

Thadhani, R., Appelbaum, E., Pritchett, Y., *et al.* (2012). Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *JAMA*, 307(7), 674–84.

Toussaint, N. D., Lau, K. K., Strauss, B. J., *et al.* (2009). Relationship between vascular calcification, arterial stiffness and bone mineral density in a cross-sectional study of prevalent Australian haemodialysis patients. *Nephrology (Carlton)*, 14(1), 105–12.

Townsend, R. R. (2008). Stroke in chronic kidney disease: prevention and management. *Clin J Am Soc Nephrol*, 3 Suppl 1, S11–16.

Turan, M. N., Gungor, O., Asci, G., *et al.* (2013). Epicardial adipose tissue volume and cardiovascular disease in hemodialysis patients. *Atherosclerosis*, 226(1), 129–33.

Turgut, F., Kanbay, M., Metin, M. R., *et al.* (20080). Magnesium supplementation helps to improve carotid intima media thickness in patients on hemodialysis. *Int Urol Nephrol*, 40(4), 1075–82.

Turkmen, K., Kayikcioglu, H., Ozbek, O., *et al.* (2011). The relationship between epicardial adipose tissue and malnutrition, inflammation, atherosclerosis/calcification syndrome in ESRD patients. *Clin J Am Soc Nephrol*, 6(8), 1920–5.

Urena-Torres, P. A., Floege, J., Hawley, C. M., *et al.* (2013). Protocol adherence and the progression of cardiovascular calcification in the ADVANCE study. *Nephrol Dial Transplant*, 28(1), 146–52.

Van Popele, N. M., Grobbee, D. E., Bots, M. L., *et al.* (2001). Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke*, 32(2), 454–60.

Venuraju, S.M., Yerramasu, A., Corder, R., *et al.* (2010). Osteoprotegerin as a predictor of coronary artery disease and cardiovascular mortality and morbidity. *J Am Coll Cardiol*, 55(19), 2049–61.

Verbeke, F., Van Biesen, W., Honkanen, E., *et al.* (2011). Prognostic value of aortic stiffness and calcification for cardiovascular events and mortality in dialysis patients: outcome of the calcification outcome in renal disease (CORD) study. *Clin J Am Soc Nephrol*, 6(1), 153–9.

Verberckmoes, S. C., Persy, V., Behets, G. J., *et al.* (2007). Uremia-related vascular calcification: more than apatite deposition. *Kidney Int*, 71(4), 298–303.

Westenfeld, R., Schäfer, C., Krüger, T., *et al.* (2009). Fetuin-A protects against atherosclerotic calcification in CKD. *J Am Soc Nephrol*, 20(6), 1264–74.

Westenfeld, R., Krueger, T., Schlieper, G., *et al.* (2012). Effect of vitamin K2 supplementation on functional vitamin K deficiency in hemodialysis patients: a randomized trial. *Am J Kidney Dis*, 59(2), 186–95.

Wexler, L., Brundage, B., Crouse, J., *et al.* (1996). Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association. Writing Group. *Circulation*, 94(5), 1175–92.

Wu-Wong, J. R., Nakane, M., Ma, J., *et al.* (2006). Effects of vitamin D analogs on gene expression profiling in human coronary artery smooth muscle cells. *Atherosclerosis*, 186(1), 20–8.

Yamamoto, H., Tsuruoka, S., Ioka, T., *et al.* (2006). Indoxyl sulfate stimulates proliferation of rat vascular smooth muscle cells. *Kidney Int*, 69(10), 1780–5.

Zeadin, M., Butcher, M., Werstuck, G., *et al.* (2009). Effect of leptin on vascular calcification in apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol*, 29(12), 2069–75.

Zittermann, A., Schleithoff, S. S., and Koerfer, R. (2007). Vitamin D and vascular calcification. *Curr Opin Lipidol*, 18(1), 41–6.

Zyryanov, A. B., Shestakov, A. S., Lahti, R., *et al.* (2002). Mechanism by which metal cofactors control substrate specificity in pyrophosphatase. *Biochem J*, 367, 901–6.

CHAPTER 121

Fractures in patients with chronic kidney disease

Alastair J. Hutchison and Michael L. Picton

Introduction

Around the world the population is ageing. The European Union (EU)'s population has passed the half billion mark, at 501.1 million, in 2010. At the same time, the percentage of people over the age of 65 years in the EU has also increased, from 15.6% in 2000 to 17.4% in 2010, with those over 80 years comprising 4.7% or 23.5 million people (European Commission and Eurostat, 2011).

Osteoporosis, defined by the World Health Organization (WHO) as a skeletal disorder characterized by compromised bone strength, predisposing to an increased risk of fracture, is rare before the age of 50 years, but the incidence of fractures in subsequent years rises progressively with age (Strom et al., 2011). The number of new fractures in 2010 was estimated at 2.35 million in the five largest EU countries combined (France, Germany, Italy, Spain, and the United Kingdom), resulting in around 34,000 excess deaths. In Europe as a whole, the number of elderly is likely to increase markedly, and improvements in life expectancy indicate that the number of fractures will continue to rise as the population ages (Strom et al., 2011). Chronic kidney disease (CKD) is also a common age-related condition, and whilst 8.5% of the total population in the United Kingdom has an estimated glomerular filtration rate (eGFR) of < 60 mL/min, over the age of 75 years the prevalence rises to > 33% (Stevens et al., 2007).

Since osteoporosis and CKD are both common conditions in the elderly, it is surprising that relatively little research has examined the relationship between them and the contribution of each to the other. It was not until around 2000 that several authors highlighted the increased risk of fracture in dialysis (CKD 5D) patients (Alem et al., 2000; Coco and Rush, 2000; Fontaine et al., 2000). However, over the past decade it has become clear that CKD stages 3, 4, and 5 are all associated with an increased risk of fracture (Nickolas et al., 2006; Kinsella et al., 2010; Jamal et al., 2012).

Fractures can occur in a variety of skeletal sites, but whereas patients with hip fractures are admitted to hospital and can be captured through hospital statistics and other healthcare agencies, patients with spine, forearm, rib, tibia, and fibula fractures are often managed as out-patients and generally do not result in hospital admission. Therefore, data capture for both incidence and outcome is much less reliable. Consequently, most of the data in this chapter relates to hip fracture, and approximately 77,000 such fractures occur annually in the United Kingdom (population 62,000,000), at an estimated cost to the National Health Service (NHS) of £2 billion (from a total NHS budget of £104 billion), and with a 30-day mortality rate of nearly 9% (Currie et al., 2012). Hip fractures can be divided into those occurring at the femoral neck, and those which are intertrochanteric. Bone strength reflects the integration of two features: bone density and bone quality. Bone density is expressed as grams of mineral per area or volume and in any given individual is determined by peak bone mass and amount of bone loss. Bone quality refers to architecture, turnover, damage accumulation (e.g. microfractures), and mineralization. A fracture occurs when a failure-inducing force (e.g. trauma) is applied to osteoporotic bone. Thus, osteoporosis is a significant risk factor for fracture, and a distinction between risk factors that affect bone metabolism and risk factors for fracture must be made.

Fracture risk and mortality in dialysis patients

US patients on haemodialysis have a greater than fourfold increase in hip fractures compared to age- and gender-matched controls (Alem et al., 2000). Across all 12 countries participating in the Dialysis Outcomes and Practice Patterns Study II (DOPPS II), 2.6% of the prevalent cross-section of patients (N = 12782) had a prior hip fracture (Jadoul et al., 2006). The overall unadjusted incidence of new hip fracture events was 8.9 per 1000 patient-years at risk, compared to around 1.8 per 1000 patient-years in the UK General Practice Research Database (Yang et al., 2006). The incidence of new fracture events of any type in DOPPS II was 25.6 per 1000 patient-years. Furthermore, patients with CKD 5D had a 1-year mortality of 64% following a hip fracture, compared to 15–20% in the general population.

Risk factors for fracture in dialysis patients include the usual risk factors for osteoporotic fracture of older age, female gender, low body mass index, postmenopausal status, previous fracture, and use of psychoactive medications, such as antidepressant drugs, benzodiazepines, and narcotics. In addition, dialysis patients' risk increases in proportion to the duration of renal replacement therapy, exposure to glucocorticoids, history of previous kidney transplantation, and suppressed or very elevated parathyroid hormone (PTH) levels (Coco and Rush, 2000; Stehman-Breen et al., 2000; Cueto-Manzano et al., 2003; Jadoul et al., 2006; Jamal et al., 2012). This combination of factors results in a hip fracture incidence for haemodialysis patients of both genders being similar to the incidence observed among non-uraemic individuals older by 10–20 years (Jadoul et al., 2006).

Fracture risk in patients with chronic kidney disease stages 3 and 4

In a group of 33,000 male US veterans, CKD 4, but not CKD 3, was associated with an almost fourfold increase in risk of incident hip fractures (Dooley et al., 2008). Using data from the Study of Osteoporotic Fractures among 9704 women (Cummings et al., 1990), Ensrud et al. found that decreasing eGFR (by Cockcroft and Gault method) was associated with increased risk of hip fracture. Compared with women with an eGFR of 60 mL/min or greater, the hazard ratio for hip fracture was 1.57 in those with an eGFR 45–59 mL/min and 2.32 in those with an eGFR < 45 mL/min. In particular, women with a reduced eGFR were at increased risk of trochanteric hip fracture with a hazard ratio of 3.93 in women with an eGFR 45–59 mL/min and 7.17 in women with an eGFR < 45 mL/min (Ensrud et al., 2007). No statistically significant association between CKD and risk of vertebral fracture was found. Black women were excluded from the analyses because of their very low fracture rate, which is probably related to higher bone mineral density in Afro-Caribbean subjects (Nam et al., 2010). Several other studies have confirmed these associations between severity of CKD and risk of fracture (Jassal et al., 2007; LaCroix et al., 2008; Yenchek et al., 2012).

Osteoporosis and chronic kidney disease-mineral and bone disorder

Osteoporosis is defined as a metabolic bone disease characterized by low bone mass and microarchitectural deterioration of bony tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. This definition was refined by the WHO to include measurement of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA). The resulting BMD is then converted into a T score or Z score. The T score is the number of standard deviations below the average for a young adult at peak bone density; there are different T scores, depending on which racial group of young adults is used as the reference. The Z score is the number of standard deviations below the average for a person of the same age. The WHO developed guidelines for use in the clinical diagnosis of osteoporosis, based on the T score, with a T score of < −1.0 being defined as osteopenic and a T score of < −2.5 being referred to as osteoporotic (Kanis, 1994). However, BMD testing alone is not optimal for the detection of individuals at high risk of fracture, since it has high specificity but low sensitivity. In other words, the risk of fracture is high when osteoporosis is present, but not necessarily low when BMD is normal. Indeed, the majority of osteoporotic fractures will occur in individuals with a negative test and, therefore, many agencies do not recommend BMD as a population screening tool (Kanis et al., 2013).

The quality of bone is determined by the microarchitecture, bone remodelling activity, mineralization, collagen properties, and presence of microdamage (Sroga and Vashishth, 2012). Histologically, osteoporosis is characterized by a reduced quantity of normally mineralized bone, which is also structurally abnormal. Typically, bone resorption by osteoclasts is increased and bone formation by osteoblasts is also increased, but to a lesser extent, resulting in a net loss of bone. This imbalance between osteoclast and osteoblast activity may vary between trabecular bone (also called cancellous) and cortical bone (also called compact bone). Trabecular bone is found in long bones such as the femur, in vertebrae, and in flat bones such as the pelvis, whilst cortical bone is much denser and forms the outer shell around trabecular bone—for example, the shaft of the femur

The recognition that abnormalities of serum calcium, phosphorus (P), PTH, and vitamin D metabolism in CKD have deleterious effects on both the skeleton and the vascular tree led to the KDIGO committee proposal that this constellation of problems should be referred to as 'chronic kidney disease-mineral and bone disorder' (CKD-MBD) (Moe et al., 2006; Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009). Clearly, CKD-MBD is associated with a variety of bone metabolism and hormonal disorders, which may variably influence trabecular or cortical bone, and could be predicted to significantly decrease bone quality and alter bone remodelling, but without necessarily reducing the BMD.

CKD and decreased bone strength

Metabolic and hormonal changes begin early in the course of CKD stage 3, so that PTH levels begin to rise once GFR falls below 60 mL/min. As CKD progresses, 25(OH)D and $1,25(OH)_2D$ levels tend to fall, while fibroblast growth factor 23 (FGF23) rises rapidly, followed later by a rise in serum P (Isakova et al., 2011), and development of acidosis and hypogonadism becomes increasingly apparent (Albaaj et al., 2006). These changes are likely to play varying roles in altering the bone remodelling process. Bone resorption may increase, bone formation may decrease, and mineralization can be impaired, with the result that microarchitecture deteriorates, with trabecular thinning or loss, cortical thinning, and increased porosity. Bone biopsies taken early in the course of CKD demonstrate evidence of early renal osteodystrophy in 75% of subjects, although routine biochemistry results and radiological examinations remain normal (Hamdy et al., 1995). By the time patients are about to commence dialysis, all have histological evidence of advanced osteodystrophy, yet in one study > 90% of them had normal range BMD measurements (Hutchison et al., 1993).

Therefore, in CKD there is likely to be a variable reduction in bone quality and strength, which may be further influenced by the time course of CKD progression, the underlying cause and the therapeutic interventions utilized. Evidence for this has been found in a study of 70 patients with CKD stages 2–4, over 50 years of age, utilizing high-resolution peripheral quantitative computed tomography (HR-pQCT) to examine bone microarchitecture at the tibia and radius, compared with results from healthy subjects matched for age and gender. CKD men and women were found to have moderate, but significant trabecular impairment and, in men only, reduced cortical thickness, demonstrating that impairment of trabecular microarchitecture can occur in the early stages of CKD (Bacchetta et al., 2010). Furthermore, measurement of BMD by both DXA and HR-pQCT correlates with fracture history in patients with CKD stages 3–5, although the sensitivity and specificity of the techniques varies depending on the part of the skeleton studied and whether trabecular or cortical bone is considered (Nickolas et al., 2010).

From a patient's perspective, fractures, bone pain, and tendon rupture are probably the most serious skeletal manifestations of renal osteodystrophy, yet methods of risk assessment and management remain uncertain. Attempts to correlate bone histology, PTH level, other biomarkers of bone turnover, and fracture risk have

not proved useful for individual patient management (Hutchison et al., 1993, 1994; Lehmann et al., 2008), and BMD measurements in advanced CKD are known to be less reliable than in the general population.

Prediction of fracture risk in chronic kidney disease and dialysis patients

It is generally accepted that the WHO criteria or the presence of low-trauma fractures can be used for the diagnosis of osteoporosis in patients with CKD stages 1–3 but without biochemical evidence of osteodystrophy, since many of the osteoporosis treatment trials unintentionally included such patients. No such consensus exists regarding patients with CKD stages 4–5D, where diagnosis and treatment is largely opinion based.

Whilst DXA BMD can retrospectively distinguish between CKD patients who have already suffered a fracture and those who have not, prospective prediction of risk in the CKD population overall is much more difficult. It is now clear that even in the non-CKD population measurement of BMD alone is not as useful a tool for predicting fracture as was once thought. So, whilst a T score of < -2.5 is predictive, denser bone does not necessarily mean that future fracture is unlikely.

Studies in postmenopausal women demonstrate that around 50% of all fractures occur in women with BMD T score values which are > -2.5 (Stone et al., 2003; Schuit et al., 2004). This is because the technique has relatively good specificity (63–82%), but low sensitivity (only 26% in some studies) (Nickolas et al., 2008). Furthermore, treatment of osteoporosis produces relatively modest increases in bone density of up to 7%, yet is associated with reduction in the fracture risk of up to 60% (Delmas and Seeman, 2004; Delmas et al., 2004). Treatment with sodium fluoride can produce substantial increases in DXA BMD, but without a corresponding reduction in risk of fracture (Vestergaard et al., 2008). Simple demographic and clinical factors, such as gender, age, weight, race, history of prior fracture, and corticosteroid use, are in themselves predictive of risk and are independent of BMD (Nickolas et al., 2008). It is easy to appreciate why fracture prediction based on BMD becomes even more unreliable in the CKD population, with the additional and highly variable overlay of renal osteodystrophy. DXA measurements can be low, normal, or elevated in the presence of histologically confirmed secondary hyperparathyroidism, mixed osteodystrophy, adynamic bone, or osteomalacia, and relevance to fracture risk is difficult to ascertain. FGF23 level is now known to be independently associated with risk of vertebral fracture, but how this association could be utilized is unclear.

Whereas in the general population low BMD at one site predicts risk of fracture at other sites, this is not the case in CKD patients with osteodystrophy, where low BMD at a particular site does not reliably predict fracture even at that site. This is probably related to the differential effect of hyperparathyroidism on different types of bone, tending to cause catabolism of cortical bone with subperiostial erosion, but tending to increase osteoblastic bone formation in other areas and increase trabecular thickness and number. Since resolution with DXA is inadequate to differentiate cortical and trabecular bone, it produces a composite measurement, which does not detect the predominant loss of cortical bone that typifies primary and secondary hyperparathyroidism.

Bone biopsy and histomorphometry to assess bone quality in chronic kidney disease

Double tetracycline-labelled trans-iliac bone biopsy is currently the only reliable method of visually and numerically assessing the microarchitecture of both cortical and trabecular bone in patients with CKD who also have renal osteodystrophy. Two doses of oral tetracycline are given to the patient with a 10-day gap between, and the biopsy is taken 4 days after the second dose. This produces a 5 or 7 mm diameter cylinder of full thickness iliac bone, comprising cortical bone at either end with trabecular bone between. Provided the operator separates the subcutaneous muscle layers and the trephine does not trap any muscle beneath it before it enters the bone, it is a relatively well tolerated procedure with minimal pain or bleeding afterwards. It can be performed as a day-case procedure under local anaesthesia and, in the authors' opinion, is less hazardous than a renal biopsy in terms of possible complications.

Intact biopsy samples can also be imaged by micro-CT scanning to create three-dimensional (3D) pictures of trabecular microarchitecture and used to estimate mechanical strength. Once the bone sample has been processed, it can be viewed by a variety of techniques, including light microscopy, where the two bands of tetracycline will fluoresce in ultraviolet light and the distance between them can be measured, then divided by 10 to give measurements of daily mineralization rate. Image analysis software can be used to analyse much of the biopsy, but only in the hands of an experienced osteopathologist. The analysis produces a wealth of descriptive and numerical data which has to be understood and interpreted by a nephrologist with a special interest in osteodystrophy to give it a clinical meaning and relevance. For these reasons and also because of its perceived invasiveness, bone biopsy in CKD patients is not undertaken routinely and is only available in a few renal centres around the world. Consequently, there remains great interest in developing non-invasive imaging techniques that can provide clinically useful data.

Imaging techniques other than DXA in chronic kidney disease patients

DXA is only able to assess BMD in a two-dimensional areal fashion and has poor spatial resolution; referred to as areal BMD or aBMD. Quantitative computed tomography (QCT) scanning produces a volumetric measurement referred to as vBMD, and has higher resolution of around 300 μm, so can distinguish cortical from trabecular bone in some sites. It utilizes a standard whole-body CT scanner and results correlate well with trabecular bone volume measured by histomorphometry on bone biopsy samples (Torres et al., 1986), but is still not able to predict type of osteodystrophy (Hutchison et al., 1993; Cueto-Manzano et al., 1999) or bone strength. Unlike DXA, QCT provides real bone density per bone volume (mg/mm^3) but subjects the patient to relatively high radiation exposure of 1–3 mSv.

HR-pQCT works on the same principles as conventional QCT but with a resolution of 82 μm. This enables it to provide details of trabecular microarchitecture that correlate with bone strength such as trabecular number, thickness, and separation. Like standard QCT it offers the possibility of analysing cortical and trabecular

bone separately, and is usually performed on a smaller scanner specifically developed for the quantitative determination of BMD in the forearm and tibia. They are less expensive and more mobile than whole-body scanners and the patient receives a radiation dose of only around 0.01 mSv, none of which is directed through critical radiosensitive organs. However, HR-pQCT cannot image proximal femur or spine.

Micro-magnetic resonance imaging (MRI) using 3 T and even 7 T MR scanners can produce 3D images of trabecular bone architecture which can then be analysed in a similar way to a bone biopsy. Micro-MRI techniques are at present in their infancy but the absence of radiation dose makes this an attractive technique for the future.

Falls prevention in chronic kidney disease

Strategies to prevent fractures in patients with CKD comprise prevention of falls, pharmacological treatments for CKD-MBD, and pharmacological treatments for osteoporosis where present.

Muscular weakness and neuropathy are common in patients with all stages of CKD but vary in severity according to the underlying cause (West et al., 2012). These problems may be specifically associated with diabetes, in which case the patient may also have decreased vision and autonomic neuropathy leading to postural hypotension, plus the possibility of hypoglycaemic episodes. Postural hypotension is not uncommon in any patient taking diuretics or antihypertensive agents, which would likely include most patients with CKD stages 4, 5, and most dialysis patients. Active involvement of physiotherapists in such patients' care may be beneficial, and a Cochrane review has shown that group and home-based exercise programmes, and home safety interventions reduce rate of falls but not risk of falling (Gillespie et al., 2012). Interestingly t'ai chi exercise does reduce risk of falling. This review also highlighted the fact that in the general population vitamin D supplementation does not reduce falls but may be effective in people who have lower vitamin D levels before treatment.

Pharmacological treatment of renal osteodystrophy

Pharmacological treatments that can normalize 25-hydroxyvitamin D_3 levels might well be beneficial to bone strength, and native vitamin D replacement is becoming more widespread. However, evidence for the efficacy of this approach has yet to be produced, although it is well established that vitamin D analogues can reduce serum PTH levels. Controlling elevated PTH levels, which may lead to proximal myopathy as well as cortical bone loss, might be expected to reduce risk of fracture and falls, and such management is described in Chapter 118.

A combined post hoc analysis of safety data (parathyroidectomy, fracture, hospitalizations, and mortality) from four similarly designed randomized, double-blind, placebo-controlled clinical trials enrolling 1184 subjects (697 of whom were treated with cinacalcet, plus 487 control subjects) with end-stage kidney disease and uncontrolled secondary hyperparathyroidism suggested that randomization to cinacalcet resulted in a significant reduction in the risk of fracture (Cunningham et al., 2005). However, the prospective randomized controlled EVOLVE study of cinacalcet treatment failed to demonstrate such benefits (The EVOLVE Trial investigators 2012). The association of FGF23 with fracture risk is a relatively recent discovery, and its clinical significance is completely unclear (Kanda et al., 2012).

Pharmacological treatment of osteoporosis in CKD

Treatment with pharmacological agents known to be effective for osteoporosis in the general population depends on being able to establish a diagnosis in the patient with CKD. Since DXA BMD measurements are unreliable in CKD 4, 5, and dialysis patients, and fractures in such patients may be secondary to osteodystrophy rather than osteoporosis, establishing a diagnosis without resorting to bone biopsy is difficult. Yet it is in these patients specifically that the mortality rate associated with fractures is exceptionally high. The available literature on the use of pharmacological agents in patients with CKD is mostly culled from large population-based studies that have incorporated subjects subsequently shown to have mild to moderate CKD. There is very little literature to guide the clinician in use of such agents in CKD 5 and 5D.

Oral bisphosphonates are widely prescribed in the general population and appear to be effective and safe in CKD 1–3. Retrospective analyses suggest they are also safe in CKD stage 4, although IV administration can be nephrotoxic if given too quickly, or to patients who are not adequately hydrated, and particularly in the presence of other nephrotoxins such as radio-contrast media. Less than 1% of an oral bisphosphonate dose is absorbed but up to 60% of the drug available in the blood is bound rapidly to bone hydroxyapatite, impairing osteoclast cell function by inhibiting enzyme activity. The remainder is excreted unchanged via glomerular filtration and active proximal tubular secretion, so that it is usual to reduce the dose by 50% in patients with CKD 4, 5, or 5D. Bisphosphonates accumulate in bone with a half-life of > 10 years. Little is known about removal by dialysis, which has not been well studied. Hypocalcaemia has been reported following bisphosphonate administration to patients with vitamin D deficiency which is of course common in CKD.

In CKD 5, bisphosphonates should only be given where the risk of mortality from further fractures is considered to be very high and low turnover states have been excluded. This is difficult without bone histology, but low turnover is likely in patients with serum PTH levels of less than twice the assay's upper normal limit. It is unknown whether administration of bisphosphonates to patients with low bone turnover would be harmful or beneficial, but since there is a long established link between low turnover and vascular calcification, the consequences might not be only skeletal.

Oestrogen deficiency increases bone resorption by osteoclasts, and replacement therapy in postmenopausal women increases bone mass and risk of fracture. In the dialysis population, oestrogen deficiency and amenorrhoea is common even in premenopausal women. Replacement therapy has been shown to be effective in stabilizing or even increasing BMD in such women on dialysis but is rarely prescribed—possibly as a result of concerns around risks of breast cancer and vascular disease.

Raloxifene is a selective oestrogen receptor modulator or SERM licensed for prevention and treatment of osteoporosis in the general population. In a 12-month study of raloxifene use in 25 postmenopausal haemodialysis patients, treatment was associated with significant improvements in lumbar spine BMD compared to placebo, and no evidence of increased risk of venous thrombosis or dialysis access thrombosis was seen (Hernandez et al., 2003). BMD at other sites did not change, but as explained above, BMD measurements are unreliable in this population. Subsequent similar small studies have confirmed

these findings but the significance is unclear (Ishani et al., 2008; Tanaka et al., 2011).

Teriparatide is a 34-amino acid fragment of human PTH which has anabolic properties similar to the intact molecule. It is effective in increasing BMD in patients with CKD 1–3 and normal PTH levels. It is contraindicated in patients with secondary hyperparathyroidism where it would only add to the problem. One might expect it to be beneficial to turnover in patients with adynamic bone, and a report of just seven such patients suggested a beneficial effect, but its use remains controversial with no randomized trials in CKD 5 (Cejka et al., 2010; Cejka and Haas, 2011).

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor kappa B ligand (RANKL). It blocks the binding of RANKL to RANK and thereby decreases osteoclast activity and bone resorption, resulting in an increase in BMD. It does not depend on renal clearance for metabolism or clearance and is given as a single subcutaneous dose every 6 months (Block et al., 2012). The 36-month Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial enrolled 7808 women, some of whom had CKD 3 and 4, and randomized them to denosumab or placebo (Jamal et al., 2011). The CKD patients were analysed post hoc and found to have the same benefit in terms of fracture risk reduction and increase in BMD as the non CKD subjects, although the benefit was not statistically significant in CKD 4 patients, possibly because they were few in number (N = 73). Hyperparathyroidism, hypocalcaemia, and vitamin D deficiency were all exclusion criteria in this study.

All antiresorptive agents can reduce serum calcium significantly, particularly in advanced CKD and therefore attention should be paid to ensuring that patients are calcium and vitamin D replete prior to start of therapy.

Non-pharmacological treatments

Progressive load-bearing exercise is known to have osteogenic effects on the adult skeleton, and even moderate intensity walking may have beneficial effects on osteoporotic bone. Unfortunately such exercise effects have not been examined in CKD specifically, but there is a direct correlation between muscle strength and BMD, and muscle strength in dialysis patients is known to improve with strength training.

Dietary restrictions in CKD 4 and 5 may play a role in loss of bone mass. In a study of the use of low-protein diets and strict P reduction in pre-dialysis patients, around 50% developed at least moderate osteoporosis over the 5 years of follow-up. Whether this related to inadequate P intake or some other iatrogenic dietary deficiency is not clear. Supplementary calcium and vitamin D in patients with severe kidney impairment is increasingly frowned upon given the association with increased vascular calcification and cardiovascular disease (2009), but clearly a careful dietary assessment is important to ensure that intake of all essential nutrients is adequate.

References

Albaaj, F., Sivalingham, M., Haynes, P., *et al.* (2006). Prevalence of hypogonadism in male patients with renal failure. *Postgrad Med J*, 82(972), 693–6.

Alem, A. M., Sherrard, D. J., Gillen, D. L., *et al.* (2000). Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int*, 58(1), 396–9.

Bacchetta, J., Boutroy, S., Vilayphiou, N., *et al.* (2010). Early impairment of trabecular microarchitecture assessed with HR-pQCT in patients with stage II-IV chronic kidney disease. *J Bone Miner Res*, 25(4), 849–57.

Block, G. A., Bone, H. G., Fang, L., *et al.* (2012). A single-dose study of denosumab in patients with various degrees of renal impairment. *J Bone Miner Res*, 27(7), 1471–9.

Cejka, D. and Haas, M. (2011). Should teriparatide ever be used for adynamic bone disease? *Semin Dial*, 24(4), 431–3.

Cejka, D., Kodras, K., Bader, T., *et al.* (2010). Treatment of hemodialysis-associated adynamic bone disease with teriparatide (PTH1-34): a pilot study. *Kidney Blood Press Res*, 33(3), 221–6.

Coco, M. and Rush, H. (2000). Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *Am J Kidney Dis*, 36(6), 1115–21.

Cueto-Manzano, A. M., Konel, S., Crowley, V., *et al.* (2003). Bone histopathology and densitometry comparison between cyclosporine a monotherapy and prednisolone plus azathioprine dual immunosuppression in renal transplant patients. *Transplantation*, 75(12), 2053–8.

Cueto-Manzano, A. M., Konel, S., Hutchison, A. J., *et al.* (1999). Bone loss in long-term renal transplantation: histopathology and densitometry analysis. *Kidney Int*, 55(5), 2021–9.

Cummings, S. R., Black, D. M., Nevitt, M. C., *et al.* (1990). Appendicular bone density and age predict hip fracture in women. The Study of Osteoporotic Fractures Research Group. *JAMA*, 263(5), 665–8.

Cunningham, J., Danese, M., Olson, K., *et al.* (2005). Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. *Kidney Int*, 68(4), 1793–800.

Currie, C., Partridge, M., Plant, F., *et al.* (2012). *The National Hip Fracture Database National Report 2012*. London: British Geriatrics Society.

Delmas, P. D., Li, Z., and Cooper, C. (2004). Relationship between changes in bone mineral density and fracture risk reduction with antiresorptive drugs: some issues with meta-analyses. *J Bone Miner Res*, 19(2), 330–7.

Delmas, P. D. and Seeman, E. (2004). Changes in bone mineral density explain little of the reduction in vertebral or nonvertebral fracture risk with anti-resorptive therapy. *Bone*, 34(4), 599–604.

Dooley, A. C., Weiss, N. S., and Kestenbaum, B. (2008). Increased risk of hip fracture among men with CKD. *Am J Kidney Dis*, 51(1), 38–44.

Ensrud, K. E., Lui, L. Y., Taylor, B. C., *et al.* (2007). Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med*, 167(2), 133–9.

European Commission and Eurostat (2011). *Demography Report 2010. Older, more numerous and diverse Europeans*. Luxembourg: Publications Office of the European Union.

Fontaine, M. A., Albert, A., Dubois, B., *et al.* (2000). Fracture and bone mineral density in hemodialysis patients. *Clin Nephrol*, 54(3), 218–26.

Gillespie, L. D., Robertson, M. C., Gillespie, W. J., *et al.* (2012). Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev*, 9, CD007146.

Hamdy, N. A., Kanis, J. A., Beneton, M.N., *et al.* (1995). Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. *BMJ*, 310(6976), 358–63.

Hernandez, E., Valera, R., Alonzo, E., *et al.* (2003). Effects of raloxifene on bone metabolism and serum lipids in postmenopausal women on chronic hemodialysis. *Kidney Int*, 63(6), 2269–74.

Hutchison, A. J., Whitehouse, R. W., Boulton, H. F., *et al.* (1993). Correlation of bone histology with parathyroid hormone, vitamin D3, and radiology in end-stage renal disease. *Kidney Int*, 44(5), 1071–7.

Hutchison, A. J., Whitehouse, R. W., Freemont, A. J., *et al.* (1994). Histological, radiological, and biochemical features of the adynamic bone lesion in continuous ambulatory peritoneal dialysis patients. *Am J Nephrol*, 14(1), 19–29.

Isakova, T., Wahl, P., Vargas, G. S., *et al.* (2011). Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int*, 79(12), 1370–8.

Ishani, A., Blackwell, T., Jamal, S. A., *et al.* (2008). The effect of raloxifene treatment in postmenopausal women with CKD. *J Am Soc Nephrol*, 19(7), 1430–8.

Jadoul, M., Albert, J. M., Akiba, T., *et al.* (2006). Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Kidney Int*, 70(7), 1358–66.

Jamal, S. A., Ljunggren, O., Stehman-Breen, C., *et al.* (2011). Effects of denosumab on fracture and bone mineral density by level of kidney function. *J Bone Miner Res*, 26(8), 1829–35.

Jamal, S. A., West, S. L., and Miller, P. D. (2012). Fracture risk assessment in patients with chronic kidney disease. *Osteoporos Int*, 23(4), 1191–8.

Jassal, S. K., von Muhlen D., and Barrett-Connor, E. (2007). Measures of renal function, BMD, bone loss, and osteoporotic fracture in older adults: the Rancho Bernardo study. *J Bone Miner Res*, 22(2), 203–10.

Kanda, E., Yoshida, M., and Sasaki, S. (2012). Applicability of fibroblast growth factor 23 for evaluation of risk of vertebral fracture and chronic kidney disease-mineral bone disease in elderly chronic kidney disease patients. *BMC Nephrol*, 13(1), 122.

Kanis, J. A. (1994). Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporos Int*, 4(6), 368–81.

Kanis, J. A., McCloskey, E. V., Johansson, H., *et al.* (2013). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporosis Int*, 24(1), 23–57.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009). KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*, 113, S1–30.

Kinsella, S., Chavrimootoo, S., Molloy, M. G., *et al.* (2010). Moderate chronic kidney disease in women is associated with fracture occurrence independently of osteoporosis. *Nephron Clin Pract*, 116(3), c256–c262.

LaCroix, A. Z., Lee, J. S., Wu, L., *et al.* (2008). Cystatin-C, renal function, and incidence of hip fracture in postmenopausal women. *J Am Geriatr Soc*, 56(8), 1434–41.

Lehmann, G., Ott, U., Kaemmerer, D., *et al.* (2008). Bone histomorphometry and biochemical markers of bone turnover in patients with chronic kidney disease stages 3–5. *Clin Nephrol*, 70(4), 296–305.

Moe, S., Drueke, T., Cunningham, J., *et al.* (2006). Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*, 69(11), 1945–53.

Nam, H. S., Shin, M. H., Zmuda, J. M., *et al.* (2010). Race/ethnic differences in bone mineral densities in older men. *Osteoporos Int*, 21(12), 2115–23.

Nickolas, T. L., Leonard, M. B., and Shane, E. (2008). Chronic kidney disease and bone fracture: a growing concern. *Kidney Int*, 74(6), 721–31.

Nickolas, T. L., McMahon, D. J., and Shane, E. (2006). Relationship between moderate to severe kidney disease and hip fracture in the United States. *J Am Soc Nephrol*, 17(11), 3223–32.

Nickolas, T. L., Stein, E., Cohen, A., *et al.* (2010). Bone mass and microarchitecture in CKD patients with fracture. *J Am Soc Nephrol*, 21(8), 1371–80.

Schuit, S. C., van der Klift, M., Weel, A. E., *et al.* (2004). Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. *Bone*, 34(1), 195–202.

Sroga, G. E. and Vashishth, D. (2012). Effects of bone matrix proteins on fracture and fragility in osteoporosis. *Curr Osteoporos Rep*, 10(2), 141–50.

Stehman-Breen, C. O., Sherrard, D. J., Alem, A. M., *et al.* (2000). Risk factors for hip fracture among patients with end-stage renal disease. *Kidney Int*, 58(5), 2200–5.

Stevens, P. E., O'Donoghue, D. J., de Lusignan, S., *et al.* (2007). Chronic kidney disease management in the United Kingdom: NEOERICA project results. *Kidney Int*, 72(1), 92–9.

Stone, K. L., Seeley, D. G., Lui, L. Y., *et al.* (2003). BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. *J Bone Miner Res*, 18(11), 1947–54.

Strom, O., Borgstrom, F., Kanis, J. A., *et al.* (2011). Osteoporosis: burden, health care provision and opportunities in the EU: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos*, 6(1–2), 59–155.

Tanaka, M., Itoh, K., Matsushita, K., *et al.* (2011). Effects of raloxifene on bone mineral metabolism in postmenopausal Japanese women on hemodialysis. *Ther Apher Dial*, 15 Suppl 1, 62–6.

The EVOLVE Trial investigators (2012). Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med*, 367(26), 2482–94.

Torres, A., Lorenzo, V., and Gonzalez-Posada, J. M. (1986). Comparison of histomorphometry and computerized tomography of the spine in quantitating trabecular bone in renal osteodystrophy. *Nephron*, 44(4), 282–7.

Vestergaard, P., Jorgensen, N. R., Schwarz, P., *et al.* (2008). Effects of treatment with fluoride on bone mineral density and fracture risk—a meta-analysis. *Osteoporos Int*, 19(3), 257–68.

West, S. L., Jamal, S. A., and Lok, C. E. (2012). Tests of neuromuscular function are associated with fractures in patients with chronic kidney disease. *Nephrol Dial Transplant*, 27(6), 2384–88.

Yang, Y. X., Lewis, J. D., Epstein, S., *et al.* (2006). Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA*, 296(24), 2947–53.

Yenchek, R. H., Ix, J. H., Shlipak, M. G., *et al.* (2012). Bone mineral density and fracture risk in older individuals with CKD. *Clin J Am Soc Nephrol*, 7(7), 1130–6.

CHAPTER 122

Spectrum of bone pathologies in chronic kidney disease

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Bone biopsy and histomorphometry in chronic kidney disease-mineral and bone disorder

Bone abnormalities are common complications of CKD. They start in patients with CKD stage 2 and are found in almost all patients, as they reach end-stage kidney disease (Malluche et al., 1976a). The Kidney Disease: Improving Global Outcomes (KDIGO) recommendations are that bone disease should be defined on the basis of bone histomorphometry, obtained by examination of bone biopsy (Moe et al., 2006). Bone biopsy is a standardized procedure of harvesting trabecular bone from the iliac crest or, less commonly, from a long bone (Dempster et al., 2013). The technique involves administration of tetracycline or a tetracycline derivative approximately 3–4 weeks prior to the biopsy and then a different tetracycline derivative 3–5 days prior to the biopsy. The biopsy procedure itself consists of removing a core of predominately trabecular bone and is followed by histologic processing, without the use of decalcification. This entails fixation of bone in 70–100% ethanol, which is then replaced stepwise by acetone and then methacrylate monomer dissolved in acetone. The methacrylate, which has now infiltrated the bone biopsy, is induced to polymerize, so that the bone becomes embedded in a hardened polyethacrylate block. Sections of 4–8 microns are cut from this block with a heavy duty microtome, mounted on glass slides and stained for microscopic evaluation. This process is a highly specialized technique and performed in relatively few laboratories. It allows differentiation of mineralized from unmineralized bone by light microscopy with standard stains, such as haematoxylin and eosin or Goldner's trichrome, which cannot be done with decalcified bone, which is much easier to process. The tetracyclines administered before biopsy also act as stains, since they are incorporated into the hydroxyapatite matrix as it is laid down, where they show their presence by emitting light of a specific wavelength when illuminated by light at a different wavelength (fluorescence). Under a fluorescence microscope, the tetracycline stains identify newly mineralized bone as lines of varying thickness at the bone–osteoid interface. Dividing the distance between the two tetracycline-labelled lines by the time interval between their administration yields the rate of bone apposition, an important dynamic measure of bone metabolism and turnover. This measurement, when combined with quantitative light microscopic measurements of bone structures (histomorphometry) is particularly important in diagnosing different types of renal osteodystrophy. The nomenclature for these two types of measurement, static and dynamic, has been standardized (Dempster et al., 2013).

Clinically, bone biopsies are most useful for diagnosing diseases of bone turnover, as well as other metabolic disorders. However, with the advent of several new markers of bone turnover, bone biopsy has recently been reserved primarily for the diagnosis of renal osteodystrophy and for research purposes. For the past 20–30 years, the classification of renal osteodystrophy has utilized fractional osteoid (unmineralized bone) volume and fibrosis with bone formation rate or activation frequency to distinguish different forms of renal osteodystrophy (Sherrard et al., 1993; Malluche and Monier-Faugere, 1994). Based upon these parameters, diagnostic nomenclature of renal osteodystrophy includes normal bone, osteitis fibrosa cystica, adynamic bone, osteomalacia, and mixed uraemic osteodystrophy.

Normal bone is characterized by osteoblasts and scant osteoid lining trabeculae, along with scattered osteoclasts (Fig. 122.1A). High-turnover disease (predominant hyperparathyroidism or osteitis fibrosa cystica) shows simultaneously increased rates of bone formation and resorption, extensive osteoclastic and osteoblastic activity, and a progressive increase in endosteal peritrabecular marrow space fibrosis (Fig. 122.1B). High osteoblast activity is manifested by an increase in unmineralized bone matrix. The number of osteoclasts and the total resorption surface are also increased in osteitis fibrosa cystica. There may be numerous dissecting cavities through which the osteoclasts tunnel into individual trabeculae. In osteitis fibrosa cystica, collagen fibrils in the bone matrix are arranged in an irregular woven pattern in contrast to their parallel (lamellar) alignment in normal bone. Although woven bone has thicker trabeculae than normal bone, it is actually less strong, due to the non-parallel, disorderly arrangement of collagen fibrils.

The histologic features of low-turnover (adynamic) bone disease (Fig. 122.1C) are absence of cellular (osteoblast and osteoclast) activity, as shown by lack of osteoblast or osteoclast proliferation, osteoid formation , and endosteal fibrosis. New bone ceases to form or mineralize. Although low-turnover disease is common in the absence of aluminium, it was initially described as a result of aluminium toxicity. Special histochemical stains, such as aurintricarboxylic acid, demonstrate aluminium deposits at the mineralization front (Fig. 122.1D) (Ott et al., 1982). Frequently, aluminium

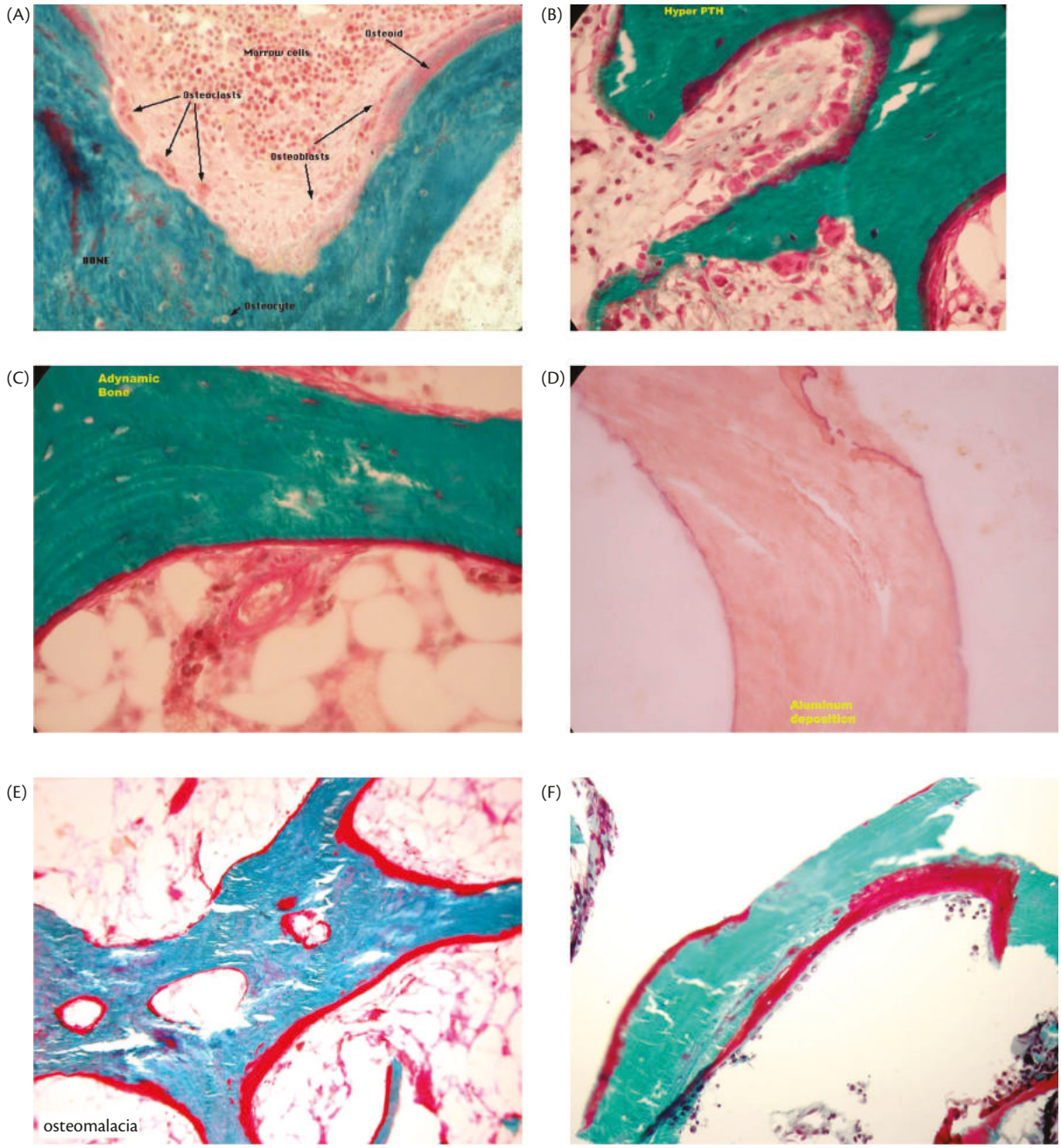


Fig. 122.1 Spectrum of bone histology. Bone biopsies obtained after double tetracycline labelling. (Magnification 20×.)
(A) Normal bone. (B) Osteitis fibrosis cystica. (C) Adynamic bone. (D) Aluminium bone disease. (E) Osteomalacia.
(F) Mixed uraemic bone disease

bone disease is associated with osteomalacia, which is characterized by wide osteoid seams, a markedly decreased mineralization rate, absence of cell activity, and endosteal fibrosis (Fig. 122.1E). However, the presence of increased osteoid per se does not necessarily indicate a mineralization defect, because increased osteoid can also appear when mineralization lags behind increased bone matrix synthesis.

Mixed uraemic osteodystrophy describes bone biopsies with features of secondary hyperparathyroidism and mineralization defect simultaneously (Fig. 122.1F). It involves variably increased osteoclastic and osteoblastic activity, endosteal peritrabecular fibrosis, and osteoid deposition, but with decreased tetracycline labelling, the latter being indicative of defective mineralization. Unfortunately, mixed uraemic osteodystrophy in particular, as well as high- and low-turnover bone disease, has been inconsistently and poorly defined.

The spectrum of bone histomorphometry in chronic kidney disease

Utilizing the classification system just described, the prevalence of different forms of renal osteodystrophy has changed

over the past decade (Table 122.1). Whereas osteitis fibrosa cystica due to severe hyperparathyroidism had previously been the predominant lesion, the prevalence of mixed uraemic osteodystrophy and adynamic bone disease has recently increased. However, the overall percentage of patients with high bone turnover, compared to low bone turnover, has not changed dramatically over the last 20–30 years, although adynamic bone disease has essentially replaced osteomalacia in the latter category. Differences in mixed uraemic osteodystrophy are seen in patients not yet on dialysis; the series of bone biopsies yield widely different results, depending on the level of glomerular filtration rate, and the country in which the study was done (Gal-Moscovici and Sprague, 2008). However, it is clear from these data that histologic abnormalities of bone begin very early in the course of CKD. Also of importance is that histologic changes due to secondary hyperparathyroidism remain common.

In contrast, low-turnover bone disease has diverse pathophysiology. Aluminium was initially recognized as a neurotoxin (Alfrey, 1978), however, in the 1980s, aluminium-induced osteomalacia was common, resulting in fractures, as well as myopathy and microcytic anaemia (Alfrey, 1993). The source of aluminium in these severe cases was felt to be elevated concentrations in dialysate water. Subsequently, aluminium-containing phosphate (P) binders were also identified as a source (Goodman, 1985; Salusky et al., 1991). Fortunately, exposure to aluminium is greatly limited and the incidence of aluminium bone disease is relatively rare. However, the diagnosis of aluminium-induced bone disease can be difficult, as aluminium toxicity is due to tissue burden, not serum levels. Thus, if aluminium bone disease is suspected, bone biopsy remains the gold standard to make the diagnosis (National Kidney Foundation, 2003; Jorgetti, 2009).

In the past 15–20 years, as aluminium has been removed as a cause of low bone turnover, a new entity, called adynamic bone disease, has been described (Andress, 2008). In adynamic bone disease (Fig. 122.1C), there is a paucity of cells, with resultant low bone turnover. In contrast to osteomalacia, in adynamic bone there is no increase in osteoid or unmineralized bone. The lack of bone cell activity led to the initial description of the disease as 'aplastic' bone disease. Early studies suggested that the disease was still due to aluminium, but it was later identified in the absence of positive staining for aluminium. The aetiology of adynamic bone disease is unknown, but major contributory factors are diabetes, ageing, and malnutrition (Andress, 2008). Pathophysiological mechanisms of low bone turnover include vitamin D deficiency, high serum P, metabolic acidosis, elevated circulating levels of cytokines like interleukin-1 and tumour necrosis factor, low oestrogen and testosterone levels, resistance to parathyroid hormone (PTH), and, possibly, elevated fibroblast growth factor 23 levels. PTH receptor downregulation is one potential mechanism to explain the bone resistance to PTH, due in part to persistently elevated PTH (PTH downregulates its own receptor) and to low $1,25(OH)_2D$ levels (Massry et al., 1976). Other potential mechanisms of low bone formation include decreased osteoblast proliferation from the direct effect of accumulated uraemic inhibitors, and decreased circulating insulin-like growth factor 1 activity (Andress, 2008). Circulating fragments of PTH (so-called 7–84 amino acid fragments) may also be antagonists to PTH (Slatopolsky et al., 2000), resulting in an effective resistance to 1–84 amino acid PTH at the level of bone. There is also abnormal regulation of cell differentiation in the presence of renal failure, which may explain, in part, the relative paucity of cells in adynamic bone, although this remains to be proven. The pathophysiology of altered bone cell responsiveness is multifactorial. While most patients with low-turnover bone disease are asymptomatic, they are at increased risk of fracture, due to impaired remodelling (Coco and Rush, 2000; Ott et al., 2009), and are at risk of vascular calcification, due to

Table 122.1 Bone biopsies results in predialysis patients[a]

Reference	N	OFC (%)	MHPTH (%)	OM (%)	MUO (%)	ABD (%)	Normal (%)
Ballanti et al., 2001	27	8		11	55	26	
Coen et al., 1996	76	27		9	40	11	13
Dahl et al., 1988	60	80		2			18
Eastwood, 1982	38	87		45[b]			10
Hamdy et al., 1995	176	73		0.5	21	5.5	
Hernandez et al., 1994	92	59	26	15			
Hutchison et al., 1993	39	28	23	8	13	28	
Lehmann et al., 2008	36	47				53	
Mora Palma et al., 1983	327	54		34			12
Shin et al., 1999	58	9	36	10	12	24	9
Spasovski et al., 2003	84	9		12	18	23	38
Torres et al., 1995	38	30	10	2	10	48	

[a]ABD = adynamic bone disease; MHPTH = mild hyperparathyroidism; MUO = mixed uremic osteodystrophy; OFC = osteitis fibrosa cystica; OM = osteomalacia; SHPTH = severe hyperparathyroidism.

[b]Percentage of patients with SHPTH who also had OM.

the inability of bone to buffer an acute calcium (Ca) load (Kurz et al., 1994).

New classification of bone disease in chronic kidney disease

As previously mentioned, the recommendations of KDIGO are that the definition of renal osteodystrophy be limited to describing the alterations of bone morphology in patients with CKD and is one measure of the skeletal component of the systemic disorder of chronic kidney disease-mineral and bone disorder (CKD-MBD) (Box 122.1) that can be quantifiable by histomorphometry (Moe et al., 2006). Historically, renal osteodystrophy has been defined, as detailed above, as a spectrum of disorders ranging from low-turnover (adynamic bone) to high-turnover disease (osteitis fibrosa), including a poorly defined entity termed mixed uraemic osteodystrophy, which combined various degrees of bone turnover with a defect in mineralization (Sherrard et al., 1993). Unfortunately, mixed uraemic osteodystrophy has been defined differently by different investigators. As our understanding of bone biology progresses, there is increased appreciation of diverse physiologic processes leading to similar bone biopsy findings. In addition, there has been new information on bone volume, as an independent parameter (Barreto et al., 2006). Thus, the previous classification system has been updated.

In order to clarify the interpretation of bone biopsy results in the evaluation of renal osteodystrophy, KDIGO decided to use three key histologic descriptors—turnover, mineralization, and volume (TMV system)—with any combination of types of each of the descriptors being possible in a given specimen, to describe bone disease (Moe et al., 2006) (Box 122.1). The TMV classification (Table 122.2) provides a clinically relevant description of the underlying bone pathology, as assessed by histomorphometry, which in turn helps define the pathophysiology, and thereby guide therapy.

Box 122.1 Kidney Disease Improving Global Outcomes (KDIGO) classification of CKD-MBD and renal osteodystrophy

Definition of CKD-MBD

A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Vascular or other soft tissue calcification.

Definition of renal osteodystrophy

- Renal osteodystrophy is an alteration of bone morphology in patients with CKD.
- It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy.

From Moe, S., Drueke, T., Cunningham, J., *et al.* (2006). Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 69(11), 1945–53.

Table 122.2 TMV classification system for renal osteodystrophy

Turnover	Mineralization	Volume
Low	Normal Abnormal	Low
Normal		Normal
High		High

From Moe, S., Drueke, T., Cunningham, J., *et al.* (2006). Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*, 69(11), 1945–53.

Turnover reflects the rate of skeletal remodelling, which is normally the coupled process of bone resorption and bone formation. It is assessed by obtaining dynamic measurements of osteoblast function, using double-tetracycline labelling. Either the bone formation rate or the activation frequency represents acceptable parameters for assessing bone turnover. Bone turnover is affected mainly by hormones, cytokines, mechanical stimuli, and growth factors that influence the recruitment, differentiation, and activity of osteoclasts and osteoblasts. Clinically, disorders in bone turnover are associated with disturbed mineral homeostasis (Kurz et al., 1994; Hruska et al., 2007) and increased fracture risk (Coco and Rush, 2000).

Mineralization reflects how well bone collagen becomes calcified during the formation phase of skeletal remodelling. It is assessed by static measurements of osteoid volume and osteoid thickness and by dynamic, tetracycline-based measurements of mineralization lag time, and osteoid maturation time. Causes of impaired mineralization include inadequate vitamin D nutrition, mineral (Ca or P) deficiency, acidosis, or aluminium toxicity. Clinically, defective mineralization may result in bone pain and/or fracture (Goldstein et al., 1980).

Bone volume represents the amount of bone per unit volume of tissue area. It is assessed as static measurements of bone volume in cancellous bone. Determinants of bone volume include age, gender, race, genetic factors, nutrition, endocrine disorders, mechanical stimuli, toxicities, neurological function, vascular supply, growth factors, and cytokines. Clinically, changes in bone volume would indicate changes in bone balance, which result in either osteoporosis or osteosclerosis (Malluche et al., 1976b).

In dialysis patients, low bone volume and low bone turnover are more frequent than heretofore appreciated, whereas defective mineralization is relatively rare. Malluche et al. (2011) evaluated bone biopsies of 630 dialysis patients by the TMV system. They found racial differences: white patients exhibited predominantly low turnover (62%), whereas black patients showed mostly normal or high turnover (68%). A mineralization defect was observed in only 3% of patients. In white patients, cancellous bone volume was low, normal, or high in approximately the same number of patients, whereas in black patients, cancellous bone volume was high in two-thirds of the patients. A subsequent study demonstrated that low-turnover bone had microstructural abnormalities, such as lower cancellous bone volume and reduced trabecular thickness,

whereas high-turnover bone had material and nano-mechanical abnormalities, such as reduced mineral-to-matrix ratio and lower stiffness (Malluche et al., 2012). These data suggest that turnover-related alterations in bone quality may contribute to the diminished mechanical competence of bone in CKD.

Bone pathology following renal transplantation

Bone fractures occur in up to 44% of successful renal transplant recipients (Sprague and Josephson, 2004). There are limited studies evaluating bone histology in these patients. The main alteration is an uncoupling of bone remodelling, resulting in a decrease of bone formation with persistent bone resorption, resulting in net bone loss. In a small cohort of young patients transplanted prior to the initiation of dialysis and treated predominantly with corticosteroids, bone biopsies revealed a mineralization defect as early as 6 months post transplantation (Julian et al., 1991). Another study showed that both bone formation and mineralization were reduced following transplantation. Bone resorption that was above the normal range before transplantation remained increased at 35 days after transplantation, whereas osteoid and osteoblast surfaces, which were also increased before transplantation, decreased significantly thereafter (Rojas et al., 2003). An important observation was that, although none of the pretransplant biopsy specimens showed evidence of apoptosis, 45% of post-transplant biopsy specimens showed significant apoptosis after only an average of 35 days. Thus, the development of apoptosis and a decrease in osteoblast number and osteoblast surface play a contributory role in the pathogenesis of post-transplant bone disease, which may be related directly to the use of glucocorticoids (Rojas et al., 2003). The long-term effect of renal transplantation on bone histology most often results in adynamic bone disease (Monier-Faugere et al., 2000; Lehmann et al., 2007); however, the evaluation of bone biopsies approximately 4 years post transplant may show any of the seven histologic aspects: normal bone, osteitis fibrosa cystica, mild hyperparathyroidism, mixed uraemic bone disease, osteomalacia, adynamic bone disease, or osteoporosis.

The effect of other immunosuppressive agents on bone histology has also been examined. Bone biopsies performed approximately 10 years after renal transplantation in patients whose treatment included ciclosporin monotherapy, azathioprine plus prednisone, or triple therapy revealed no differences related to immunosuppressant regimens (Cueto-Manzano et al., 1999, 2003). A subgroup analysis of 21 patients with normal PTH levels showed that ciclosporin monotherapy was associated with a more pronounced decrease in bone thickness, compared with the other regimens (Cueto-Manzano et al., 1999). In the multivariate analysis, male gender, time after transplantation, old age, and time on dialysis prior to transplantation were significant predictive factors for a negative effect on bone mass.

Treatment options for renal osteodystrophy

The mainstay of therapy for renal osteodystrophy should be aimed towards prevention. Thus, early detection of disorders in mineral metabolism is essential.

Treatment of osteitis fibrosa cystica should be focused on the prevention and correction of the factors leading to secondary hyperparathyroidism. It is reasonable to correct vitamin D deficiency with either ergocalciferol (Zisman et al., 2007) or cholecalciferol (Chandra et al., 2008), though there are limited data about the effects of such therapies on the bone. Hyperphosphataemia should be addressed with dietary P restriction, use of P binders, and adequate dialysis (Sprague et al., 2007; Sherman and Mehta, 2009). The prevention and treatment of hypocalcaemia involves appropriate use of oral Ca supplements, correction of vitamin D deficiency, or adjustment of dialysate Ca concentration. If hyperparathyroidism persists, vitamin D receptor activators (Gal-Moscovici and Sprague, 2010; Sprague and Coyne, 2010) and/or calcimimetics (Sprague et al., 2009) are necessary. In severe cases, parathyroidectomy may be required; however, a bone biopsy should be considered prior to proceeding with parathyroidectomy (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009).

Patients with CKD are frequently diagnosed with osteoporosis or osteopenia based upon BMD measurements. Although the World Health Organization (WHO) has defined osteopenia and osteoporosis in the general population on the basis of BMD measurements at the lumbar spine or the femoral neck, CKD patients were excluded from studies used in the development of these criteria (Kanis, 1994). Patients with osteoporosis are frequently treated with bisphosphonates, in an attempt to decrease their fracture risk. Bisphosphonates are synthetic analogues of pyrophosphates that bind to hydroxyapatite in the bone and reduce osteoclastic activity by decreasing osteoclast progenitor development and promoting osteoclast apoptosis (Rodan and Fleisch, 1996). There are limited prospective studies with bisphosphonates in patients with CKD. However, bone biopsies in both CKD and kidney transplants patients who have received bisphosphonates often revealed adynamic bone disease (Coco et al., 2003; Amerling et al., 2010); furthermore, in a cohort analysis of 554 transplant recipients, the use of bisphosphonates attenuated femoral neck bone loss, but did not result in fracture prevention (Conley et al., 2008). Therefore, the use of bisphosphonates for osteoporosis is controversial in patients with CKD.

The management of CKD-MBD should be focused on maintaining normal bone turnover, by controlling the serum levels of P, Ca, vitamin D, and PTH. Unfortunately, there are no solid outcome data to support biochemical targets. Optimal PTH levels are especially uncertain. For dialysis patients, the KDIGO guidelines recommend target-PTH concentrations of two to nine times the upper limit of the reference range for the particular assay being utilized. It is also recommended to adjust therapy according to trends in PTH changes (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009).

References

Alfrey, A. C. (1978). Dialysis encephalopathy syndrome. *Annu Rev Med*, 29, 93–8.

Alfrey, A. C. (1983). Aluminum and renal disease. *Contrib Nephrol*, 102, 110–24.

Amerling, R., Harbord, N. B., Pullman, J., *et al.* (2010). Bisphosphonate use in chronic kidney disease: association with adynamic bone disease in a bone histology series. *Blood Purif*, 29(3), 293–9.

Andress, D. L. (2008). Adynamic bone in patients with chronic kidney disease. *Kidney Int*, 73(12), 1345–54.

Ballanti, P., Coen, G., Mazzaferro, S., *et al.* (2001). Histomorphometric assessment of bone turnover in uraemic patients: comparison between activation frequency and bone formation rate. *Histopathology*, 38(6), 571–83.

Barreto, F. C., Barreto, D. V., Moyses, R. M., *et al.* (2006). Osteoporosis in hemodialysis patients revisited by bone histomorphometry: a new insight into an old problem. *Kidney Int*, 69(10), 1852–7.

Chandra, P., Binongo, J. N., Ziegler, T. R., *et al.* (2008). Cholecalciferol (vitamin D3) therapy and vitamin D insufficiency in patients with chronic kidney disease: a randomized controlled pilot study. *Endocr Pract*, 14(1), 10–7.

Coco, M., Glicklich, D., Faugere, M. C., *et al.* (2003). Prevention of bone loss in renal transplant recipients: a prospective, randomized trial of intravenous pamidronate. *J Am Soc Nephrol*, 14(10), 2669–76.

Coco, M. and Rush, H. (2000). Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *Am J Kidney Dis*, 36(6), 1115–21.

Coen, G., Mazzaferro, S., Ballanti, P., *et al.* (1996). Renal bone disease in 76 patients with varying degrees of predialysis chronic renal failure: a cross-sectional study. *Nephrol Dial Transplant*, 11(5), 813–19.

Conley, E., Muth, B., Samaniego, M., *et al.* (2008). Bisphosphonates and bone fractures in long-term kidney transplant recipients. *Transplantation*, 86(2), 231–7.

Cueto-Manzano, A. M., Konel, S., Crowley, V., *et al.* (2003). Bone histopathology and densitometry comparison between cyclosporine a monotherapy and prednisolone plus azathioprine dual immunosuppression in renal transplant patients. *Transplantation*, 75(12), 2053–8.

Cueto-Manzano, A. M., Konel, S., Hutchison, A. J., *et al.* (1999). Bone loss in long-term renal transplantation: histopathology and densitometry analysis. *Kidney Int*, 55(5), 2021–9.

Dahl, E., Nordal, K. P., Attramadal, A., *et al.* (1988). Renal osteodystrophy in predialysis patients without stainable bone aluminum. A cross-sectional bone-histomorphometric study. *Acta Med Scand*, 224(2), 157–64.

Dempster, D. W., Compston, J. E., Drezner, M. K., *et al.* (2013). Standardized nomenclature, symbols, and units for bone histomorphometry: a 2012 update of the report of the ASBMR Histomorphometry Nomenclature Committee. *J Bone Miner Res*, 28(1), 2–17.

Eastwood, J. B. (1982). Quantitative bone histology in 38 patients with advanced renal failure. *J Clin Pathol*, 35(2), 125–34.

Gal-Moscovici, A. and Sprague, S. M. (2008). Role of bone biopsy in stages 3 to 4 chronic kidney disease. Clin *J Am Soc Nephrol*, 3 Suppl 3, S170–4.

Gal-Moscovici, A. and Sprague, S. M. (2010). Use of vitamin D in chronic kidney disease patients. *Kidney Int*, 78(2), 146–51.

Goldstein, D. A., Malluche, H. H., and Massry, S. G. (1980). Long-term effects of 1,25(OH)2D3 on clinical and biochemical derangements of divalent ions in dialysis patients. *Contrib Nephrol*, 18, 42–54.

Goodman, W. G. (1985). Bone disease and aluminum: pathogenic considerations. *Am J Kidney Dis*, 6(5), 330–5.

Hamdy, N. A., Kanis, J. A., Beneton, M. N., *et al.* (1995). Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. *BMJ*, 310(6976), 358–63.

Hernandez, D., Concepcion, M. T., Lorenzo, V., *et al.* (1994). Adynamic bone disease with negative aluminium staining in predialysis patients: prevalence and evolution after maintenance dialysis. *Nephrol Dial Transplant*, 9(5), 517–23.

Hruska, K. A., Saab, G., Mathew, S., *et al.* (2007). Renal osteodystrophy, phosphate homeostasis, and vascular calcification. *Semin Dial*, 20(4), 309–15.

Hutchison, A. J., Whitehouse, R. W., Boulton, H. F., *et al.* (1993). Correlation of bone histology with parathyroid hormone, vitamin D3, and radiology in end-stage renal disease. *Kidney Int*, 44(5), 1071–7.

Jorgetti, V. (2009). Review article: Bone biopsy in chronic kidney disease: patient level end-point or just another test? *Nephrology (Carlton)*, 14(4), 404–7.

Julian, B. A., Laskow, D. A., Dubovsky, J., *et al.* (1991). Rapid loss of vertebral mineral density after renal transplantation. *N Engl J Med*, 325(8), 544–50.

Kanis, J. A. (1994). Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporos Int*, 4(6), 368–81.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009). KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*, 113, S1–130.

Kurz, P., Monier-Faugere, M. C., Bognar, B., *et al.* (1994). Evidence for abnormal calcium homeostasis in patients with adynamic bone disease. *Kidney Int*, 46(3), 855–61.

Lehmann, G., Ott, U., Kaemmerer, D., *et al.* (2008). Bone histomorphometry and biochemical markers of bone turnover in patients with chronic kidney disease stages 3–5. *Clin Nephrol*, 70(4), 296–305.

Lehmann, G., Ott, U., Stein, G., *et al.* (2007). Renal osteodystrophy after successful renal transplantation: a histomorphometric analysis in 57 patients. *Transplant Proc*, 39(10), 3153–8.

Malluche, H. H., Mawad, H. W., and Monier-Faugere, M. C. (2011). Renal osteodystrophy in the first decade of the new millennium: analysis of 630 bone biopsies in black and white patients. *J Bone Miner Res*, 26(6), 1368–76.

Malluche, H. H. and Monier-Faugere, M. C. (1994). The role of bone biopsy in the management of patients with renal osteodystrophy. *J Am Soc Nephrol*, 4(9), 1631–42.

Malluche, H. H., Porter, D. S., Monier-Faugere, M. C., *et al.* (2012). Differences in bone quality in low- and high-turnover renal osteodystrophy. *J Am Soc Nephrol*, 23(3), 525–32.

Malluche, H. H., Ritz, E., Lange, H. P., *et al.* (1976a). Bone histology in incipient and advanced renal failure. *Kidney Int*, 9(4), 355–62.

Malluche, H. H., Ritz, E., Lange, H. P., *et al.* (1976b). Bone mass in maintenance haemodialysis. Prospective study with sequential biopsies. *Eur J Clin Invest*, 6(4), 265–71.

Massry, S. G., Stein, R., Garty, J., *et al.* (1976). Skeletal resistance to the calcemic action of parathyroid hormone in uremia: role of 1,25 (OH)2 D3. *Kidney Int*, 9(6), 467–74.

Moe, S., Drüeke, T., Cunningham, J., *et al.* (2006). Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*, 69(11), 1945–53.

Monier-Faugere, M. C., Mawad, H., Qi, Q., *et al.* (2000). High prevalence of low bone turnover and occurrence of osteomalacia after kidney transplantation. *J Am Soc Nephrol*, 11(6), 1093–9.

Mora Palma, F. J., Ellis, H. A., Cook, D. B., *et al.* (1983). Osteomalacia in patients with chronic renal failure before dialysis or transplantation. *QJM*, 52(207), 332–48.

National Kidney Foundation (2003). K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*, 42(4 Suppl 3), S1–201.

Ott, S. M. (2009). Bone histomorphometry in renal osteodystrophy. *Semin Nephrol*, 29(2), 122–32.

Ott, S. M., Maloney, N. A., Coburn, J. W., *et al.* (1982). The prevalence of bone aluminum deposition in renal osteodystrophy and its relation to the response to calcitriol therapy. *N Engl J Med*, 307(12), 709–13.

Rodan, G. A. and Fleisch, H. A. (1996). Bisphosphonates: mechanisms of action. *J Clin Invest*, 97(12), 2692–6.

Rojas, E., Carlini, R. G., Clesca, P., *et al.* (2003). The pathogenesis of osteodystrophy after renal transplantation as detected by early alterations in bone remodeling. *Kidney Int*, 63(5), 1915–23.

Salusky, I. B., Foley, J., Nelson, P., *et al.* (1991). Aluminum accumulation during treatment with aluminum hydroxide and dialysis in children and young adults with chronic renal disease [see comments]. *N Engl J Med*, 324(8), 527–31.

Sherman, R. A. and Mehta, O. (2009). Dietary phosphorus restriction in dialysis patients: potential impact of processed meat, poultry, and fish products as protein sources. *Am J Kidney Dis*, 54(1), 18–23.

Sherrard, D. J., Hercz, G., Pei, Y., *et al.* (1993). The spectrum of bone disease in end-stage renal failure—an evolving disorder. *Kidney Int*, 43(2), 436–42.

Shin, S. K., Kim, D. H., Kim, H. S., *et al.* (1999). Renal osteodystrophy in pre-dialysis patients: ethnic difference? *Perit Dial Int*, 19 Suppl 2, S402–7.

Slatopolsky, E., Finch, J., Clay, P., *et al.* (2000). A novel mechanism for skeletal resistance in uremia. *Kidney Int*, 58(2), 753–61.

Spasovski, G. B., Bervoets, A. R., Behets, G. J., *et al.* (2003). Spectrum of renal bone disease in end-stage renal failure patients not yet on dialysis. *Nephrol Dial Transplant*, 18(6), 1159–66.

Sprague, S. M. (2007). A comparative review of the efficacy and safety of established phosphate binders: calcium, sevelamer, and lanthanum carbonate. *Curr Med Res Opin*, 23(12), 3167–75.

Sprague, S. M. and Coyne, D. (2010). Control of secondary hyperparathyroidism by vitamin D receptor agonists in chronic kidney disease. *Clin J Am Soc Nephrol*, 5(3), 512–8.

Sprague, S. M., Evenepoel, P., Curzi, M. P., *et al.* (2009). Simultaneous control of PTH and CaxP Is sustained over three years of treatment with cinacalcet HCl. *Clin J Am Soc Nephrol*, 4(9), 1465–76.

Sprague, S. M. and Josephson, M. A. (2004). Bone disease after kidney transplantation. *Semin Nephrol*, 24(1), 82–90.

Torres, A., Lorenzo, V., Hernández, D., *et al.* (1995). Bone disease in predialysis, hemodialysis, and CAPD patients: evidence of a better bone response to PTH. *Kidney Int*, 47(5), 1434–42.

Zisman, A. L., Hristova, M., Ho, L. T., *et al.* (2007). Impact of ergocalciferol treatment of vitamin D deficiency on serum parathyroid hormone concentrations in chronic kidney disease. *Am J Nephrol*, 27(1), 36–43.

CHAPTER 123

Clinical aspects and overview of renal anaemia

Iain C. Macdougall

Introduction

The first suggestion that the kidney might be involved in erythropoiesis has been attributed to Richard Bright, when in 1835 he described the association between 'anaemia' and 'kidney dysfunction'. It was not until 70 years later that Carnot and Deflandre (1906) observed that serum from an anaemic donor rabbit injected into a normal rabbit resulted in increased erythropoiesis. A potential circulating factor was postulated, initially called haematopoietin. Erslev extended these observations, also showing that plasma from anaemic rabbits contained a factor able to stimulate erythropoiesis, and indeed he described its potential as a therapeutic strategy (Erslev, 1953). Four years later, in 1957, Jacobson, Goldwasser, and others showed that the kidney was the source of this hormone, which is now known as erythropoietin (Jacobson et al., 1957). Removal of renal mass by nephrectomy rendered animals anaemic; this could be corrected by administration of plasma from animals with normal kidneys. Thus, the relative lack of erythropoietin produced by diseased kidneys remains the major causative factor in the pathogenesis of renal anaemia today.

Much of the morbidity associated with chronic kidney disease (CKD) can be attributed to the consequences of their chronic anaemia. The introduction of recombinant human erythropoietin in the early 1990s transformed the management of this condition, particularly in dialysis patients, many of whom were transfusion dependent and iron overloaded. The striking response to administration of recombinant human erythropoietin confirmed the notion that a relative lack of erythropoietin was the major causative factor (Winearls et al., 1986; Eschbach et al., 1987). The use of recombinant human erythropoietin and other erythropoiesis-stimulating agents is discussed in greater detail in Chapter 124, and this particular chapter will focus on the physiological processes relevant to red cell production, as well as the prevalence, characteristics, pathogenesis, and physiological consequences of renal anaemia.

Physiology

A number of physiological processes are relevant to normal red cell production, and it is the disturbance of these processes that result in chronic anaemia, including that associated with renal dysfunction. The main processes are erythropoiesis, regulation of erythropoietin production including the role of hypoxia-inducible factor (HIF), and regulation of iron supply including the role of hepcidin.

Erythropoiesis

The erythroid marrow is responsible for the production of red cells to maintain a red cell mass of approximately 30 ± 5 mL/kg in males and 25 ± 5 mL/kg in females. This is more usually assessed by measurement of the red cell count and haemoglobin concentration (for normal values see Table 123.1). The maintenance of the red cell mass, 1% of which is destroyed each day, depends on continual erythropoiesis, with the production of 2 million new red cells every second, or 173,000,000,000 new red cells every day. Pluripotent stem cells, primitive cells capable of both self-renewal and differentiation, are present in the marrow at lower concentrations. These cells give rise to progenitor cells, committed to become either myeloid, erythroid, lymphoid, or megakaryocytic cells. Their differentiation and multiplication is controlled by an array of growth factors (Fig. 123.1). Differentiation of the committed erythroid precursor into the primitive erythroid progenitor cell, 'the burst forming unit-erythroid' (usually abbreviated to BFU-E), is largely under the influence of interleukin-3 (IL-3) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Multiplication and differentiation of the BFU-E and the later 'colony forming unit-erythroid' (CFU-E) requires the presence of erythropoietin. The CFU-E is more sensitive to erythropoietin than the BFU-E, requiring lower concentrations for *in vitro* culture. Apart from erythropoietin, CFU-E growth in culture requires the presence of insulin or insulin-like growth factor 1 (Sawada et al., 1989). The CFU-E undergoes successive divisions and gives rise to proerythroblasts and then erythroblasts. It is at the erythroblast state of red cell development that iron is incorporated into haem, a subunit of haemoglobin, which is the major oxygen-carrying pigment of the blood. Reticulocytes are then created, which are released into the bloodstream and become mature red cells.

Regulation of erythropoietin production and the role of hypoxia-inducible factor

Normal serum erythropoietin concentrations in man are of the order of 10–30 mU/mL as determined by immunoassay, which corresponds to between 2 and 7 pmol/L. Assuming a mean circulating half-life of 5–9 hours and a mean distribution volume of 0.07 L/kg, as determined in pharmacokinetic studies with recombinant erythropoietin, it can be estimated that the endogenous production of the hormone normally amounts to about 2–4 U/kg/24 hours.

Erythropoietin concentrations are decreased or increased under a variety of conditions, largely reflecting alterations of oxygen

Table 123.1 Normal haematological values

Haemoglobin (g/dL)	
Male	13.5–18
Female	11.5–16
Haematocrit:	
Male	0.40–0.54
Female	0.37–0.47
Red cell count ($\times 10^{12}$/L):	
Male	4.5–6.5
Female	3.9–5.6
Mean cell volume (MCV) (fL)	81–100
Mean cell haemoglobin (pg)	27–32
Mean cell haemoglobin concentration (g/dL)	32–36
Reticulocyte count (%)	0.8–2.0
Absolute reticulocyte count ($\times 10^9$/L)	25–100
Total blood volume (mL/kg)	70 ± 10
Plasma volume (mL/kg)	45 ± 5
Red cell volume (mL/kg):	
Male	30 ± 5
Female	25 ± 5
Erythron transferrin uptake (μmol/L/day)	60 ± 12
Platelet count ($\times 10^9$/L)	150–400
White cell count ($\times 10^9$/L)	4.0–11.0

delivery to tissues. Anaemia of whatever cause is the most powerful stimulus to an increase in serum erythropoietin, with an inverse relationship between the concentration of erythropoietin and the haemoglobin concentration (Eckardt et al., 1991) (Fig. 123.2). In severely anaemic patients, up to 1000-fold increases in plasma erythropoietin can be found.

The body contains no significant stores of erythropoietin, and there is no evidence to suggest that the clearance rate of the hormone is subject to any physiological regulation. It would therefore appear that any change in serum erythropoietin concentration results from a change in the rate of production, the latter of which has been shown to be primarily determined by the expression of mRNA in liver and kidneys (Bondurant and Koury, 1986; Tan et al., 1992). The relative contribution of liver and kidneys is primarily age dependent, with the liver being the predominant production site in the fetus, and the kidneys producing most of the erythropoietin in adults (Eckardt et al., 1992). However, it is possible for the liver to increase its erythropoietin production, such as under conditions of severe hypoxia (Tan et al., 1992; Eckardt et al., 1992) or following administration of pharmacological agents (Bernhardt et al., 2010). In renal failure, however, the liver does not compensate for loss or failure of the renal production of erythropoietin (Tan et al., 1991), and in anephric patients, serum erythropoietin concentrations are very low (Naets et al., 1986).

The cells producing erythropoietin in the kidney are peritubular fibroblasts in the renal cortex (Bachmann et al., 1993; Maxwell et al., 1993) (Fig. 123.3). The mechanism controlling erythropoietin production is oxygen-dependent, and is regulated by an oxygen sensor. Thus, the presence of local tissue hypoxia translates into increased erythropoietin gene activity in the liver and kidneys. This mechanism is a key element in the feedback control of erythropoiesis. Tissue hypoxia may occur secondary to a reduced arterial pO_2 (hypoxic hypoxia) or alternatively in conditions in which the arterial pO_2 is normal and only tissue pO_2 is reduced (anaemic hypoxia).

The major stimulus to increasing erythropoietin production is upregulation of HIF, which is the major transcription factor controlling the erythropoietin gene. HIF was discovered in the late 1980s by Semenza and colleagues (Semenza and Wang, 1992), and is a heterodimer of an oxygen-regulated α-subunit and a constitutive β-subunit. Both subunits exist as a set of different isoforms, all belonging to the basic-helix-loop-helix PAS protein superfamily. The major regulation of the α-subunit occurs through oxygen-dependent degradation. This is mediated by the von Hippel–Lindau protein (pVHL), which acts as a ubiquitin ligase and targets HIFα for proteasomal destruction through the addition of a chain of ubiquitin molecules (Maxwell et al., 1999).

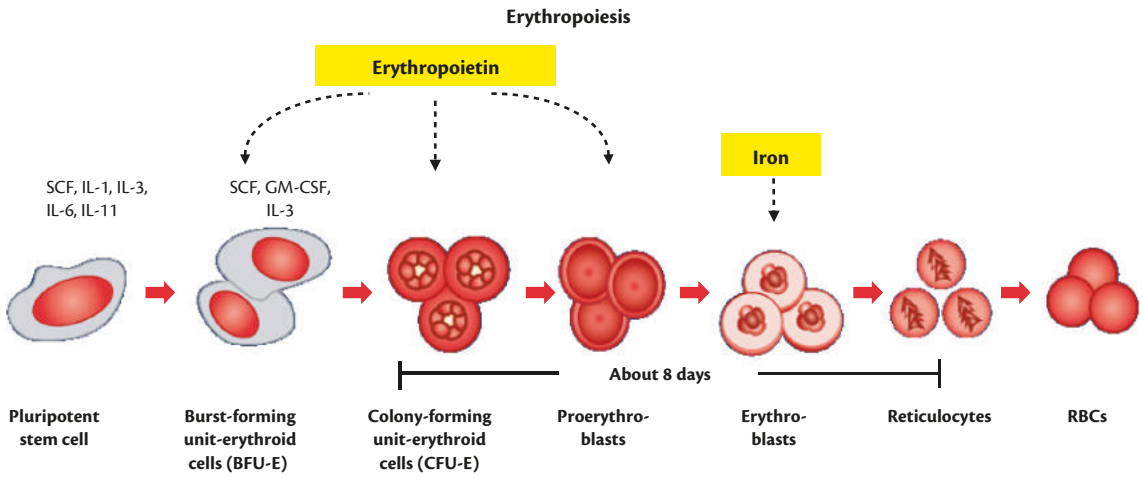


Fig. 123.1 Normal erythropoiesis.

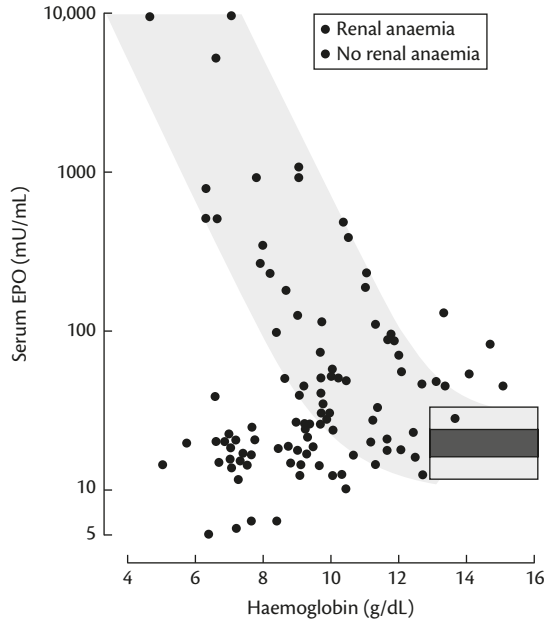


Fig. 123.2 Serum erythropoietin (EPO) levels in relation to the haemoglobin concentration in patients with anaemia due to both renal and non-renal causes. From Eckardt et al. (1991)

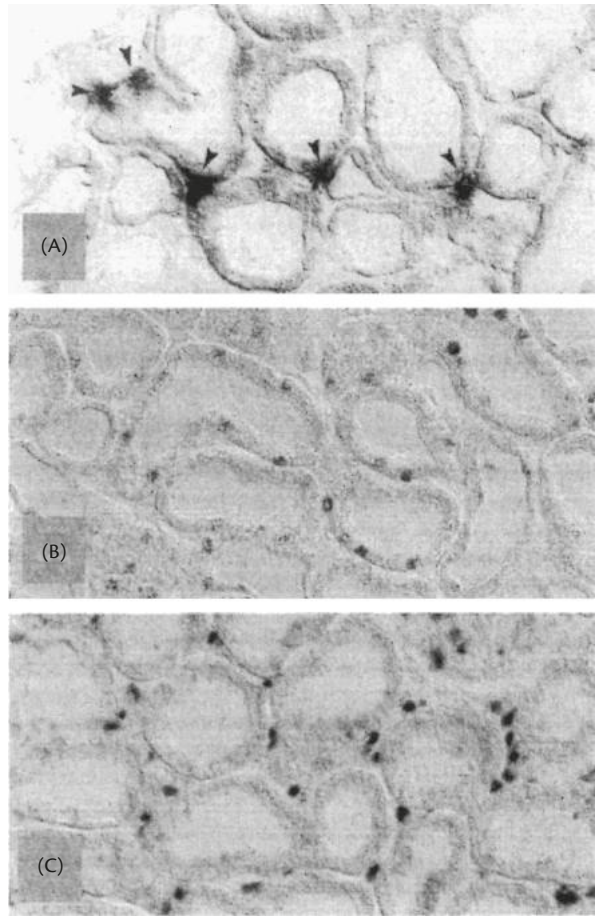


Fig. 123.3 *In situ* hybridization, demonstrating erythropoietin mRNA in peritubular fibroblasts of the renal cortex. Bachmann et al. (1999).

pVHL only binds to HIFα in the presence of oxygen, and this interaction depends on hydroxylation of prolyl residues of the HIFα protein (Fig. 123.4). HIF prolyl hydroxylation is achieved through a family of prolyl hydroxylases, which require molecular oxygen as a substrate (Epstein et al., 2001; Jaakkola et al., 2001). An additional hydroxylation step was found to regulate HIF transcriptional activity (Lando et al., 2002). HIF-1α and HIF-2α are the two principal oxygen-regulated HIF subunits. Although both are regulated in a very similar fashion *in vitro* (Wiesener et al., 1998), their expression *in vivo* appears to be cell-type specific. In the kidney, HIF-1α is normally expressed in tubular cells and HIF-2α in peritubular endothelial cells and fibroblasts (Rosenberger et al., 2002). It is now recognized that HIF-2α rather than HIF-1α is the isoform that is most relevant for transcriptional induction of the erythropoietin gene *in vivo*. HIF acts at the 3′ enhancer of the erythropoietin gene, but there are other transcription factors that may influence erythropoietin gene regulation (Fig. 123.5). These include GATA2 and nuclear factor kappa B (NF-κB), which act at the 5′ promoter of the erythropoietin gene. GATA2 and NF-κB are

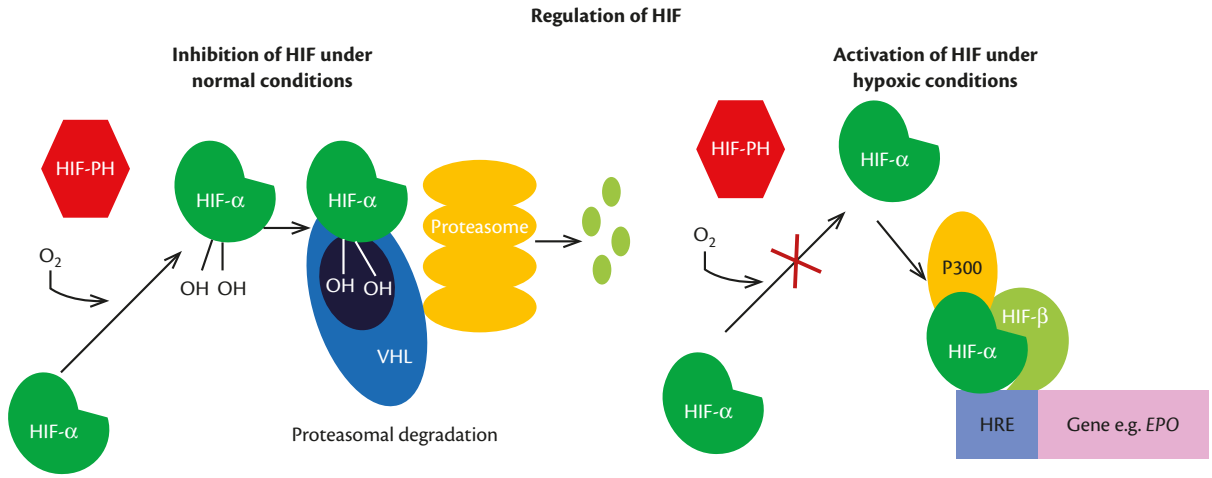


Fig. 123.4 Regulation of HIF.

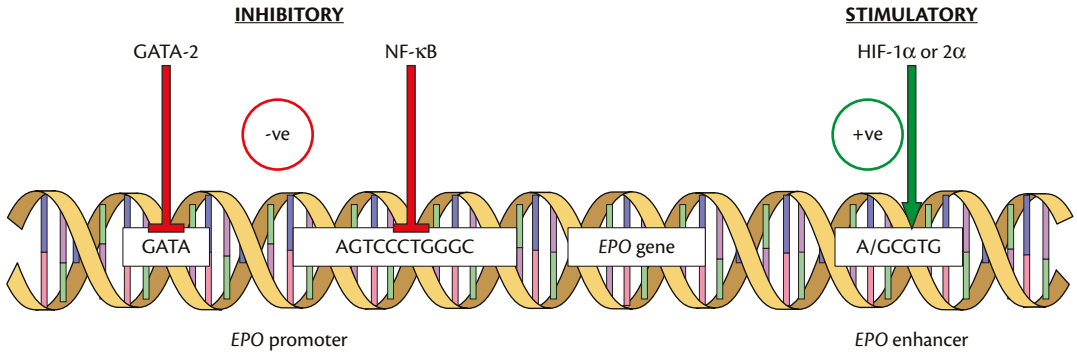


Fig. 123.5 Regulation of erythropoietin (*EPO*) gene expression.

inhibitory to the erythropoietin promoter. Both HIF and GATA2 have been targets for the development of future anti-anaemic therapies. Thus, inhibiting the enzyme that degrades HIF (prolyl hydroxylase) will stabilize this transcription factor, and allow continued stimulation of the erythropoietin gene. Several prolyl hydroxylase inhibitors (HIF stabilizers) are now in phase 1, 2, or 3 clinical trials (see Chapter 124).

Regulation of iron supply and the role of hepcidin

Along with other factors required for normal erythropoiesis (such as vitamin B_{12}, folic acid, pyridoxine, ascorbic acid, thyroxine, and various trace elements), iron is pivotal to the development to a normal healthy red cell. The majority of iron in the body is contained in the red cell mass, in the form of haemoglobin. It is transported in plasma bound to transferrin, and is delivered to developing red cells via a specific membrane receptor.

The average obligatory daily iron loss is around 1–2 mg. This is compensated for by dietary iron intake, and under normal healthy conditions the same amount of iron is absorbed from the gut. Thus, an average Western diet contains about 14 mg daily, and of this, around 5–10% will be absorbed. Thus, dietary intake will provide sufficient iron to balance the daily losses. The iron in the body is recirculated in a closed loop; thus, red cells become obsolescent after 120 days, and the intracellular iron is recirculated via the reticuloendothelial system in the liver, spleen, and macrophages.

Understanding the regulation of iron supply was greatly enhanced just over a decade ago by the discovery of a peptide hormone, hepcidin, which is produced in the liver. This peptide is encoded for by the *HAMP* gene (hepatic anti-microbial peptide) gene and indeed this peptide has antimicrobial properties. Its major physiological role, however, is in the regulation of iron supply to the bone marrow (Ganz, 2011). Many factors control hepcidin production. It is upregulated in conditions in which there is iron sufficiency, inflammation, active infection, and following intravenous administration. It is downregulated in iron deficiency, anaemia, or hypoxia. The major cytokine controlling hepcidin expression is interleukin 6, which is upregulated in inflammatory states. The major action of hepcidin is to inhibit the efflux of iron from a number of cell types, due to its interaction with ferroportin, the only known cellular iron exporter protein in mammals (Ganz, 2011). Thus, hepcidin upregulation, as commonly occurs in patients with CKD, particularly those on dialysis, is another major factor in the pathogenesis of renal anaemia. It explains why the majority of dialysis patients do not absorb iron in sufficient quantities to maintain a healthy iron balance, and this had led to the widespread use of intravenous iron in this patient population.

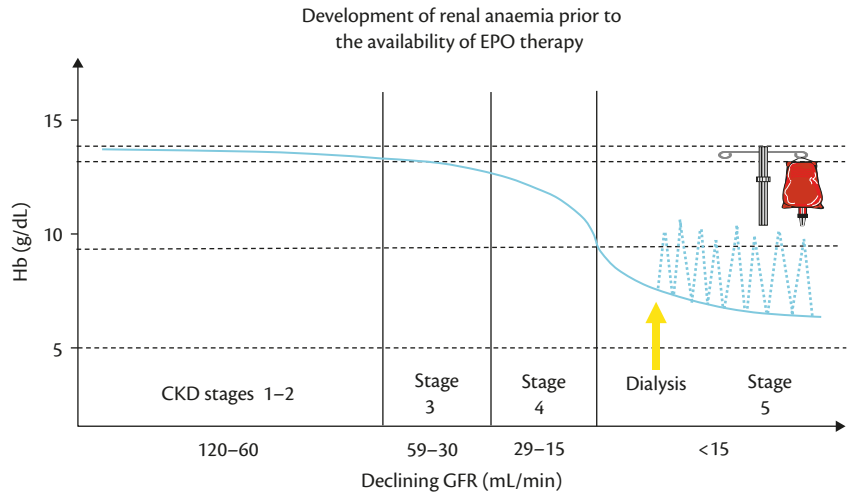


Fig. 123.6 NHANES III data of haemoglobin versus CKD stage.

Prevalence

The prevalence of anaemia in patients with CKD increases according to the severity of renal dysfunction. Thus, anaemia is very uncommon in CKD stages 1 and 2. It becomes significantly more common in late-stage 3, is reasonably common in stage 4, and is almost universal in stage 5 patients on dialysis. This can be shown schematically (Fig. 123.6), based on data from the National Health & Nutrition Examination Survey III (NHANES III) (Astor et al., 2002), which shows the average haemoglobin in this large US population survey, in relation to the stage of CKD. Prior to the introduction of erythropoietin as a therapy for chronic anaemia, the majority of dialysis patients were transfusion dependent, many requiring top-up red cell transfusions every 2–4 weeks to prevent debilitating symptoms of severe anaemia. It is also evident that patients with diabetic nephropathy have more severe anaemia than patients with CKD of other aetiologies, and some diabetics with fairly early nephropathy and only a mildly reduced glomerular filtration rate, suffer from an erythropoietin-deficient anaemia (Bosman et al., 2001).

As a group, haemodialysis patients tend to have more severe anaemia than those on peritoneal dialysis. Thus, the prevalence in the latter group of patients is less, and a number of factors have been proposed to explain this. Such factors include a greater degree of blood loss and haemolysis in haemodialysis patients, better removal of 'uraemic middle molecules', greater degrees of chronic inflammation in haemodialysis patients causing higher hepcidin levels, and a higher prevalence of iron deficiency. Prior to the availability of erythropoietin, peritoneal patients tended to show a greater increase in haemoglobin concentration after starting dialysis compared to their haemodialysis counterparts.

The severity of anaemia in dialysis patients is independent of the aetiology of kidney disease, with the exception of patients with adult polycystic disease who tend to have higher haemoglobin concentrations. This is due to higher erythropoietin levels as a result of erythropoietin production by the cysts. Similarly, a marked increase in haemoglobin, and even occasional polycythaemia, can occur in dialysis patients who develop acquired cystic disease of the kidneys. Again, the mechanism of the latter effect is thought to be increased secretion of erythropoietin from the cyst walls.

Characteristics

The anaemia associated with CKD is usually normochromic and normocytic. Thus, the mean cell volume (MCV) and mean cell haemoglobin concentration (MCHC) are usually within the normal range. However, if there is an additional factor contributing to the anaemia (such as iron deficiency), this may not be the case. On a practical note, if the MCV or MCHC are abnormal, then careful steps should be taken to exclude other contributing causes of anaemia.

The anaemia associated with CKD is hypoproliferative in origin, that is, erythropoietic activity in the bone marrow is reduced due to a relative lack of erythropoietin. This is reflected in a low-normal reticulocyte count, and low-reduced erythroid activity in a bone marrow sample.

Usually, the white cell and platelet counts are normal in CKD, and significant abnormalities of the leucocyte and megakaryocyte lineage should alert the physician to the presence of an underlying haematological condition.

Measurement of the serum vitamin B_{12}, folate, and ferritin levels should be requested in any anaemic CKD patient. Concomitant iron deficiency is common and deficiencies of all of these haematinics are easily corrected by vitamin or iron supplementation. Although there may be a wide variability of haemoglobin at each stage of CKD, it may be helpful to relate the degree of anaemia to the degree of renal dysfunction. Thus, particularly in the early stages of CKD, anaemia is uncommon, and this may well be the presenting feature of another condition, such as occult bowel malignancy.

CKD patients with haemoglobinopathies, such as sickle cell disease or beta thalassaemia, are likely to have low MCV and MCH levels as a result of their genetic defect causing abnormal haemoglobin synthesis. Screening for these conditions in patients in whom their ethnic backgrounds suggest a higher likelihood of a haemoglobinopathy may be indicated.

Pathogenesis

Reduced erythropoietin production

A relative deficiency of erythropoietin production is the major cause of renal anaemia. Until recently, it was believed that this was due to progressive destruction of erythropoietin-producing cells in the kidney, leading to a reduced cellular capacity for erythropoietin production. More recent work, involving pharmacological inhibition of prolyl hydroxylase, suggests that there may be a defect of the oxygen-sensing system, rendering functioning cells less sensitive to hypoxia (Bernhardt et al., 2010). Earlier work also suggested that the production capacity for erythropoietin may be preserved in chronic renal disease. For example, animals with experimentally induced kidney failure show a large rise in erythropoietin mRNA and plasma erythropoietin levels in response to severe hypoxia (Tan et al., 1991, 1992).

Regardless of the detailed mechanisms, patients with CKD generally have inappropriately lower levels of circulating plasma erythropoietin for their degree of anaemia compared to non-uraemic individuals (Eckardt et al., 1991). This was the strong rationale for suggesting that erythropoietin supplementation may ameliorate the anaemia of CKD.

Reduced red cell lifespan

The red cell lifespan in normal healthy individuals is around 120 days, but this may be shortened to 60–90 days in patients with severe renal dysfunction. Some historical experiments showed that red cell survival normalized when cells from uraemic individuals were transfused into non-uraemic recipients (and conversely, red cells from non-uraemic donors were prematurely destroyed after transfusion into uraemic patients). This suggested that the main explanation for shortened red cell survival is extra-corpuscular (Loge et al., 1958). Such studies were, however, limited by the small number of patients enrolled, many of whom were in the terminal stages of uraemia. It seems likely, however, that red cells from uraemic patients have an increased susceptibility towards mechanical, alternative, and osmotic stresses (Rosenmund et al., 1975), suggesting that corpuscular factors may also play a role in premature red cell destruction. Several abnormalities of uraemic red cells have been described, including abnormalities in sodium transport. However, the exact mechanisms by which uraemia affects red cell metabolism, and the precise biochemical basis for reduced erythrocyte survival have not been resolved. Low-grade haemolysis may occur in many patients and this may be more profound if there is any toxic contamination of dialysis fluid with zinc (Petrie and Row,

1977), copper (Manzler and Schreiner, 1970), nitrates (Carlson and Shapiro, 1970), formaldehyde (Orringer and Mattern, 1976), and chloramines (Eaton et al., 1973; Richardson et al., 1999).

'Uraemic inhibitors' of erythropoiesis

There has long been debate over whether substances present in uraemic serum may inhibit erythropoiesis. Such substances have included spermine, spermidine, putrescine, and parathyroid hormone, amongst others.

CKD is also recognized as a chronic inflammatory state, in which a number of pro-inflammatory cytokines are upregulated. Several of these, including tumour necrosis factor alpha and interferon gamma, have been shown to inhibit erythropoiesis *in vitro* (Means and Krantz, 1992), and these factors are heavily implicated in the pathogenesis of the anaemia of chronic disease, outside the renal setting.

The ability of recombinant human erythropoietin to correct renal anaemia has, however, indicated that the action of such inhibitors, if present at all, can easily be overcome. Thus, 'uraemic inhibition' of erythropoiesis does not have a major pathogenetic role, although it may explain why (prior to the days of erythropoietin therapy), the initiation of dialysis was followed by an improvement in haemoglobin concentration (Zappacosta et al., 1982; De Paepe et al., 1983). There is also some evidence that an increase in the intensity of dialysis can induce a rise in haemoglobin concentration with and without recombinant human erythropoietin therapy (Koch et al., 1974; Ifudu et al., 1996).

Blood loss

Patients with CKD are prone to blood loss caused by the regular dialysis procedure, regular blood sampling, and occult gastrointestinal bleeding. It has been estimated that the annual blood loss in haemodialysis patients from dialysers and blood tests alone is between 1 and 4 L (Hocken and Marwah, 1971). Although dialyser blood loss has been reduced by modern dialysers and dialysis techniques, it remains significant. In renal patients with unusually severe anaemia, excessive blood loss is often identified as the predominant cause (Linton et al., 1977). Mild gastrointestinal blood loss is common in patients with CKD, and may not be detected by faecal occult blood testing (Linton et al., 1977).

Iron and folate deficiency

Patients with CKD are often in negative iron balance. This is due to a combination of reduced iron intake, and also increased iron losses. Reduced intake is due to poor appetite, reduced dietary iron intake, poor absorption of oral iron due to upregulation of hepcidin activity, and interaction with various medications and foodstuffs that bind iron (such as phosphate binders, omeprazole, ciprofloxacin, and tea). Increased iron losses are due to blood loss as indicated in the previous paragraph and this may be exacerbated by the use of heparin during dialysis, or the use of aspirin as cardiovascular risk prophylaxis.

Adequacy of folate supply is best estimated by measuring red cell folate rather than serum folate, although the latter is often used as the initial screening test. Although folate losses through dialysis are greater than by urinary excretion, these losses are usually balanced by a normal healthy diet. Occasionally, however, folate deficiency may be present and this should certainly be considered in any patient with a raised MCV (Hampers et al., 1967; Schaefer et al., 2002). Several drugs may also exacerbate folate deficiency, including phenytoin, methotrexate, etc.

Aluminium toxicity

In the past, aluminium intoxication was a significant cause of anaemia, classically associated with red cell microcytosis. Aluminium toxicity arose from a combination of high aluminium levels in the dialysate, as well as ingestion of aluminium-containing phosphate binders. With the use of modern-day dialysis techniques, dialysate aluminium levels are now negligible, and aluminium-containing phosphate binders are now rarely used. Thus, the contribution of aluminium overload to anaemia has largely disappeared.

Physiological consequences

In anaemic conditions, there is a reduced delivery of oxygen to the tissues, which in turn causes a variety of signs and symptoms in patients with CKD that may be difficult to distinguish from the symptoms of uraemia. If the anaemia is uncorrected, various physiological adaptive mechanisms may occur to compensate for the suboptimal oxygen delivery, including modulation of the affinity of haemoglobin for oxygen (with a shift in the oxygen dissociation curve), as well as an increase in 2, 3 diphosphoglycerate levels, an increase in cardiac output, and redistribution of blood flow from the skin to other organs. The symptoms and signs of anaemia include tiredness, lethargy, muscle fatigue, breathlessness at rest or on exertion, angina, palpitations, tachycardia, increased sensitivity to cold, loss of appetite, loss of libido, menstrual irregularity, poor memory and concentration, and impaired cognitive and neurophysiological function.

Bleeding diatheses

Severe renal impairment is often associated with a bleeding tendency characterized by a prolonged skin bleeding time (Lindsay et al., 1975). Although uraemia results in various minor abnormalities of clotting factors and platelet function, the degree of anaemia is of considerable importance. Thus, correction of anaemia usually results in a return of the bleeding time to normal; this has been shown in response to both red cell transfusion (Livio et al., 1982; Fernandez et al., 1985) and erythropoietin therapy (Moia et al., 1987; Macdougall et al., 1991a). The mechanism of this effect is poorly understood, but improved contact of platelets with the vessel wall, enhanced adenosine diphosphate production, and improved platelet function may all play a part.

Cardiovascular effects

There are various adaptive cardiovascular mechanisms to anaemia, including an increase in cardiac output (partly due to an increase in stroke volume and partly due to an increased heart rate) and hypoxia-induced peripheral vasodilatation (which, with the decreased viscosity of anaemic blood, reduces peripheral vascular resistance). In the long-term, the chronic increase in cardiac output leads to a compensatory increase in left ventricular mass, and this contributes to the left ventricular hypertrophy that is common in uraemic patients. Other cardiac effects include an increase in left ventricular end-diastolic dimensions, impaired myocardial contractility, and both systolic and diastolic dysfunction. Exercise capacity in CKD patients with anaemia is severely impaired, as are

measures of respiratory physiology, such as the maximum oxygen consumption, anaerobic threshold, and diffusion capacity of the lungs. Many of these adverse effects are reversed with correction of anaemia by red cell transfusion (Neff et al., 1971), renal transplantation (Himelman et al., 1988), or recombinant human erythropoietin (Macdougall et al., 1990b), suggesting that anaemia contributes significantly to the cardiac abnormalities associated with CKD.

Management

The management of CKD anaemia consists largely of the use of three treatment strategies: erythropoiesis-stimulating agents, iron supplementation, and blood transfusions. Erythropoiesis-stimulating agents are discussed in Chapter 124 and iron therapy in Chapter 126. Blood transfusions are usually the last resort in chronic anaemia, and are reserved for patients resistant to erythropoiesis-stimulating agents or when such agents are inappropriate. Their effects are transient, and they are used mainly for short-term symptomatic relief. Excessive use is associated with iron overload, and there are also risks of transmission of infectious agents, as well as human leucocyte antigen sensitization (which may render subsequent successful renal transplantation problematic).

Haematinic supplements should be used when there are concomitant haematinic deficiencies, such as vitamin B_{12} and folate deficiencies. Likewise, thyroxine supplementation may improve anaemia in cases of subclinical hypothyroidism.

Dialysis adequacy

Prior to the introduction of erythropoietin therapy, an improvement in anaemia was seen in some patients during the first few months after dialysis, and this may be related to enhanced red cell survival (Koch et al., 1974). A cohort study of > 6000 haemodialysis patients in the United States from 1994 to 1998 showed that the dose requirements for recombinant human erythropoietin decreased as the urea reduction ratio (URR) increased, while the haematocrit increased as the URR increased (Coladonato et al., 2002). Similarly, in a study of 68 haemodialysis patients, Movilli et al. (2001) found that the weekly dose requirements of erythropoietin decreased as Kt/V increased. Multivariate regression analysis showed that Kt/V was the only independent variable affecting the dose of erythropoietin (Fig. 123.7). Increase in the intensity of dialysis can also improve the haemoglobin response to erythropoietin therapy (Ifudu et al., 1996). More recent studies designed to compare conventional haemodialysis with high-flux dialysis or haemodiafiltration have also shown some positive results.

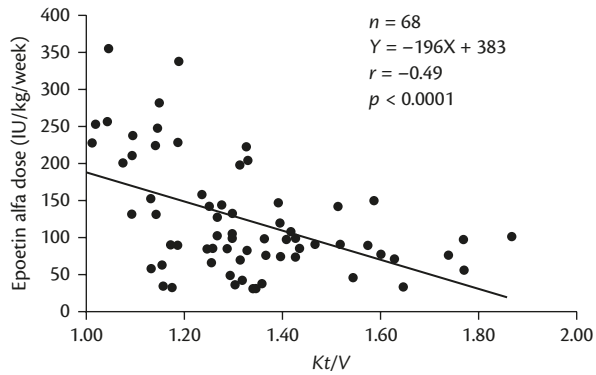


Fig. 123.7 Dialysis adequacy on erythropoietin (EPO) response.
From Movilli et al. (2001).

Androgen therapy

Prior to the advent of erythropoietin therapy, androgens were used to increase erythropoiesis, although their use has largely disappeared in most countries of the world. There is some evidence that they may be able to reduce the dose requirements of erythropoietin (Navarro, 2003). They may enhance erythropoiesis by two possible mechanisms: firstly, by stimulating endogenous erythropoietin production, and secondly via direct effects on red cell precursor cells in the bone marrow (Alexanian et al., 1967; Koch et al., 1974). Previously, androgens have been shown to cause partial relief of anaemia with a reduction in transfusion requirements (Eschbach and Adamson, 1973), but they tend to be beneficial in mild cases only and are limited by a high incidence of side-effects, such as virilization, muscle and liver damage, and cholestasis (Neff et al., 1981).

Several new strategies for treating the anaemia of CKD are currently being investigated in clinical trials (Macdougall, 2012), including prolyl hydroxylase inhibitors and modulators of hepcidin activity, but their role in the management of this condition remains to be established.

References

Alexanian, R., Vaughn, W. K., and Ruchelman, M. W. (1967). Erythropoietin excretion in man following androgens. *J Lab Clin Med*, 70, 777–85.

Astor, B. C., Muntner, P., Levin, A., *et al.* (2002). Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988–1994). *Arch Intern Med*, 162, 1401–8.

Bachmann, S., LeHir, M., and Eckardt, K.-U. (1993). Co-localization of erythropoietin mRNA and ecto-5′–nucleotidase immunoreactivity in peritubular cells of rat renal cortex indicates that fibroblasts produce erythropoietin. *J Histochem Cytochem*, 41, 335–41.

Bernhardt, W. M., Wiesener, M. S., Scigalla, P., *et al.* (2010). Inhibition of prolyl hydroxylases increases erythropoietin production in ESRD. *J Am Soc Nephrol*, 21, 2151–6.

Bondurant, M. C. and Koury, M. J. (1986). Anemia induces accumulation of erythropoietin mRNA in the kidney and liver. *Mol Cell Biol*, 6, 2731–3.

Bosman, D. R., Winkler, A. S., Marsden, J. T., *et al.* (2001). Anemia with erythropoietin deficiency occurs early in diabetic nephropathy. *Diabetes Care*, 24, 495–9.

Carlson, D. J. and Shapiro, F. L. (1970). Methemoglobinemia from well water nitrates; a complication of home dialysis. *Ann Intern Med*, 73, 757–9.

Carnot, M. and Deflandre, C. (1906). Sur l'activite hemopoietique du serum au cours de la regeneration du sang. [Haemopoietic activity of the serum in blood regeneration.] *C R Acad Sci (Paris)*, 143, 384–6.

Coladonato, J. A., Frankenfield, D. L., Reddan, D. N., *et al.* (2002). Trends in anemia management among US hemodialysis patients. *J Am Soc Nephrol*, 13, 1288–95.

De Paepe, M. B. J., Schelstraete, K. H. G., Ringoir, S. M. G., *et al.* (1983). Influence of continuous ambulatory peritoneal dialysis on the anemia of endstage renal disease. *Kidney Int*, 23, 744–8.

Eaton, J. W., Kolpin, C. F., Swofford, H. S., *et al.* (1973). Chlorinated urban water: a cause of dialysis-induced hemolytic anemia. *Science*, 181, 463–4.

Eckardt, K. U., Drueke, T., Leski, M., *et al.* (1991). Unutilized reserves: the production capacity for erythropoietin appears to be conserved in chronic renal disease. *Contrib Nephrol*, 88, 18–31.

Eckardt, K. -U., Ratcliffe, P. J., Tan, C. C., *et al.* (1992). Age-dependent expression of the erythropoietin gene in rat liver and kidneys. *J Clin Invest*, 89, 753–60.

Epstein A. C., Gleadle, J. M., McNeill, L. A., *et al.* (2001). *C. elegans* EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation. *Cell*, 107, 43–54.

Erslev, A. J. (1953). Humoral regulation of red cell production. *Blood*, 8, 349–57.

Eschbach, J. W. and Adamson, J. W. (1973). Improvement in the anemia of chronic renal failure with fluoxymesterone. *Ann Inten Med*, 78, 527–32.

Eschbach, J. W., Egrie, J. C., Downing, M. R., *et al.* (1987). Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med*, 316, 73–8.

Fernandez, F., Goudable, C., Sie, P., *et al.* (1985). Low haematocrit and prolonged bleeding time in uraemic patients: effect of red cell transfusions. *Br J Haematol*, 59, 139–48.

Ganz, T. (2011). Hepcidin and iron regulation, 10 years later. *Blood*, 117, 4425–33.

Hampers, C. L., Streiff, R., Nathan, D. G., *et al.* (1967).Megaloblastic hematopoiesis in uremia and in patients on long-term hemodialysis. *N Engl J Med*, 276, 551–4.

Himelman, R. B., Landzberg, J. S., Simonson, J. S., *et al.* (1988). Cardiac consequences of renal transplantation: changes in left ventricular morphology and function. *J Am Coll Cardiol*, 12, 915–23.

Hocken, A. G. and Marwah, P. K. (1971). Iatrogenic contribution to anaemia of chronic renal failure. *Lancet*, i, 164–5.

Ifudu, O., Feldman, J., and Friedman, E. A. (1996). The intensity of hemodialysis and the response to erythropoietin in patients with end-stage renal disease. *N Engl J Med*, 334, 420–5.

Jaakkola, P., Mole, D. R., Tian, Y. M., *et al.* (2001). Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O_2-regulated prolyl hydroxylation. *Science*, 292, 468–72.

Jacobson, L. O., Goldwasser, E., Fried, W., *et al.* (1957). Role of the kidney in erythropoiesis. *Nature*, 179, 633–4.

Koch, K. M., Patyna, W. D., Shaldon, S., *et al.* (1974). Anemia of the regular hemodialysis patient and its treatment. *Nephron*, 12, 405–19.

Lando, D., Peet, D. J., Whelan, D. A., *et al.* (2002) Asparagine hydroxylation of the HIF transactivation domain a hypoxic switch. *Science*, 295, 858–61.

Lindsay, R. M., Moorthy, A. V., Koens, F., *et al.* (1975). Platelet function in dialyzed and non-dialyzed patients with chronic renal failure. *Clin Nephrol*, 4, 52–7.

Linton, A. L., Clark, W. F., Driedger, A. A., *et al.* (1977). Correctable factors contributing to the anemia of dialysis patients. *Nephron*, 19, 95–8.

Livio, M., Marchesi, D., Remuzzi, G., *et al.* (1982). Uraemic bleeding: role of anaemia and beneficial effect of red cell transfusions. *Lancet*, ii, 1013–15.

Loge, J. P., Lange, R. D., and Moore, C. V. (1958). Characterization of the anemia associated with chronic renal insufficiency. *Am J Med*, 24, 4–18.

Macdougall, I. C. (2012). New anemia therapies: translating novel strategies from bench to bedside. *Am J Kidney Dis*, 59, 444–51.

Macdougall, I. C., Davies, M. E., Hallett, I., *et al.* (1991a). Coagulation studies and fistula blood flow during erythropoietin therapy in haemodialysis patients. *Nephrol Dial Transplant*, 6, 862–7.

Macdougall, I. C., Lewis, N. P., Saunders, M. J., *et al.* (1990b). Long-term cardiorespiratory effects of amelioration of renal anaemia by erythropoietin. *Lancet*, 335, 489–93.

Manzler, A. D. and Schreiner, A. W. (1970). Copper-induced acute hemolytic anemia. A new complication of hemodialysis. *Ann Intern Med*, 73, 409–12.

Maxwell, P. H., Osmond, M. K., Pugh, C. W., *et al.* (1993). Identification of the renal erythropoietin-producing cells using transgenic mice. *Kidney Int*, 44, 1149–62.

Maxwell, P. H., Wiesener, M. S., Chang, G. W., *et al.* (1999). The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature*, 399, 271–5.

Means, R. T. Jr. and Krantz, S. B. (1992). Progress in understanding the pathogenesis of the anemia of chronic disease. *Blood*, 80, 1639–47.

Moia, M., Mannucci, P. M, Vizzotto, L., *et al.* (1987). Improvement in the haemostatic defect of uraemia after treatment with recombinant human erythropoietin. *Lancet*, ii, 1227–9.

Movilli, E., Cancarini, G. C., Zani, R., *et al.* (2001). Adequacy of dialysis reduces the doses of recombinant erythropoietin independently from the use of biocompatible membranes in haemodialysis patients. *Nephrol Dial Transplant*, 16, 111–14.

Naets, J. P., Garcia, J. F., Tousaaint, G., *et al.* (1986). Radioimmunoassay of erythropoietin in chronic uraemia or anephric patients. *Scand J Haematol*, 37, 390–4.

Navarro, J. F. (2003). In the erythropoietin era, can we forget alternative of adjunctive therapies for renal anaemia management? The androgen example. *Nephrol Dial Transplant*, 18, 2222–6.

Neff, M. S., Goldberg, J., Slifkin, R. F., *et al.* (1981). A comparison of androgens for anemia in patients on hemodialysis. *N Engl J Med*, 304, 871–5.

Neff, M. S., Kim, K. E., Persoff, M., *et al.* (1971). Hemodynamics of uremic anemia. *Circulation*, 43, 867–83.

Orringer, E. P. and Mattern, W. D. (1976). Formaldehyde-induced hemolysis during chronic hemodialysis. *N Engl J Med*, 294, 1416–20.

Petrie, J. J. B. and Row, P. G. (1977). Dialysis anaemia was caused by subacute zinc toxicity. *Lancet*, i, 1178–80.

Richardson, D., Barlett, C., Goutcher, E., *et al.* (1999). Erythropoietin resistance due to dialysate chloramine: the two-way traffic of solutes in haemodialysis. *Nephrol Dial Transplant*, 14, 2625–7.

Rosenberger, C., Mandriota, S., Jurgensen, J. S., *et al.* (2002). Expression of hypoxia-inducible factor-1α and -2α in hypoxic and ischemic rat kidneys. *J Am Soc Nephrol*, 13, 1721–32.

Rosenmund, A., Binswanger, U., and Straub, P. W. (1975). Oxidative injury to erythrocytes, cell rigidity, and splenic hemolysis in hemodialysed uremic patients. *Ann Intern Med*, 82, 460–5.

Sawada, K., Krantz, S. B., Dessypris, E. N., *et al.* (1989). Human colony-forming units–erythroid do not require accessory cells, but do require direct interaction with insulin-like growth factor 1 and/or insulin for erythroid development. *J Clin Invest*, 83, 1702–9.

Schaefer, R. M., Teschner, M., and Kosch, M. (2002). Folate metabolism in renal failure. *Nephrol Dial Transplant*, 17 Suppl 5, 24–7.

Semenza, G. L. and Wang, G. L. (1992). A nuclear factor induced by hypoxia via *de novo* protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcription activation. *Mol Cell Biol*, 12, 5447–54.

Tan, C. C., Eckardt, K. -U., and Ratcliffe P. J. (1991). Organ distribution of erythropoietin messenger RNA in normal and uremic rats. *Kidney Int*, 40, 69–76.

Tan, C. C., Eckardt, K. -U., and Ratcliffe P. J. (1992). Feedback modulation of renal and hepatic erythropoietin messenger RNA in response to graded anemia and hypoxia. *Am J Physiol*, 263, F474–81.

Wiesener, M. S., Turley, H., Allen, W. E., *et al.* (1998). Induction of endothelial PAS domain protein-1 by hypoxia: characterization and comparison with hypoxia-inducible factor-1α. *Blood*, 92, 2260–8.

Winearls, C. G., Oliver, D. O., Pippard, M, J., *et al.* (1986). Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *Lancet*, ii, 1175–8.

Zappacosta, A. R., Caro, J., and Erslev, A. J. (1982). Normalization of hematocrit in patients with end-stage renal disease on continuous ambulatory peritoneal dialysis. *Am J Med*, 72, 53–7.

CHAPTER 124

Erythropoiesis-stimulating agents in chronic kidney disease

Iain C. Macdougall

Introduction

As discussed in Chapter 123, the major contributory factor to the pathogenesis of renal anaemia is an inappropriately low level of erythropoietin for the degree of anaemia. This was recognized in the 1970s, and it was postulated at that time that erythropoietin replacement therapy might be effective in the treatment of this condition. However, making therapeutic erythropoietin available was much more problematic than making insulin available for diabetics, and it was not until the advent of recombinant DNA technology that this became possible.

The first major breakthrough that laid the foundations for the large-scale production of therapeutic erythropoietin was the isolation of the protein from 2500 L of urine obtained from patients with aplastic anaemia who had normal kidney function. These patients produced very high levels of erythropoietin in response to their severe anaemia, and this allowed a few picograms of the human protein to be isolated (Miyake et al., 1977). Using a cDNA library, the gene for human erythropoietin was successfully isolated and cloned by Fuk-Kuen Lin and colleagues in the mid 1980s (Lin et al., 1985). A mammalian cell line (Chinese hamster ovary cells) was selected for the expression of this gene since, in contrast to recombinant insulin which could be produced in bacteria such as *Escherichia coli*, erythropoietin is a much more heavily glycosylated molecule that requires mammalian cells for its production. The large-scale synthesis of recombinant human erythropoietin in Chinese hamster ovary cells was begun, and there was remarkable fast-tracking of this product from bench to bedside. This was largely due to the realization that this was a breakthrough product that could potentially rescue dialysis patients from an existence of heavy transfusion dependence and iron overload. Groups of researchers on both sides of the Atlantic performed the first clinical trials of recombinant human erythropoietin (later named epoetin), and two seminal proof-of-concept studies were published in *The Lancet* and *The New England Journal of Medicine*, respectively (Winearls et al., 1986; Eschbach et al., 1987). Large-scale clinical trials of erythropoietin were initiated, and the first epoetins were licensed for clinical use in renal anaemia in 1999 (United States) and 1990 (Europe). Since then, two biotechnological modifications have been made to the erythropoietin molecule to produce agents with a longer duration of action, and this class of drugs became known as erythropoiesis-stimulating agents (ESAs). Darbepoetin alfa (Aranesp®) was the first of these two to appear, and this was followed by methoxypolyethylene glycol-epoetin beta (Mircera®). More recently, an erythropoietin-mimetic peptide has been licensed for clinical use in dialysis patients in the United States (peginesatide; Omontys®).

Epoetin

The first two recombinant human erythropoietins to be produced were epoetin alfa and epoetin beta. Both proved to be highly efficacious in correcting the anaemia associated with chronic kidney disease (CKD), and the majority of dialysis patients who were previously heavily transfusion dependent had a sustained increase in haemoglobin in response to this therapy. The usage of red cell transfusions in dialysis units fell dramatically, and transfusional iron overload was gradually replaced by a condition of iron deficiency as the iron became utilized in red cell production (Fig. 124.1).

As with other protein therapeutics, epoetin had to be injected, either intravenously or subcutaneously, and the circulating half-life of epoetin is around 6–8 hours (Macdougall et al., 1991). Thus, injections are usually given two or three times per week. Haemodialysis patients may receive the drug either intravenously or subcutaneously, whereas other CKD patients (peritoneal dialysis, kidney transplant recipients, and non-dialysis patients) receive the drug subcutaneously. A haemoglobin concentration usually shows a significant increase at around 2 weeks following initiation of treatment, although a reticulocyte response may be detected earlier (at around 3–4 days). Serum ferritin and other markers of iron status will often decline significantly by 1 month, and iron supplementation may be required (see Chapter 126). Titration of the epoetin dose is often required to maintain haemoglobin levels within the desired target range (see below).

The effects of epoetin therapy in the early days were so striking, and a large number of publications appeared, documenting the secondary benefits of a sustained increase in haemoglobin concentration (Table 124.1). These benefits were largely on the cardiovascular system, but also included improved physical capacity and quality of life. Improvements in platelet function and bleeding tendency, brain and cognitive function, skeletal muscle function, immunological response, endocrine and sexual function, and nutrition were all reported. Adverse effects in the early days were felt to be mild and treatable, such as an increase in blood pressure in up to 20% of patients, vascular access thrombosis, and occasional hyperkalaemia due to less efficient dialysis. Adjustment to dosing strategies rendered such adverse effects less common. Rather strangely, there were few randomized controlled trials of epoetin performed in

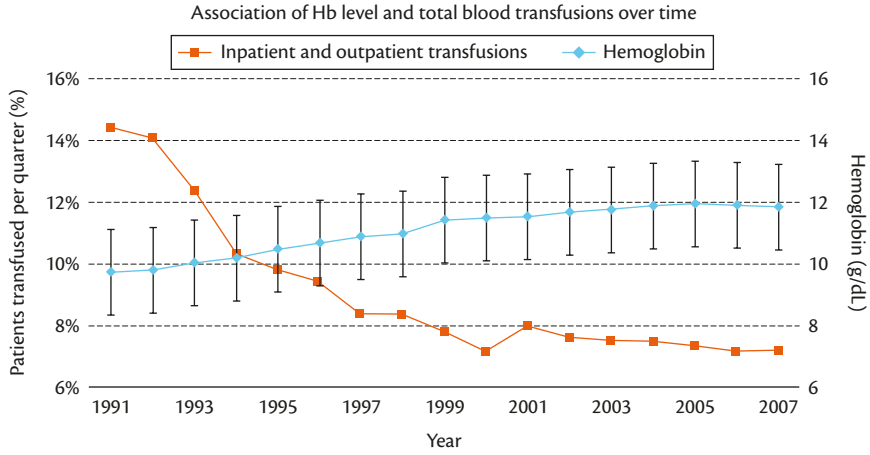


Fig. 124.1 Reduction in blood transfusions following the introduction of erythropoietin as a therapeutic agent.
From *USRDS 2009 Annual Data Report* (US Renal Data System, 2009).

the early days, one exception being the Canadian Erythropoietin Study Group, who conducted a double-blind, randomized, placebo-controlled trial of epoetin alfa in 118 haemodialysis patients with a haemoglobin of < 9 g/dL (Canadian Erythropoietin Study Group, 1990). The placebo group maintained a mean haemoglobin of 7.4 ± 1.2 g/dL, and the two active epoetin-treated groups achieved mean haemoglobin concentrations of 10.2 ± 1.0 and 11.7 ± 1.7 g/dL, respectively. Improvements in quality of life and exercise capacity were seen, although there was a significant increase in diastolic blood pressure in the epoetin-treated patients, who also had a higher rate of vascular access clotting (11 of 78 epoetin-treated patients versus 1 of 40 placebo-treated patients) (Canadian Erythropoietin Study Group, 1990). Larger randomized controlled trials were initiated to investigate whether normalizing anaemia completely (i.e. aiming for haemoglobin concentrations of around 14 or 15 g/dL) could provide additional benefits (discussed below under 'Target haemoglobin').

Biosimilar epoetins

The expiration of the patents for manufacturing epoetin a few years ago led to the development of new recombinant human erythropoietins. It became apparent though, in contrast to small-molecule 'generics', that complex biological molecules such as proteins could not be reproduced identically to the originator products. The European Medicines Agency took a lead in developing a regulatory pathway for the approval of these reproductions of the originator molecules, and the term 'biosimilar' was introduced to classify the nature of these products.

The regulatory pathway requires that biosimilar epoetins must have similar efficacy and safety to the originator epoetins, accepting that the molecular structure (in terms of glycosylation patterns), and physicochemical properties of the compound may be different from the originator molecules. Two distinct biosimilar epoetin molecules were approved in Europe, and were manufactured under five different brand names (Retacrit®, Silapo®, Binocrit®, Hexal®, and Abseamed®). All of these biosimilar epoetins have very similar pharmacokinetic and pharmacodynamic responses to the originator epoetins, and in some countries are considerably cheaper than the originators. While the efficacy is relatively easy to prove, the safety of the products is much harder, particularly the potential for increased immunogenicity. The development of antibodies against epoetin causing pure red cell aplasia (PRCA) (see below) may occur with all products, but there is a baseline incidence of around 1 in 1000 cases. Proving conclusively that the biosimilar epoetins do not have a higher incidence of PRCA requires large numbers of patients and longer term exposure than is usually possible at the time of approval. For this reason, the European Medicines Agency introduced a requirement for biosimilar epoetins to be subjected to increased pharmacovigilance via mandated surveillance registries.

Table 124.1 Secondary effects of anaemia correction

↑ brain/cognitive function	↓ angina
↑ endocrine function	↓ bleeding tendency
↑ exercise capacity	↓ cardiac output
↑ immune function	↓ depression
↑ muscle metabolism	↓ hospitalizations
↑ nutrition	↓ left ventricular hypertrophy
↑ quality of life	↓ transfusions
↑ sexual function	
↑ sleep patterns	

Darbepoetin alfa

As indicated above, the circulating half-life of epoetin is fairly short, at around 6–8 hours. For this reason, injections of the recombinant hormone have generally to be given two or three times a week, and since this is a long-term therapy (lifelong in patients unsuitable for kidney transplantation), efforts were directed at creating a longer-acting erythropoietic molecule. Experiments in mice conducted by Egrie and colleagues (Egrie et al., 1993) showed that the higher isomers of erythropoietin (those with a greater number of sialic acid residues) generated a more pronounced haemoglobin response compared with the lower isomers. This was due to a reduced clearance and longer half-life. Attempts were therefore

made to create a molecule with an even greater number of sialic acid residues, and to achieve this, an extra two glycosylation chains were required. Using site-directed mutagenesis, an epoetin analogue was created with five amino acid substitutions, and an additional two N-linked carbohydrate chains (Elliott et al., 2003). A pharmacokinetic study of darbepoetin alfa in peritoneal dialysis patients indicated an intravenous half-life of 25.3 hours compared with 8.5 hours for epoetin alfa (Macdougall et al., 1999). The half-life of this molecule following subcutaneous administration is also significantly prolonged, at around two- or threefold.

The molecule was initially named novel erythropoiesis stimulating protein (NESP), and later named darbepoetin alfa (Aranesp®). Darbepoetin alfa is still administered intravenously or subcutaneously, but the injections may be less frequent than for epoetin. Initial studies investigated the efficacy of once-weekly or once-every-2-weeks administration, and in some non-dialysis patients, dosing frequencies up to once monthly may be effective (Jadoul et al., 2004). However, for the majority of patients, once-weekly and once-every-alternate-week administration is optimal. Other than the pharmacokinetic properties and reduced dosing frequency, the biological effects of darbepoetin alfa would appear to be the same as for epoetin.

Methoxypolyethylene glycol-epoetin beta

The next strategy to prolong the biological action of erythropoietin to be investigated was pegylation of the molecule. Attaching a polyethylene glycol moiety to a protein is known to prolong its clearance from the circulation, and various pegylation chains of different chain lengths and different cross-linkage groups were investigated in both cell culture and animal models. The most active molecule was found to be a 30 kDa polyethylene glycol moiety integrated with epoetin via a succinimidyl butanoic acid (SBA) linkage group. This new molecule was initially called continuous erythropoietin receptor activator (CERA), and later termed methoxypolyethylene glycol-epoetin beta (Mircera®) (Curran et al., 2008). Pharmacokinetic studies in CKD patients indicated a very long half-life for this molecule, of around 130 hours both intravenously and subcutaneously (Macdougall et al., 2006). A comprehensive clinical trial development programme investigated dosing strategies of once-every-alternate-week and once-monthly administration, and it became clear that once-monthly dosing of this molecule was effective. Again, the biological effects and adverse event profile of methoxypolyethylene glycol-epoetin beta appears to be similar to that of the epoetins or darbepoetin alfa.

Peginesatide

Peginesatide is different from the previously discussed ESAs. It is an erythropoietin-mimetic peptide that shares the biological actions and molecular signalling characteristics of epoetin, but the molecule has no structural homology with the native or recombinant hormone.

The concept that a peptide could share functional mimicry with the erythropoietin protein was first reported by Wrighton and colleagues (Wrighton et al., 1996). The initial molecule to be assessed and characterized was erythropoietin-mimetic-peptide-1 (EMP-1). EMP-1 was shown to bind to the erythropoietin receptor, evoke an identical intracellular signalling cascade involving the JAK2/STAT-5 pathway. It promotes increased proliferation of both erythroleukaemic and primary bone marrow cells, and results in increased erythropoiesis in animals. Unfortunately, its biological potency was considered inadequate to justify further development of EMP-1 per se.

Peginesatide is, however, a similar molecule, but is dimerized and pegylated to prolong its biological activity. A pegylation chain is attached to the dimeric peptide spacer-linker (Fig. 124.2). As with EMP-1, peginesatide has the same biological actions as erythropoietin, as shown in extensive cell and animal experiments (Fan et al., 2006). Since then, phase 1 (Stead et al., 2006), phase 2 (Macdougall et al., 20011, and phase 3 (Fishbane et al., 2013; Macdougall et al., 2013) studies have been successfully completed, testing the erythropoietic activity of peginesatide administered once-monthly intravenously or subcutaneously. In contrast to epoetin, darbepoetin alfa, and methoxypolyethylene glycol-epoetin beta, peginesatide is manufactured by synthetic peptide chemical techniques rather than using recombinant DNA technology. Like methoxypolyethylene glycol-epoetin beta, it appears to be effective with once-monthly administration. It is also immunologically distinct from the other ESAs, in that anti-peginesatide antibodies do not cross-react with erythropoietin, and similarly anti-erythropoietin antibodies do not cross-react with peginesatide. This characteristic has been used to treat patients who have developed PRCA due to anti-erythropoietin antibodies from the protein-based ESAs. Thus, peginesatide can rescue such patients who would otherwise be transfusion dependent, allowing ongoing stimulation of erythropoiesis despite the presence of anti-erythropoietin antibodies (Macdougall et al., 2009).

The phase 3 clinical studies were subjected to a detailed safety assessment, including a composite cardiovascular safety endpoint. Overall non-inferiority of peginesatide with the comparator ESAs (epoetin for dialysis patients; darbepoetin alfa for non-dialysis patients) was achieved, but somewhat unexpectedly, the subgroup analysis of the non-dialysis patients indicated a 32% higher

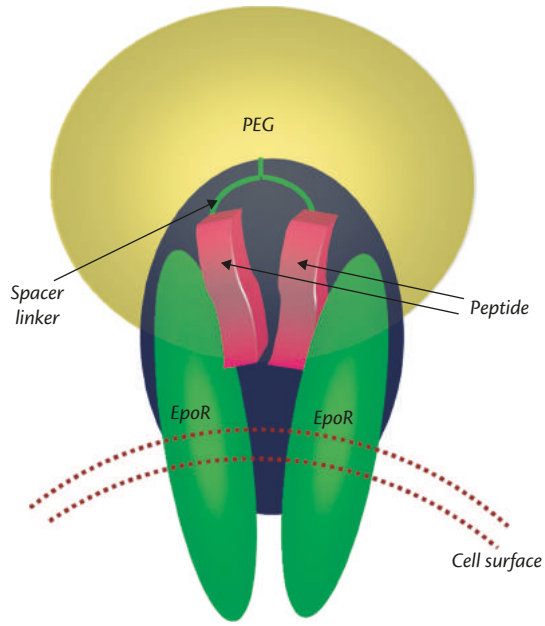


Fig. 124.2 Schematic representation of the peginesatide (Hematide®; Omontys®) molecule.

incidence of the composite safety endpoint compared to darbepoetin alfa (Macdougall et al., 2013). This was not seen in the dialysis patients (Fishbane et al., 2013), and peginesatide was then licensed for treating anaemia in dialysis patients in the United States, under the brand name of Omontys®. Unfortunately, within 1 year of launching the product, the manufacturers of peginesatide had to withdraw the product from the market due to life-threatening anaphylactic reactions, several of them fatal (US Food and Drug Administration, 2013).

Normal Hematocrit Trial, CREATE, CHOIR, and TREAT

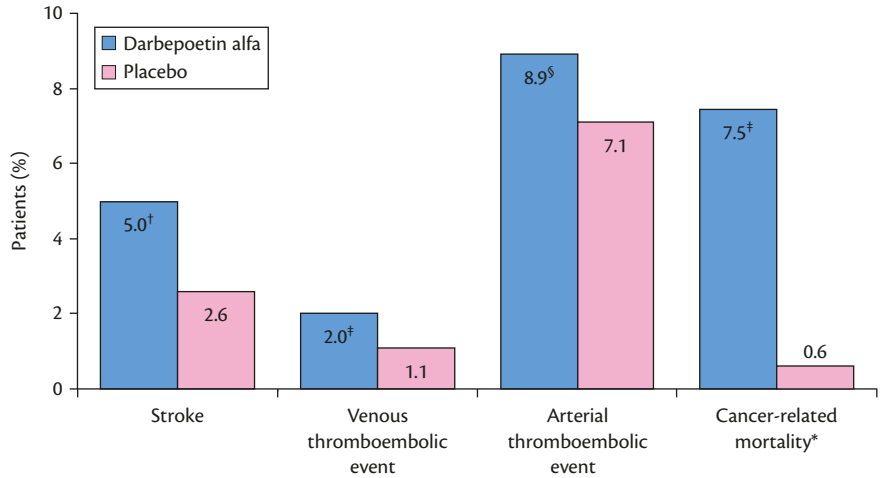
Four large randomized controlled trials of ESA therapy have hugely influenced anaemia management in CKD (Besarab et al., 1998; Drüeke et al., 2006; Singh et al., 2006; Pfeffer et al., 2009). The first of these was the *Normal Hematocrit Trial* conducted in US haemodialysis patients receiving epoetin alfa, randomized to a haemoglobin concentration of around 14 g/dL versus a haemoglobin concentration of around 10 g/dL (Besarab et al., 1998). Observational data had suggested that a higher haemoglobin might improve survival and cardiovascular events, and the primary endpoint in the study was a composite of death and first non-fatal myocardial infarction. Their study was stopped prematurely at 29 months. At this point, there was a higher incidence of vascular access thrombosis, a suggestion of a higher incidence of death or non-fatal myocardial infarction, and a threefold greater dose requirement for epoetin in patients randomized to the higher haemoglobin arm. The patients recruited to this trial, however, were a highly co-morbid group with heart failure and/or diabetes, and it was not clear at that time whether a higher haemoglobin might also be harmful in less co-morbid haemodialysis patients or even non-dialysis patients (Besarab et al., 1998).

Three further randomized controlled trials, in non-dialysis patients, however, have made it very clear that there are safety concerns associated with normalizing haemoglobin with ESA therapy in CKD patients. The *CREATE* study showed no difference in the primary composite cardiovascular endpoint between the group of patients randomized to target a haemoglobin of between 13 and 15 g/dL versus the control group targeting a haemoglobin of between 10.5 and 11.5 g/dL (Drüeke et al., 2006). Furthermore, the higher haemoglobin group had an earlier initiation of renal replacement therapy.

The *CHOIR* study randomized a group of 1432 non-dialysis patients in the United States to a target haemoglobin of 13.5 versus 11.3 g/dL (Singh et al., 2006). There were a greater number of events (composite of death, myocardial infarction, stroke, and hospitalization for heart failure) in the higher haemoglobin group ($P = 0.03$) as well as a non-statistically-significant higher death rate in the patients randomized to the higher haemoglobin target (Singh et al., 2006).

The study with the greatest impact, however, has been the *TREAT* study (Pfeffer et al., 2009). This was a randomized, double-blind, placebo-controlled trial in 4038 non-dialysis CKD patients. The first group was randomized to target a haemoglobin of 13 g/dL with darbepoetin alfa, while the second group received placebo, being rescued only if their haemoglobin concentration fell below 9 g/dL. Targeting a higher haemoglobin concentration showed a significant reduction in the use of blood transfusions, but only a fairly modest improvement in quality of life (Pfeffer et al., 2009).

Furthermore, TREAT failed to show a reduction in time to death or a cardiovascular event (myocardial infarction, congestive heart failure or stroke) or end-stage renal disease. Among the components of the primary cardiovascular composite endpoint, the risk of venous and arterial thromboembolism improved significantly, and the risk of stroke increased by twofold in patients targeting the higher haemoglobin (5% vs 2.6%; hazard ratio 1.92; 95% CI 1.38–2.68) (Fig. 124.3). Furthermore, in patients with a history of malignancy at baseline, there was a > 10-fold increased rate of death from cancer (7.4% vs 0.6%; $P = 0.02$) (Pfeffer et al., 2009 (Fig. 124.3).



†, P < 0.001 versus placebo
‡, P = 0.02 versus placebo
§, P = 0.04 versus placebo
*Amongst patients with a history of malignancy at baseline

Fig. 124.3 Safety concerns in the TREAT Study.
Source data from Pfeffer et al. (2009).

Results from all of these four studies taken as a whole do not suggest significant benefits in targeting a higher haemoglobin concentration, and suggest possible harm. This has led to more conservative recommendations regarding the management of renal anaemia with ESA therapy in the United Kingdom (National Institute for Health and Clinical Excellence (NICE), 2011), Europe (Locatelli et al., 2013), and globally (National Kidney Foundation, 2012).

Practical aspects of erythropoiesis-stimulating agent use

Trigger haemoglobin

The results of the TREAT study suggested that many non-dialysis patients with advanced renal impairment do not have as rapid a fall in haemoglobin concentration as was previously thought. Thus, many patients randomized to the placebo group were able to continue with a haemoglobin of around 9–10 g/dL for considerable periods of time. Whereas, previously, a trigger for the introduction of ESA therapy was a haemoglobin of < 11 g/dL, this has now been largely reduced to < 10 g/dL. Indeed, the Kidney Disease: Improving Global Outcomes (KDIGO) Anaemia Management Guideline 2012 suggests that ESA therapy should be introduced somewhere around 9 or 10 g/dL, with the aim of preventing patients falling below 9 g/dL (National Kidney Foundation, 2012). Intervening at a later stage appears to increase transfusion use, and this too carries risk, particularly in patients considering future kidney transplantation.

Target haemoglobin concentration

Likewise, the randomized controlled trials have hugely influenced the target haemoglobin concentration. It is now recognized that targeting a haemoglobin > 13g/dL confers more risks than benefits, and the current anaemia guidelines advise against this. The UK NICE Anaemia Guideline update from February 2011 suggests a haemoglobin target of between 10 and 12 g/dL. The KDIGO anaemia management guideline 2012 suggests that 'ESAs should not be used to maintain a haemoglobin concentration above 11.5 g/dL' (National Kidney Foundation, 2012). The US Food and Drug Administration's response to ESA therapy is to stipulate less emphasis on target haemoglobin and greater focus on using ESA therapy to avoid blood transfusion.

Table 124.2 Causes of hyporesponsiveness to erythropoiesis-stimulating agent therapy

Common	Iron deficiency
	Infection/inflammation
	Underdialysis
Less common	Blood loss
	Hyperparathyroidism
	Aluminium toxicity
	Vitamin B_{12}/folate deficiency
	Haemolysis
	Bone marrow disorders
	Haemoglobinopathies
	Angiotensin converting enzyme inhibitors
	Carnitine deficiency
	Obesity (in subcutaneous administration)
	Anti-EPO antibodies (pure red cell aplasia)

Resistance to ESA therapy

A small proportion of patients will exhibit a suboptimal response to ESA therapy (Johnson et al., 2007). This may be manifest by a failure to show an increase in haemoglobin concentration despite repeated increases in ESA dose. Alternatively, the patient might have previously shown a response to treatment, and subsequently developed resistance.

The causes of hyporesponsiveness to ESA therapy are listed in Table 124.2. Common causes include iron deficiency, infection or inflammation, and underdialysis. Less common causes include blood loss, vitamin B_{12} or folate deficiency, haemolysis, primary bone marrow disorders, haemoglobinopathies, and antibody-mediated PRCA. Investigating a patient who is responding suboptimally to ESA therapy demands a stepwise approach (Fig. 124.4). If a patient is self-injecting, compliance with therapy should be questioned and confirmed. The reticulocyte count may give some indication of whether there is a primary problem with erythropoiesis, or whether the bone marrow is producing adequate numbers of red cells, but their survival is reduced as a result of bleeding or haemolysis.

The possibility of either absolute or functional iron deficiency should be entertained (see Chapter 126), and a trial of intravenous iron may be indicated. A raised C-reactive protein may suggest underlying infection or inflammation, and this should be vigorously investigated. Occult conditions should as tuberculosis or malignancy may prove somewhat elusive. An increase in dialysis prescription, and/or a change from conventional haemodialysis to haemodiafiltration may be of benefit. Screening for vitamin B_{12} or folate deficiency, occult bleeding, or haemolysis may be indicated. A sharp fall in haemoglobin coupled with a very low reticulocyte count should alert the physician to the very rare condition of antibody-mediated PRCA. Bone marrow examination may be required to exclude some haematological conditions such as myelodysplastic syndrome. A higher reticulocyte count makes it more likely that bleeding or haemolysis is the cause, and a full haemolysis screen and possible gastrointestinal investigations may be indicated.

Whereas, previously, physicians tended to escalate the dose of ESA therapy to higher levels, the randomized controlled trials reported above have suggested that this practice may be harmful. It is not clear whether the poor outcomes in ESA-resistant patients are due to higher doses of ESA therapy per se, or whether this simply represents a group of sicker patients. Nevertheless, repeated dose escalation in ESA-resistant patients is no longer generally advised, although all recent anaemia guidelines recommend individualization of therapy with tailoring of the anaemia management strategy to the individual patient.

Adjuvant therapy

From the earliest days of ESA use, it became clear that intravenous iron supplementation enhanced the response to epoetin therapy, and allowed lower doses to be used. It became rapidly apparent that an inadequate iron supply to the bone marrow was a rate-limiting step in the process of erythropoiesis. Over the years, several other adjuvant therapies have been studied to ascertain whether similar results could be seen with these agents. The studies included

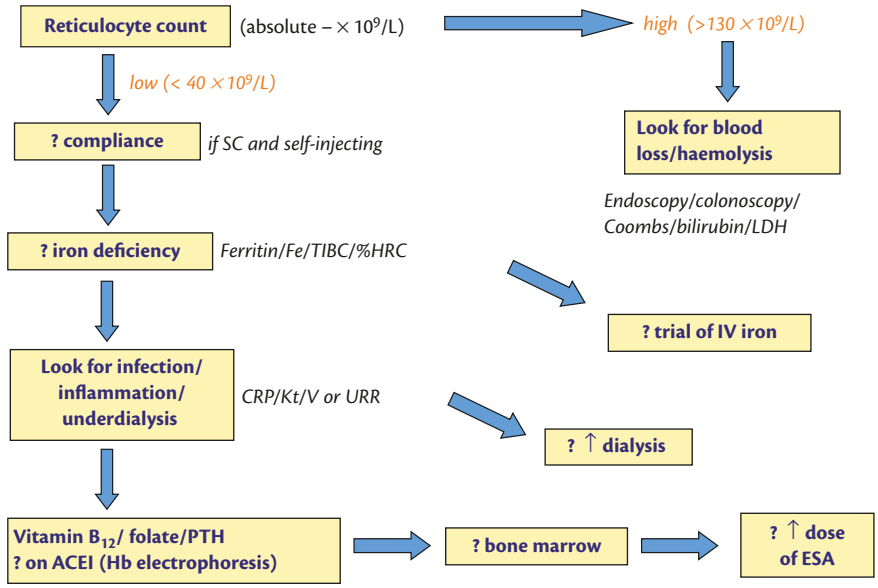


Fig. 124.4 Investigation of hyporesponsiveness to erythropoiesis-stimulating agent therapy. ACEI = angiotensin-converting enzyme inhibitors; CRP = C-reactive protein; ESA = erythropoiesis-stimulating agent; Hb = haemoglobin; PTH = parathyroid hormone; URR = urea reduction ratio.

trials of vitamin C and E supplementation, as well as vitamin B_{12} and folate supplementation, L-carnitine supplementation, androgens, and pentoxifylline. Some of these studies were conducted in a placebo-controlled, double-blind fashion (e.g. carnitine), but the cohorts in all studies were small and the studies have not been of a high enough calibre to influence clinical practice guidelines or support the use of any of these adjuvants in the routine management of renal anaemia. There may, however, be individual instances when these adjuvants could be considered, and particularly if there is evidence of vitamin B_{12} or folate insufficiency in any patient, then the deficient vitamin should be supplemented.

Antibody-mediated pure red cell aplasia

A very rare complication of ESA therapy is the development of PRCA caused by anti-erythropoietin antibodies (Rossert et al., 2004). These antibodies not only neutralize the therapeutically administered ESA, but also the remaining endogenous erythropoietin in the CKD patient (Schellekens, 2008). Thus, there is almost complete shutdown of red cell production in the bone marrow, and the patient usually becomes transfusion dependent. The condition is characterized by a fairly rapid fall in haemoglobin concentration in a patient receiving ESA therapy, associated with a dramatic reduction in reticulocyte count (usually to < 20 × 10^9/L). A bone marrow examination will show absence or near-absence of erythroid progenitor cells, and a test for anti-erythropoietin antibodies will be positive.

In 2002, there was an 'epidemic' of cases of antibody-mediated PRCA, largely associated with a specific formulation of epoetin alfa (Eprex®; Erypo® in Germany). This evoked a root cause analysis, and it seemed likely that a number of factors may be responsible, including subcutaneous administration of epoetin alfa, a break in the cold storage chain, and increased immunogenicity to leachates in the rubber stoppers of the syringes (Boven et al., 1996). Discontinuation of the use of rubber stoppers appears to have reduced the incidence of this complication, although a low background incidence of antibody-mediated PRCA remains, at approximately 1 in 100,000 cases.

Treatment of this condition requires immediate cessation of the current ESA, red cell transfusional support as required, and possible measures to reduce anti-erythropoietin antibody formation. Thus, a number of immunosuppressive therapeutic regimens have been suggested, including steroids, cyclophosphamide, and ciclosporin (Verhelst et al., 2004). More recently, a small proof-of-concept study of administering peginesatide to patients suffering from this condition suggests that this treatment is effective (Macdougall et al., 2009).

A recent clinical trial of a biosimilar epoetin alfa, administered subcutaneously, detected two possible cases of PRCA, and again a detailed root cause analysis was initiated (Haag-Weber et al., 2012). This revealed the possibility that tungsten in the syringe was causing dimerization of the epoetin molecule, which in turn was increasing its immunogenicity (Seidl et al., 2012).

The future of erythropoiesis-stimulating agent therapy

Other strategies for enhancing erythropoietic activity have been investigated as a means of generating future treatments for anaemia (Macdougall, 2012). These include stabilization of hypoxia-inducible factor (HIF stabilizers), erythropoietin gene therapy, modulators of hepcidin activity (see Chapter 126), and inhibition of GATA-2.

Of these, the most advanced is the stabilization of HIF activity. This involves inhibition of a prolyl hydroxylase enzyme that is responsible for the degradation of HIF. Since HIF is the major transcription factor for upregulation of the erythropoietin gene, prolyl hydroxylase inhibition will enhance HIF activity, and in turn upregulate erythropoietin production (Bernhardt et al., 2010) (see Chapter 123 for molecular mechanisms).

A number of candidate HIF stabilizers are in phase 1, 2, and 3 clinical trials. They are normally administered once daily or three times a week, and the main advantage of these agents is that they are orally active. Thus, instead of patients having to receive regular injections of ESAs, the HIF stabilizers would allow the patients to increase their own endogenous erythropoietin production. It would appear also that these agents are potentially effective in anephric patients (Bernhardt et al., 2010), and it is assumed that, in such cases, the increased production of erythropoietin is occurring in the liver. One potential limitation of this strategy, however, is that there are many other hypoxia-sensitive genes that may be upregulated by stabilization of HIF. These include genes involved in angiogenesis, gluconeogenesis, and connective tissue synthesis. The results of the ongoing clinical trials of these agents will determine their potential role in the management of renal anaemia.

References

Bernhardt, W. M., Wiesener, M. S., Scigalla, P., *et al.* (2010). Inhibition of prolyl hydroxylases increases erythropoietin production in ESRD. *J Am Soc Nephrol*, 21, 2151–6.

Besarab, A., Bolton, W. K., Browne, J. K., *et al.* (1998). The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*, 339, 584–90.

Boven, K., Stryker, S., Knight, J., *et al.* (2005). The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. *Kidney Int*, 67, 2346–53.

Canadian Erythropoietin Study Group (1990). Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. *Br Med J*, 300, 573–8.

Curran, M. P. and McCormack, P. L. (2008). Methoxy polyethylene glycol-epoetin beta: a review of its use in the management of anaemia associated with chronic kidney disease. *Drugs*, 68, 1139–56.

Drüeke, T. B., Locatelli, F., Clyne, N., *et al.* (2006). Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*, 355, 2071–84.

Egrie, J. C., Grant, J. R., Gillies, D. K., *et al.* (1993). The role of carbohydrate on the biological activity of erythropoietin. *Glycoconj J*, 10, 263.

Elliott, S., Lorenzini, T., Asher, S., *et al.* (2003). Enhancement of therapeutic protein in vivo activities through glycoengineering. *Nat Biotechnol*, 21, 414–21.

Eschbach, J. W., Egrie, J. C., Downing, M. R., *et al.* (1987). Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med*, 316, 73–8.

Fan, Q., Leuther, K. K., Holmes, C. P., *et al.* (2006). Preclinical evaluation of Hematide, a novel erythropoiesis stimulating agent, for the treatment of anemia. *Exp Hematol*, 34, 1303–11.

Fishbane, S., Schiller, B., Locatelli, F., *et al.* (2013). Peginesatide in patients with anemia undergoing hemodialysis. *N Engl J Med*, 368, 307–19.

Haag-Weber, M., Eckardt, K. U., Hörl, W. H., *et al.* (2012). Safety, immunogenicity and efficacy of subcutaneous biosimilar epoetin-α (HX575) in non-dialysis patients with renal anemia: a multi-center, randomized, double-blind study. *Clin Nephrol*, 77, 8–17.

Jadoul, M., Vanrenterghem, Y., Foret, M., *et al.* (2004). Darbepoetin alfa administered once monthly maintains haemoglobin levels in stable dialysis patients. *Nephrol Dial Transplant*, 19, 898–903.

Johnson, D. W., Pollock, C. A., and Macdougall, I. C. (2007). Erythropoiesis-stimulating agent hyporesponsiveness. *Nephrology (Carlton)*, 12, 321–30.

Lin, F. K., Suggs, S., Lin, C. H., *et al.* (1985). Cloning and expression of the human erythropoietin gene. *Proc Natl Acad Sci U S A*, 82, 7580–4.

Locatelli, F., Bárány, P., Covic, A., *et al.* (2013). Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. *Nephrol Dial Transplant*, 28(6), 1346–59.

Macdougall, I. C. (2012). New anemia therapies: translating novel strategies from bench to bedside. *Am J Kidney Dis*, 59, 444–51.

Macdougall, I. C., Gray, S. J., Elston, O., *et al.* (1999). Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients. *J Am Soc Nephrol*, 10, 2392–5.

Macdougall, I. C., Provenzano, R., Sharma, A., *et al.* (2013). Peginesatide for anemia in patients with chronic kidney disease not receiving dialysis. *N Engl J Med*, 368, 320–32.

Macdougall, I. C., Roberts, D. E., Coles, G. A., *et al.* (1991). Clinical pharmacokinetics of epoetin (recombinant human erythropoietin). *Clin Pharmacokinet*, 20, 99–113.

Macdougall, I. C., Robson, R., Opatrna, S., *et al.* (2006). Pharmacokinetics and pharmacodynamics of intravenous and subcutaneous continuous erythropoietin receptor activator (C.E.R.A.) in patients with chronic kidney disease. *Clin J Am Soc Nephrol*, 1, 1211–15.

Macdougall, I. C., Rossert, J., Casadevall, N., *et al.* (2009). A peptide-based erythropoietin-receptor agonist for pure red-cell aplasia. *N Engl J Med*, 361, 1848–55.

Macdougall, I. C., Wiecek, A., Tucker, B., *et al.* (2011). Dose-finding study of peginesatide for anemia correction in chronic kidney disease patients. *Clin J Am Soc Nephrol*, 6, 2579–86.

Miyake, T., Kung, C. K., and Goldwasser, E. (1977). Purification of human erythropoietin. *J Biol Chem*, 252, 5558–64.

National Institute for Health and Clinical Excellence (2011). *Anaemia Management in People with Chronic Kidney Disease*. [Online] [Updated November 2012] <http://guidance.nice.org.uk/CG114>.

National Kidney Foundation (2012). KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl*, 2, v–335.

Pfeffer, M. A., Burdmann, E. A., Chen, C. Y., *et al.* (2009). A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*, 361, 2019–32.

Rossert, J., Casadevall, N., and Eckardt, K. U. (2004). Anti-erythropoietin antibodies and pure red cell aplasia. *J Am Soc Nephrol*, 15, 398–406.

Schellekens, H. (2008). Recombinant human erythropoietins, biosimilars and immunogenicity. *J Nephrol*, 21, 497–502.

Seidl, A., Hainzl, O., Richter, M., *et al.* (2012). Tungsten-induced denaturation and aggregation of epoetin alfa during primary packaging as a cause of immunogenicity. *Pharmaceut Res*, 29, 1454–67.

Singh, A. K., Szczech, L., Tang, K. L., *et al.* (2006). Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*, 355, 2085–98.

Stead, R. B., Lambert, J., Wessels, D., *et al.* (2006). Evaluation of the safety and pharmacodynamics of Hematide, a novel erythropoietic agent, in a phase 1, double-blind, placebo-controlled, dose-escalation study in healthy volunteers. *Blood*, 108, 1830–4.

US Food and Drug Administration (2013). *Affymax and Takeda Announce a Nationwide Voluntary Recall of All Lots of OMONTYS® (peginesatide) Injection*. [Online] <http://www.fda.gov/Safety/Recalls/ucm340893.htm>

US Renal Data System (2009). *USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Verhelst, D., Rossert, J., Casadevall, N., *et al.* (2004). Treatment of erythropoietin-induced pure red cell aplasia: a retrospective study. *Lancet*, 363, 1768–71.

Winearls, C. G., Oliver, D. O., Pippard, M. J., *et al.* (1986). Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *Lancet*, ii, 1175–8.

Wrighton N. C., Farrell, F. X., Chang, R., *et al.* (1996). Small peptides as potent mimetics of the protein hormone erythropoietin. *Science*, 273, 458–64.

CHAPTER 125

Iron metabolism in chronic kidney disease

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Iron biology: an overview

Iron is the most abundant transition metal in the human body and the fourth most common element in the earth's crust. During the history of the planet and the evolution of the living organism, the abundance, availability, and suitability of iron have been critical to life. When life first evolved on earth, the atmosphere was believed to have been anoxic; subsequently there was a transition to the aerobic atmosphere of today due to the presence of photosynthetic bacteria. Ferrous iron (Fe(II)) is stable under anoxic conditions and does not auto-oxidize; with a change into aerobic conditions, Fe(II) can react with environmental oxygen, causing production of hydroxyl radicals. Thus, iron is paradoxical, in the sense that it is at the same time an essential element for growth and survival to any form of life (primarily to ensure the transport of oxygen and to catalyse reactions of electron transfer, nitrogen fixation, or DNA synthesis), but it is also toxic to cells due to its ability to catalyse free radical generation. Hence, all living organisms evolved sophisticated mechanisms to maintain appropriate iron levels in their cells and within their body. Such living organisms developed many proteins to convey iron in biological fluids or through cellular membranes, and to store it in a non-toxic and easy mobilizable form. Additionally, the absence of a physiological excretion mechanism requires iron homeostasis in the organism to be regulated by iron absorption from the intestine and the recycling of iron from senescent red blood cells (Roy and Enns, 2000; Philpott, 2002). Thus, the regulation of iron metabolism involves the interaction between a number of specific proteins as well as the interplay between iron absorption and iron loss (Beaumont et al., 2009). Intestinal iron absorption is modulated in response to the level of the body iron stores and by the amount of iron needed for erythropoiesis. This regulation is thought to operate through two control mechanisms: store regulators and erythroid regulators.

Proteins involved in iron metabolism

The critical proteins involved in iron homeostasis include transferrin (usually measured in the laboratory as the total iron binding capacity (TIBC)), transferrin receptor, and ferritin (the cellular storage protein for iron and an acute phase reactant (Bridges and Seligman, 1995)). The newest proteins known to be involved in iron metabolism are described in Table 125.1 and include among others the iron responsive element-binding protein (IRE-BP), divalent metal transporter, SFT (a stimulator of iron transport), ferroportin and hephaestin, hepcidin, (Ganz, 2003; Beaumont et al., 2009), haemojuvelin (HJV) (Lin et al., 2005)), bone morphogenetic protein 6 (BMP6), (Andriopoulos et al., 2009), and matriptase-2 (TMPRSS6), (Truksa et al., 2009). Similarly, mutations in the human *TMPRSS6* gene have been identified in patients with iron-refractory iron deficiency anaemia—so-called IRIDA (Silvestri et al., 2008). IRIDA is associated with severe microcytosis, whereas the anaemia of chronic disease (ACD) is typically normocytic. In IRIDA, high serum ferritin and low transferrin saturation (TSAT) are typical findings, even after parenteral iron treatment.

Although the fact that enhanced erythropoiesis increases iron absorption regardless of body iron loading has been known for a long time, the sensors of the erythropoietic state are only just beginning to be understood. Three proteins (erythropoietin (EPO), growth differentiation factor 15 (GDF15), and twisted gastrulation (TWSG1)) participate in this process. GDF15 is a family member of the transforming growth factor-β superfamily and is secreted by haemoglobinized erythroblasts during the final stages of erythropoiesis. Elevated serum GDF15 correlates with decreased hepcidin and increased iron absorption in patients with β-thalassaemia (Tanno et al., 2007), or refractory anaemia with ring sideroblasts (Ramirez et al., 2009). All these patients have defective erythroid expansion. *In vitro* studies demonstrate a suppressive effect of GDF15 on hepcidin expression (Tanno et al., 2007). Interestingly, a more recent study shows that GDF15 expression is negatively regulated by intracellular iron levels independent of hypoxia-inducible factor (HIF) and IRP activation (Lakhal et al., 2009). These findings are of interest because they are consistent with previous proposals that erythropoiesis is positively linked to intestinal iron absorption and storage iron mobilization, and that the erythroid factor dominantly suppresses hepcidin expression in spite of iron overload. The liver is the key organ in iron metabolism, being the main site of hepcidin synthesis as well as the primary iron storage organ. An important part of this process related to the transcriptional control of hepcidin biosynthesis occurs at the hepatocyte plasma membrane. Almost all the key factors in iron metabolism mentioned earlier, are synthesized in the liver. The BMP/HJV pathway (Babitt et al., 2006; Andriopoulos et al., 2009) whose central component is the glycosylphosphatidylinositol (GPI)-anchored protein HJV encoded by the *HFE2* gene (Papanikolaou et al., 2004) is the key signalling pathway that regulates *HAMP* gene expression in response to liver iron stores. Firstly, transcriptional activation of BMP6 expression (Kautz

Table 125.1 Proteins involved in iron metabolism

Protein	Function
Transferrin (Tf)	Plasma iron transporter
Transferrin receptor (TfR)	With a specific membrane receptor, delivering iron into the cells through interaction between this receptor and transferrin
Ferritin (Ft)	Iron storage protein and an acute phase reactant
Iron responsive element-binding protein (IRE-BP)	Intracellular reporter of iron status
Iron regulatory protein 1 and 2 (IRP1 and IRP2)	Cellular iron sensing proteins
Divalent metal transporter 1 (DMT1, Nramp2, DCT1, Solute carrier family 11, member 2 (Slc11a2))	Duodenal iron transporter
SFT (a stimulator of Fe transport),	Transport protein that has been found to facilitate uptake of iron presented to cells as either Fe(II) or Fe(III)
Ferroportin (Ireg1, Slc11a2, Mtp1),	Cellular iron exporter
Hephaestin	Likely cooperates with ferroportin for exporting iron to transferrin
TFR2	Mutations of which are responsible for a rare form of hereditary hemochromatosis
Haemojuvelin, (HJV, HFE2, hemochromatosis 2 gene, RGMc: repulsive guidance molecule C)	A hepcidin regulator, mutations of which are responsible for the common form of juvenile hemochromatosis; inhibit bone morphogenetic protein-Smad-mediated signalling required for effective hepcidin transcription
Hepcidin	The key negative regulator of intestinal iron absorption as well as macrophage iron release
BMP-6	Role in regulation of hepcidin gene transcription
Smad pathway	Role in regulation of hepcidin gene transcription
Tmprss6 (matriptase)	Cleaves HJV on the plasma membrane, resulting in hepcidin inhibition by blocking the BMP/HJV activating pathway
GDF-15	Member of the TGF-β superfamily, secreted by haemoglobinized erythroblasts during the final stages of erythropoiesis, GDF15 expression is negatively regulated by intracellular iron levels

et al., 2008) initiates the signalling cascade which ultimately leads to hepcidin secretion by the hepatocyte. BMP6, produced probably by non-parenchymal liver cells (Zhang et al., 2001), subsequently binds to HJV at the extracellular side of the hepatocyte membrane, resulting in effective interaction of BMP6 with its transmembrane receptors. HJV thus serves as a BMP6 co-receptor. Therefore, the BMP/HJV pathway is now regarded as the main pathway controlling *HAMP* expression in response to liver iron levels. In addition, matriptase-2, a membrane-bound serine protease, by cleaving HJV, is proposed to remove a crucial constituent of the BMP/HJV pathway from the membrane, and thus decrease *HAMP* expression.

Iron in health

Iron absorption from the diet

The total iron content of the normal human organism is about 3–4 g (most if it being contained in haemoglobin in circulating erythrocytes: approximately 2.5 g). Smaller amounts are found in iron-containing proteins, such as myoglobin, cytochromes, catalase (about 400 mg), and bound to transferrin (3–7 mg) (Brittenham, 1995). The remainder is storage iron in the form of ferritin or haemosiderin. The daily iron requirement for erythropoiesis is about 20–25 mg. It comes largely from macrophages, which have phagocytosed senescent erythrocytes (Andrews, 2005). This process makes it possible to recycle approximately 25–30 mg of iron per day, which corresponds to the daily requirement of iron for erythropoiesis (Fig. 125.1). In men, the storage pool of iron is about 1 g (mainly in the liver, spleen, and bone marrow). Due to iron losses with blood during menstruation, deliveries, pregnancies, etc., adult women have lower iron storage. In food, iron is found in two basic forms: inorganic iron (both Fe(II) and Fe(III)) and haem, where iron is complexed to protoporphyrin IX. In an average diet, inorganic iron accounts for approximately 90% of total dietary iron (Anderson et al., 2005). The typical Western diet contains about 15 mg of iron. About 30% of this haem iron is promptly absorbed (Cook, 1982; Finch and Huebers, 1982). In the developed world, with relatively high meat consumption, more than half of all absorbed iron comes from the haem in haemoglobin or myoglobin in dietary meats. Inorganic iron, mainly from plant sources and accounting for almost all iron in the non-Western diet, is poorly absorbed. Less than 10% is taken up by mucosal cells. An alternative iron source comes from pharmaceutical iron supplements such as Fe(II) compounds. Haem iron is the most bioavailable iron, and its absorption remains unaffected by the diet composition. Diet-rich haem iron (i.e. in fish, poultry, and meat) contains more bioavailable iron than a vegetarian diet (30% versus 10%). Inorganic iron absorption is dependent on other dietary components. Non-animal sources of iron (i.e. cereals, breads, fruits, and vegetables) are absorbed better in the presence of ascorbic acid, which increases bioavailability by promoting the reduction of Fe(III) to soluble Fe (II)), whereas teas (rich in tannates), bran foods rich in phosphates, and phytates inhibit iron absorption because they form insoluble complexes. In addition, stomach acidity enhances the solubility of inorganic iron. The intestinal absorption of iron from the duodenal villi is about 1–2 mg per day (i.e. 30% of 1–2 mg of haem iron in the Western diet and about 10% of 10–15 mg of non-haem iron). This makes it possible to compensate for losses, resulting mainly from the exfoliation of epithelial cells. Thus, iron homeostasis is regulated strictly at the level of intestinal absorption (Figs 125.2 and 125.3). Iron regulation is finely tuned at the level of intestinal absorption to avoid iron overload since there is no means to eliminate any iron absorbed in excess.

Iron is essential for cell metabolism and growth, and is distributed between three compartments in the cell, the transit pool, the storage pool, and the functional pool. The intracellular transit pool is often called the 'labile iron pool', and its exact chemical nature remains uncertain, although it has been suggested that iron(II) glutathione is a dominant component (Handelman and Levin, 2008). The main storage compartment is cytosolic ferritin, from which iron can be mobilized as and when required. The functional iron pool can be divided into extra-mitochondrial and mitochondrial functional iron, the organelle in which haem synthesis and

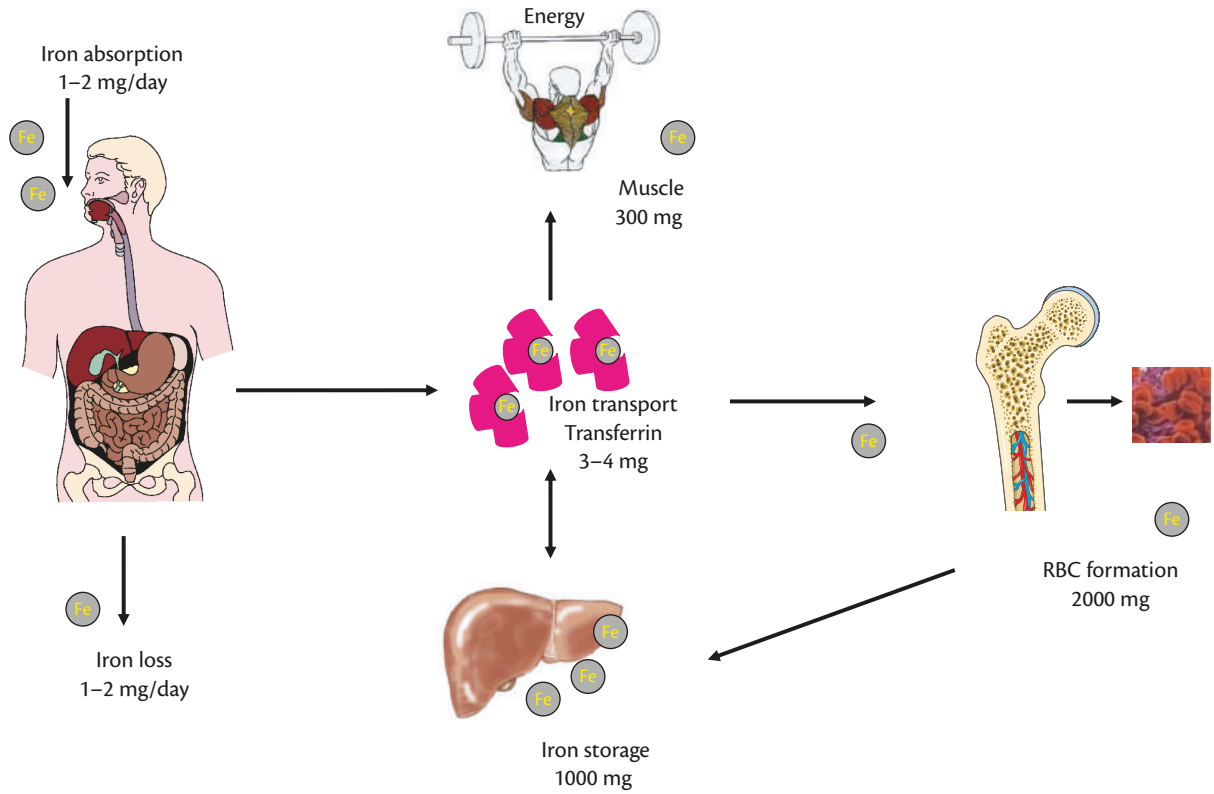

Fig. 125.1 Iron cycle in health.

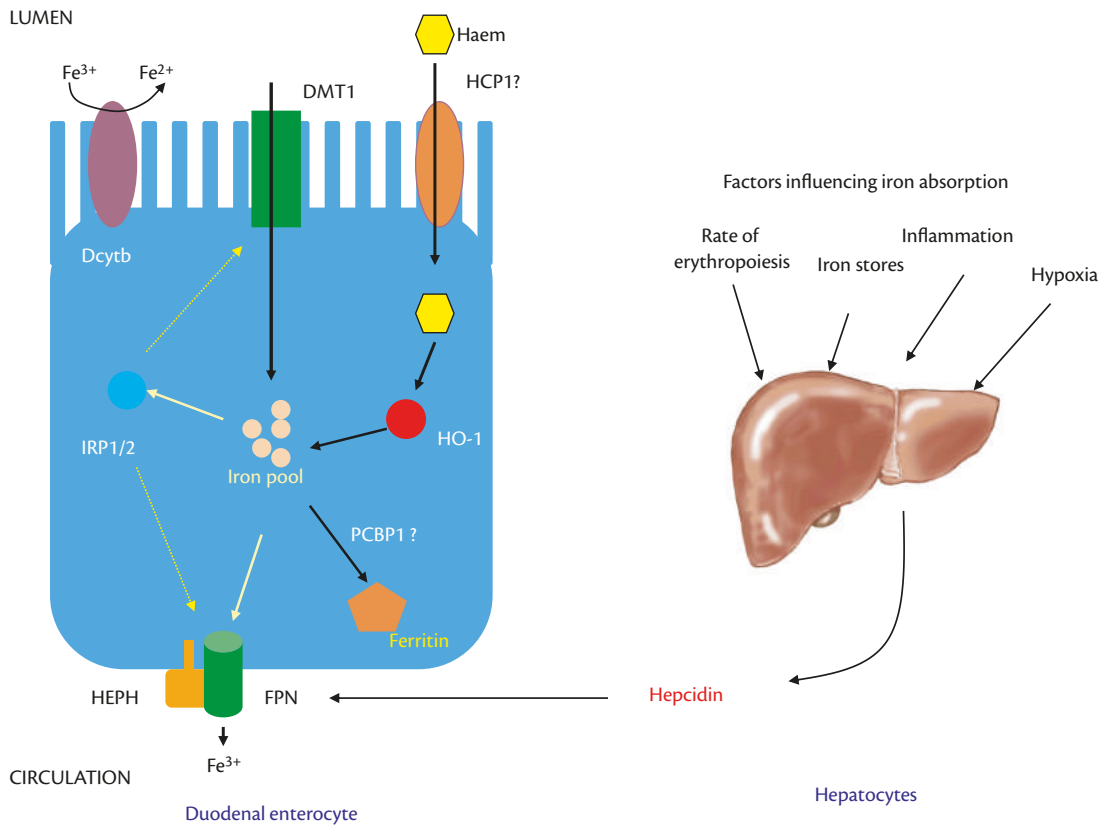

Fig. 125.2 Absorption of dietary iron.

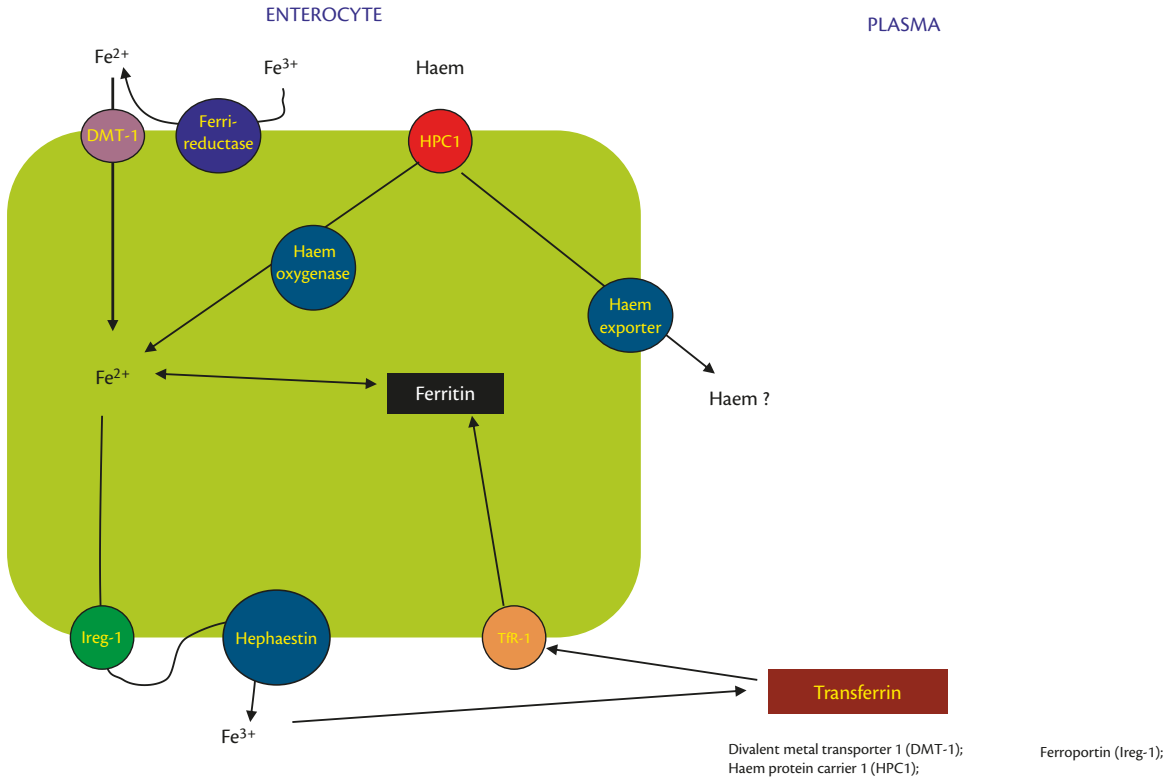

Fig. 125.3 Main pathways of iron absorption by enterocytes.

iron-sulphur protein synthesis occur. The same properties that enable iron to be an efficient cofactor in controlled redox reactions are also responsible for its toxicity. Under physiological conditions, iron mainly exists in two valence states, Fe^{2+} (ferrous) and Fe^{3+} (ferric). Cycling between the two states can lead to formation of reactive oxygen species (ROS) and thus oxidative stress. Iron is therefore highly regulated within the body, transported and stored tightly bound to iron-specific proteins in a non-redox active form. Iron in food exists largely as Fe^{3+}, which upon reduction to Fe^{2+} by a membrane reductase and subsequent transport through the enterocyte membrane, is oxidized back to Fe^{3+} after being exported out of the enterocytes. Ferric iron is tightly bound to the transport protein transferrin in the plasma for delivery to the tissues (Hider and Kong, 2011). Iron is primarily stored in the form of ferritin in the liver and in the reticuloendothelial system. Under normal circumstances, iron uptake from the gut is tightly regulated, and transferrin is only approximately one-third saturated (Hentze et al., 2010). Thus, the levels of non-transferrin bound iron (NTBI), a form of iron that might induce oxidative stress, are kept undetectably low. The NTBI is taken up from the plasma in an unregulated manner by cells of the endocrine system, the heart, and other tissues, where it can catalyse the formation of ROS, and thus induce oxidative stress (Brissot et al., 2012) The Fe^{2+} and Fe^{3+} iron redox cycling pair catalyses redox conversion of the relatively harmless oxygen products, superoxide anion and hydrogen peroxide, into the highly reactive hydroxyl radical. The reaction between Fe^{2+} and hydrogen peroxide is also called the *Fenton reaction* (Fenton, 1894):

(1) $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\cdot + OH^-$

(2) $Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + OOH\cdot + H^+$

Reaction (1) was suggested by Haber and Weiss in the 1930s (Haber and Weiss, 1932). In the net reaction the presence of iron is truly catalytic and two molecules of hydrogen peroxide are converted into two hydroxyl radicals and water. The generated radicals then engage in secondary reactions. Iron(II) sulphate is a typical iron compound in Fenton's reagent. The exact mechanisms are debated (also non-OH· oxidizing mechanisms of organic compounds have been suggested) and, therefore, it may be appropriate to broadly discuss 'Fenton chemistry' rather than a 'Fenton reaction'.

Hydroxyl radicals can damage a wide range of biological macromolecules in the immediate vicinity (Geisser, 1998). The NTBI can increase the intracellular labile iron pool (Brissot et al., 2012), which can thus initiate a chain of reactions that result in lipid peroxidation, membrane disruption, DNA strand breakage, and immunological disturbances.

Iron transport and storage

Production of red blood cells is a very active process leading to daily production of 200 billion new mature erythrocytes in order to compensate for the destruction of senescent red blood cells by macrophages. Erythropoiesis is mainly controlled by erythropoietin and availability of iron. In healthy individuals, three-quarters of their total body iron is present in circulating red blood cells, and the remaining one-quarter is stored mainly in the liver and bone marrow (Figs 125.4 and 125.5).

Normally, one-third of transferrin is saturated with iron (i.e. Fe/TIBC equals 33%) (Bothwell, 1995). TSAT is decreased when iron supply to the plasma from macrophages and other storage sites is reduced, that is, iron deficiency anaemia, anaemia of chronic inflammation (disease), and in some cases of ferroportin mutations.

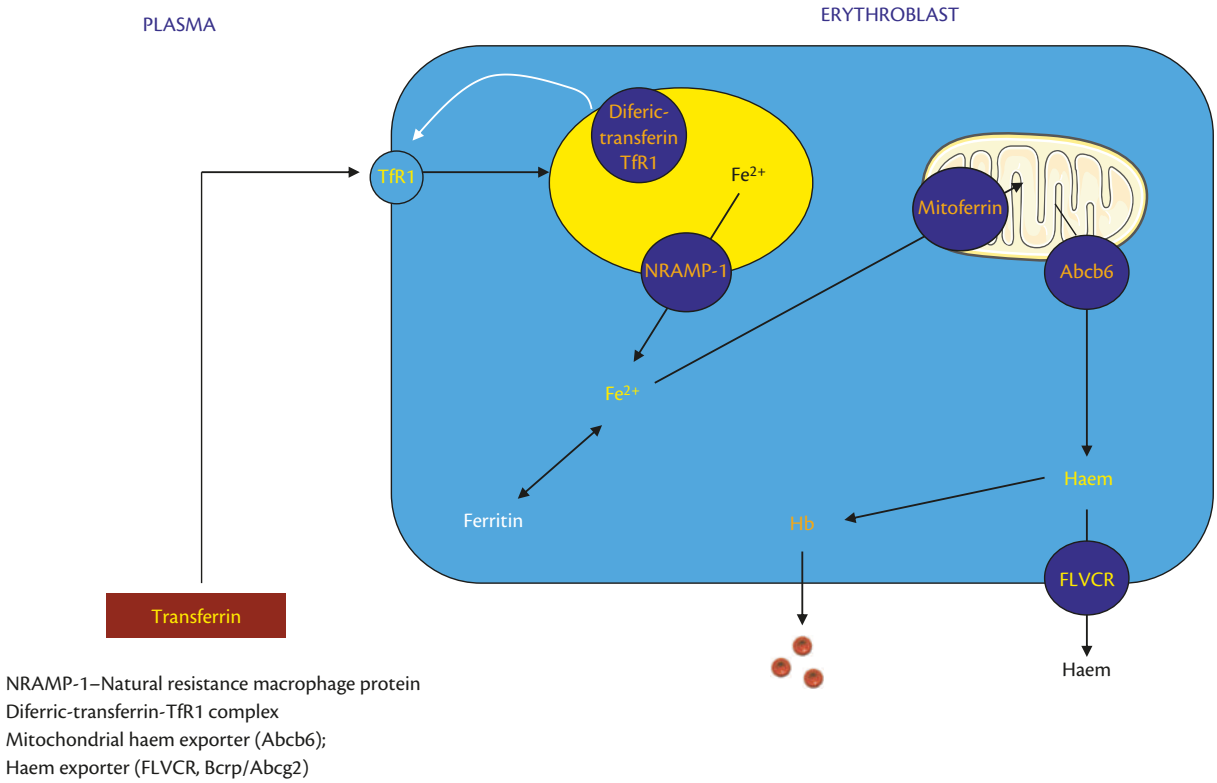

Fig. 125.4 Main pathways of iron utilization by erythroblasts.

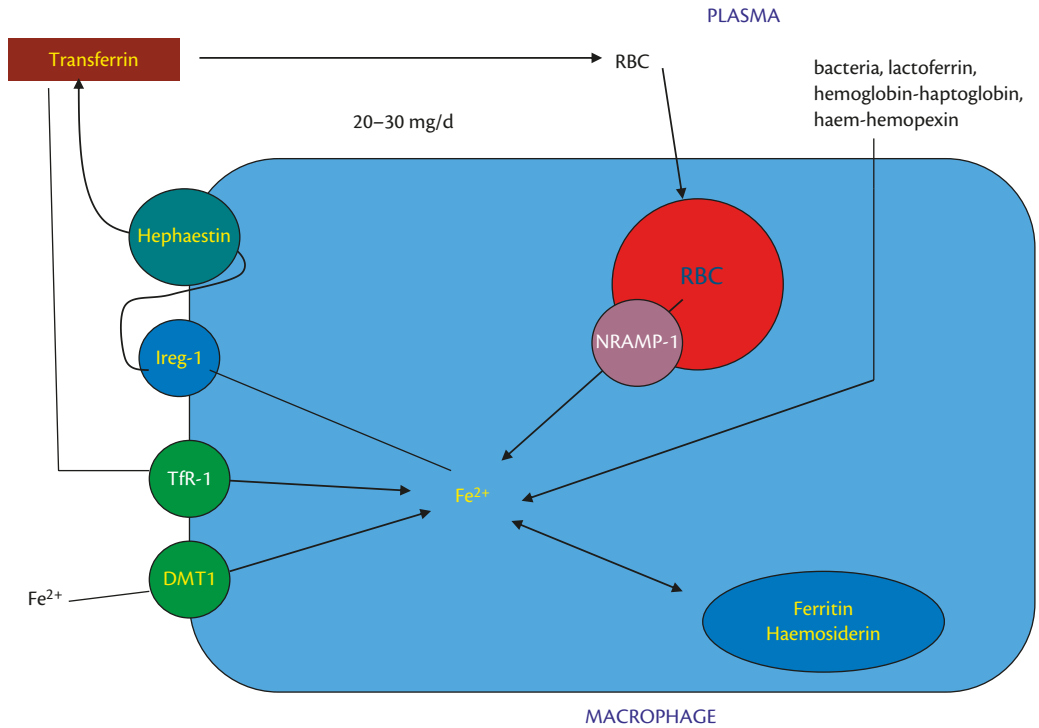

Fig. 125.5 Main pathways of iron storage and exportation by macrophages.

On the other hand, TSAT is increased when iron supply exceeds its demand, that is, aplastic, sideroblastic anaemia, hemochromatosis, liver disease, and other forms of ineffective erythropoiesis. Transferrin receptors are present in hepatocytes and epithelial cells of the small intestine, including duodenal crypts (Worwood, 1989). They probably contribute to the body's iron sensing (Kawabata et al., 2001; Deaglio et al., 2002; Robb and Wessling-Resnick, 2004). Each receptor can bind two transferrin molecules and, after their endocytosis, iron is offloaded (four Fe^{3+} atoms) in acidified vacuoles. Then the complex of the apotransferrin and transferrin receptor is recycled on the cell surface and released into circulation. Plasma iron transport is carried out by transferrin, which delivers iron into cells through its interaction with a specific membrane receptor, the transferrin receptor (Johnson and Enns, 2004). When iron deficiency exists, the soluble transferrin receptor concentration in serum rises, even before the haemoglobin concentration is significantly depressed (Das Gupta and Abbi, 2003). The sTfR concentration can therefore detect functional iron status (Baynes et al., 1994; Baynes, 1996), while ferritin reflects the iron storage status (Finch et al., 1986). Studies have shown that the level of sTfR is markedly elevated in iron deficiency anaemia but remains normal in anaemia due to chronic inflammation without iron deficiency and thus may be of some help in differentiating between iron deficiency anaemia and anaemia of chronic disorders (ACD) (Ferguson et al., 1992; Berlin et al., 2011). However, some data have demonstrated that sTfR offers little advantage over conventional laboratory indicators of iron status and might not assess the iron status of patients with ACD (Wians et al., 2001). Lee et al. (2002) demonstrated that sTfR is not superior to ferritin for detecting iron depletion, confirming the results obtained by Mast et al. (1998) previously. Therefore, the measurement of sTfR has not been introduced to the armamentarium of tests used in the routine measurement of iron status. Lack of difference in serum sTfR between the two studied groups might be due to its low sensitivity and specificity in assessing iron status in a haemodialysis population.

Once taken up by a cell, iron has two possible fates: incorporation into iron proteins usually as haem or Fe-S clusters, or storage in ferritin for a later use during iron deficiency.

Ferritin is present in virtually all cells (including hepatocytes) and is the cellular storage protein for iron; it is, however, at the same time an acute phase reactant. Ferritin is a cage-like heteropolymer of 24 subunits of H- (heavy or heart) and L- (light or liver) types, which can hold up to 4500 iron atoms (Wang et al., 2010). Ferritin is unique among enzymes in that it stores its substrate after acting upon it (Munro, 1986). As iron is transported into the ferritin multimer core, it is oxidized from Fe(II) to Fe(III) by the H-subunit (having ferroxidase activity) allowing formation of non-reactive ferrihydrate, which assembles as a solid in the core in a process involving L-subunit (Torti and Torti, 2002; Carrondo, 2003). Although ferritin is a predominantly cytoplasmic protein, a small quantity of glycosylated ferritin is secreted into the circulation. The serum level of ferritin generally reflects overall iron storage, with 1 ng of ferritin per mL indicating approximately 10 mg of total iron stores (Finch et al., 1986). The intracellular correlate of transferrin is ferritin. Aside from its useful role as an indicator of iron storage, the biological purpose of serum ferritin remains unknown. Ferritin receptors are present on lymphocytes and other cells, but its function is not fully defined (Chen et al., 2005). Bone marrow and liver biopsies and/or hepatic magnetic resonance imaging are more specific ways to measure tissue iron stores; however, serum iron indices are less invasive, less expensive, and clinically available.

Iron deficiency

Iron deficiency anaemia is the most common anaemia worldwide; on the other hand, both primary (haemochromatosis) and secondary defects in iron regulation leading to iron overload also result in human pathology. Most of the conditions associated with secondary iron overload are characterized also by anaemia. The source of iron may be parenteral (transfusions, iron compounds), from increased oral intake (diet, iron compounds), or enhanced iron absorption due to ineffective erythropoiesis or liver disease). Sometimes more than one factor can be present in the same patient. It is often crucial to diagnose the cause of disturbances in iron metabolism, in order to determine and deliver the appropriate treatment, including even organ transplantation in certain cases.

Iron deficiency may develop when unmet increased iron requirements or inadequate supply, or both, are present. The clinical presentation of iron deficiency may vary from a chance finding of laboratory abnormalities at routine screening in the absence of clinical symptoms on the one hand, to profound clinically relevant iron deficiency anaemia with pica.

Traditionally, iron deficiency has been classified in three progressive stages (Cook et al., 2003):

- Storage iron depletion, characterized only by a fall in serum ferritin below 12 ng/mL with normal haematological parameters (haemoglobin, red cell indices)
- Iron deficiency without anaemia, characterized with still normal haemoglobin levels, but with biochemical and haematological signs appearing, such as a decrease in TSAT, increase in circulating transferrin receptor, rise in erythrocyte zinc protoporphyrin, increase in % of hypochromic erythrocytes, and abnormally low reticulocyte haemoglobin content
- Iron deficiency anaemia, characterized by classical biochemical signs of iron deficiency with the haematological changes reflecting iron-deficient erythropoiesis with anaemia, decreased MCV (mean corpuscular volume), MCH (mean corpuscular haemoglobin), reticulocyte haemoglobin content and increased RDW (red distribution width).

Iron in chronic kidney disease

In chronic kidney disease (CKD), an important issue is the diagnosis of iron deficiency due to the fact that the laboratory criteria are markedly different from those in persons with normal renal function. Absolute iron deficiency is likely to be present in advanced CKD when ferritin falls below 100 ng/mL and TSAT falls below 20% (Fernandez-Rogriguez et al., 1993). In normal subjects, these values of ferritin are within the normal range. This discrepancy in serum ferritin between normal subjects and CKD patients is partly due to the fact that ferritin is an acute phase reactant and CKD is a subclinical inflammatory state. However, a functional iron deficiency (FID) may also commonly develop among patients with CKD. This is characterized by the presence of adequate iron stores as defined by conventional criteria, but with an inability to mobilize this iron rapidly enough to adequately support erythropoiesis with the administration of erythropoietin. An inadequate amount

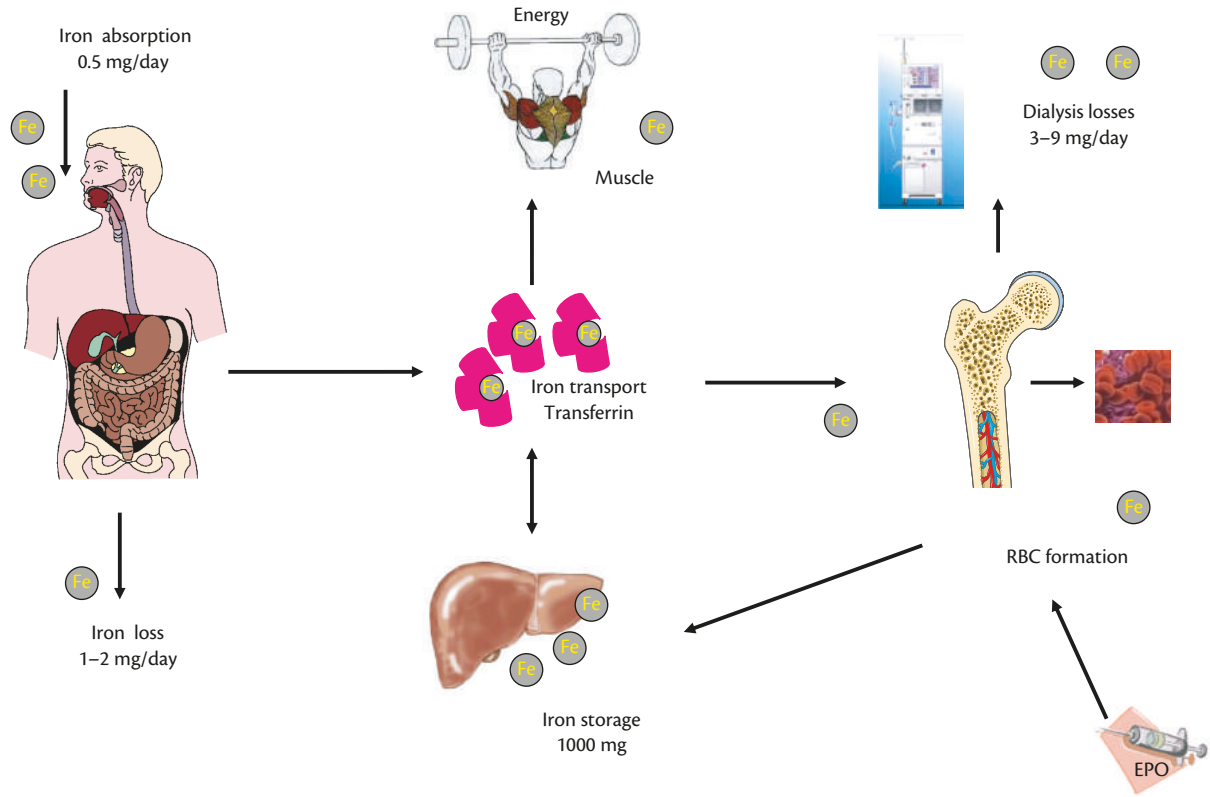

Fig. 125.6 Iron cycle in haemodialysis.

of iron is released from the liver and other storage sites. Among such patients, the serum ferritin level is either normal or elevated (often between 100 and 800 ng/mL), with a TSAT typically ≤ 20%.

The iron replete state is characterized by increased production of ferritin to permit adequate storage along with decreased production of the transferrin receptor to minimize further iron entry into the cell. To establish the presence of iron overload (increased body iron burden) serum iron studies, various radiological techniques, liver biopsy, and assessment of the response to phlebotomy or chelation therapy should be assessed (Jensen, 2004). In severe iron overload states, TSAT can approach 100% and the unsaturated iron-binding capacity can approach zero. A fasting TSAT ≥ 60% in men or ≥ 50% in women has an accuracy of > 90% in detecting patients with the homozygous form of hereditary haemochromatosis in whom clinical symptoms and/or documented iron overload is present (Edwards and Kushner, 1993). Serum ferritin concentrations > 300 ng/mL in men and 200 ng/mL in women are suggestive of iron overload, provided that acute inflammation is also not present (Edwards and Kushner, 1993).

In the older era, before the advent of erythropoietin therapy, patients with CKD had to cope with basal haemoglobin concentrations of 5 or 6 g/dL, with periodic red cell transfusions to abrogate severe symptoms of lethargy and poor physical capacity. At that time, secondary haemosiderosis due to multiple blood transfusions was not uncommon. Many of the patients became iron overloaded, with organ dysfunction due to tissue iron deposition. In the pre-erythropoietin era, high-volume blood transfusions were common practice for treating anaemia of CKD. In the recent Kidney Disease: Improving Global Outcomes guidelines even more liberal thresholds for the use of iron therapy is recommended, suggesting that clinicians consider the potential for iron to increase haemoglobin in patients who have a serum ferritin concentration of 500 ng/mL or less and a TSAT level of 30% or less (Drüeke and Parfrey, 2012). Iron metabolism in CKD/haemodialysis patients is depicted in Fig. 125.6

Functional iron deficiency

An important issue in the diagnosis of iron deficiency in patients undergoing chronic haemodialysis is the markedly different laboratory criteria compared to those of patients with relatively normal renal function. It is now recognized that FID may commonly exist among patients with renal failure. This state is characterized by the presence of adequate iron stores, as defined by conventional criteria, but with insufficient mobilization of the iron to adequately support erythropoiesis with the administration of erythropoiesis stimulating agents (Nissenson, 1997). In this setting, an inadequate amount of iron is released from the liver and other storage sites. The first reports on FID date back to 1989 (Macdougall et al., 1989; Van Wyck et al,. 1989), however, to date, no generally accepted definition has been agreed. It is, however, widely acknowledged that it is associated with lowered TSAT and elevated ferritin (Rambod et al., 2008). The diagnosis of iron deficiency or FID is particularly challenging in patients with acute or chronic inflammatory conditions, because most of the biochemical markers of iron metabolism are affected by the acute phase reaction. Thus, serum iron and ferritin may be falsely altered in complex medical situations (Rambod et al., 2008). There is also no consensus in the nephrology community on the upper level of ferritin (Dukkipati and Kalantar-Zadeh,

2007). It was reported that serum ferritin is a reliable marker of bone marrow iron stores in haemodialysis patients (Rocha et al., 2009). Although the number of iron-stained cells in bone marrow is the gold standard of iron stores, these patients may have a decreased serum iron level and thus limited iron available for erythropoiesis. Moreover, this is a cumbersome, costly and invasive method of determining body iron stores. FID usually responds to iron therapy, whereas inflammatory iron block usually does not. Unfortunately, with both FID and inflammatory iron block, the TSAT is < 20% and the ferritin level is elevated (between 100 and 800 ng/mL). The response to erythropoietin or parenteral iron may help distinguish among these two possibilities. With erythropoietin administration, ferritin levels may decrease in patients with FID but not with inflammatory iron block. Inflammatory iron block is also most likely to be present if the administration of intravenous iron is associated with a progressive increase in ferritin concentration rather than with increased erythropoiesis.

Hepcidin—the iron gate-keeper

Hepcidin, a recently discovered small, cysteine-rich cationic peptide, was isolated independently by two groups searching for novel antimicrobial peptides. In 2000, Krause et al. isolated a novel peptide from plasma. Since it was produced by the liver and had antimicrobial properties, it was named liver-expressed antimicrobial peptide-1 (LEAP-1), whereas Park et al. (2001) isolated this peptide from human urine and designated it as hepcidin (*hep*atic bacteri*cid*al prote*in*). As reviewed by Ganz (2003), the structure of hepcidin is highly conserved among mammals, suggesting a key role in major biological functions. The connections of hepcidin to iron metabolism were described by Nicolas et al. (2001) and Pigeon et al. (2001). Nicolas et al. (2001) identified that the murine gene hepcidin had a role in iron metabolism completely serendipitously. They worked on glucose metabolism-related transcription factor USF2 (upstream stimulatory factor 2) knockout mice, which unexpectedly were iron overloaded. It was found that instead of the *USF2* gene, the hepcidin gene was disrupted in these mice, whereas Pigeon et al. (2001) searching for iron upregulated genes, discovered that murine hepcidin mRNA expression was increased by iron overload and decreased by iron depletion.

Hepcidin is a product of the 2.5 kb *HAMP* gene, consisting of three exons and two introns, located on the long arm of chromosome 19 (NCBI Gene ID 57817). Hepcidin is expressed predominantly in the liver, but lower expression was also detected in the kidney, heart, skeletal muscle, and brain. Hepcidin-25, the major form of mature hepcidin, is cleaved from prohepcidin by convertases. Hepcidin-25 has both iron-regulatory and antimicrobial properties (Park et al., 2001; Rivera et al., 2005). Localization of hepcidin in the kidney implicates an iron-regulatory role of this peptide hormone in the renal tubular system, possibly in connection with the iron transporter, divalent metal transporter-1. DMT1 expression has been shown to be highest at the apical pole of epithelial cells of distal tubules and collecting ducts, where hepcidin was also found. Kulaksiz et al. (2005) suggested that hepcidin is involved in a sophisticated regulation of renal iron transport and their RT-PCR experiments show that hepcidin was intrinsically produced in the kidney. The main function of hepcidin is homeostatic regulation of iron metabolism and mediation of host defence and inflammation. Hepcidin is the predominant negative regulator of iron absorption in the small intestine, iron transport across the placenta, and iron release from the macrophages (Ganz 2003) (Fig. 125.7). Hepcidin controls intestinal iron absorption by regulating ferroportin expression on the basolateral membrane of enterocytes. Hepcidin directly regulates the expression of ferroportin on cell membranes, binding to it and inducing its internalization and degradation, thus trapping iron in enterocytes, macrophages, and hepatocytes. The net effect of hepcidin is the diminished absorption of dietary iron and sequestration of iron in macrophages and hepatic stores. The absence of hepcidin synthesis naturally leads to a major loss of control over iron release by enterocytes and macrophages followed by circulatory iron overload. Hepcidin, like other defensins, is an antimicrobial peptide killing them on contact. However, it has not been found to have chemotactic properties, and it differs structurally from other defensins (Hunter et al., 2002). Therefore, hepcidin wards off infections, in part as a defensin (it possesses antimicrobial activity) (Yang et al., 2004), an acute phase protein and by causing hypoferraemia (Nemeth et al., 2003). Hepcidin is an acute phase protein that is synthesized to restrict the body's iron stores, to prevent iron being requisitioned by invading microorganisms, but this itself does not explain how it responds to the body's iron needs.

The peptide is apparently upregulated in uraemia, as in other chronic inflammatory states (Ganz, 2006; Ashby et al., 2009; Viatte and Vaulont, 2009; Zaritsky et al., 2009) and its presence has provided a biological explanation for why CKD patients absorb iron poorly from the gut, and also why many haemodialysis patients develop FID in the presence of inflammation (Malyszko and Mysliwiec, 2007) (Fig. 125.8). Deteriorating renal function may enhance overall inflammatory responses because of the decreased renal clearance of factors that are directly or indirectly involved in inflammation, the same applied relation between residual renal function and inflammation (Malyszko et al., 2009) as well as hepcidin and residual kidney function (Malyszko et al., 2010). Ever since the discovery of hepcidin nearly 10 years ago, various groups of scientists have attempted to develop reliable assays for the measurement of this peptide in biological fluids. Hepcidin-25 was initially identified in human blood using a mass spectrometric assay (Krause et al., 2000). Then Park et al. (2001) isolated urinary hepcidin-25 and hepcidin-20 using cation exchange chromatography and reverse-phase high-performance liquid chromatography. At present, there is no consensus on the best assay method for hepcidin, and assays for hepcidin detection and quantification in serum or urine have not been generally available. The detection and quantification of hepcidin in plasma and serum have been hampered by technical difficulties (small size of hepcidin, limited availability of the antigen, isolation of hepcidin from urine involves complex, and time-consuming procedures). This might be due to the fact that free serum hepcidin is very quickly cleared from the bloodstream by binding to ferroportin and its subsequent cellular internalization. Urine hepcidin assays seem to be preferable for studies on iron metabolism however, it does not apply for dialysed patients. It has also been demonstrated that inflammation (acute and chronic), intravenous iron, and erythropoietin administration (Ashby et al., 2009) influence hepcidin levels. It was also suggested that measurement of serum hepcidin might have a role in predicting CKD patients' response to intravenous iron therapy (Swinkels and Wetzels, 2008). However, Tessitore et al. (2010) reported that serum hepcidin did not predict the haemoglobin response to

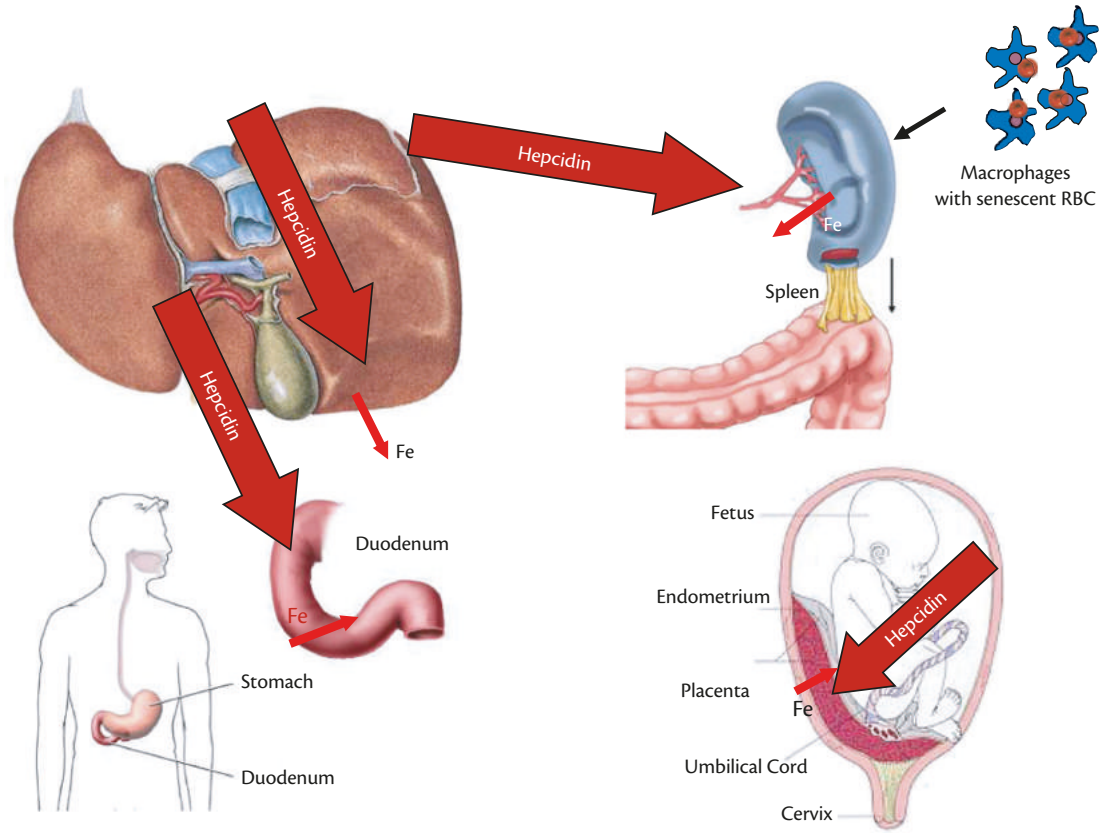

Fig. 125.7 Hepcidin and iron transport. Iron absorption is reduced by hepcidin and iron is sequestered in liver and macrophages. Hepcidin also reduces iron transport across the placenta.

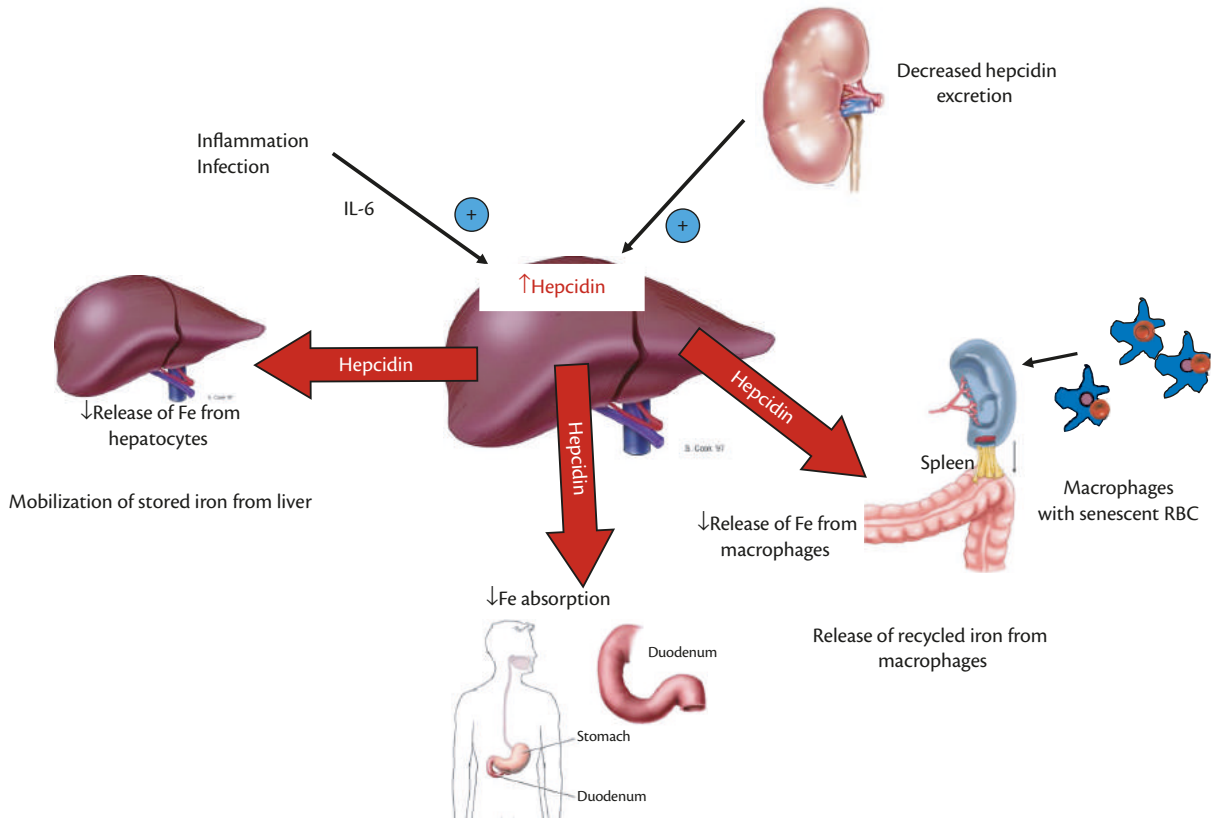

Fig. 125.8 Hepcidin in anaemia in dialysis patients. Hepcidin levels are increased, leading to functional iron deficiency.

intravenous iron loading. They used SELDI-TOF mass spectrometry assay to measure serum hepcidin-25 and hepcidin-20. While their study suggested an important role for hepcidin in regulating iron homeostasis in HD patients on ESA, they did not support its utility as a predictor of iron needs, offering no advantage over established markers of iron status. To date, none of the published studies have focused on the FID, hepcidin, and other iron players in haemodialysis populations.

Nephrologists may quite rightly have a sense of déjà vu, recalling that the early assays for parathyroid hormone (PTH) detected fragments of PTH rather than the intact molecule (Macdougall et al., 2010). The 'round robin' exercise of comparing measurements of hepcidin among different assays worldwide has highlighted this problem, with a 10-fold variation between the more sensitive mass spectrometric methods and the immunoassays, such as the recently published ELISA (Kroot et al., 2009). We should exercise caution in the interpretation of these results as intra-individual variability of serum hepcidin-25 in haemodialysis patients has been recently reported (Peters et al., 2012). They measured hepcidin-25 in haemodialysis patients using mass spectrometry and ELISA. These findings suggest considerable variability of serum hepcidin levels in HD patients. As the authors stated, further inflammation and the use of iron did not impact on the degree of variability, and hepcidin levels were higher after an interdialytic period of 3 versus 2 days.

In an experimental model, Sasu et al. (2010) reported that suppression of hepcidin mRNA improved anaemia in a mouse model of inflammation and high-affinity antibodies neutralized hepcidin and increased haemoglobin levels. Thus anti-hepcidin antibodies may be an effective treatment for inflammatory anaemia and manipulation of iron metabolism *in vivo* may allow investigation of the role of iron in other conditions. Thus, targeting hepcidin may have some utility as an adjunctive therapy in some conditions, such as β-thalassemia, iron overload, IRIDA, and ACD. Potential therapies downregulating hepcidin may include mimicking soluble HJV, inhibition of BMP receptors (dorsomorphin), interruption of IL-6 activation (tocilizumab-neutralizing antibody to IL-6, approved for rheumatoid arthritis, ameliorates anaemia in Castleman disease), inhibition of STAT3—curcumin and others. Inhibition of HIF prolyl hydrolylase has also been shown to decrease hepcidin levels.

On the other hand, modulation of hepcidin activity may be associated with some risks: inhibition of hepcidin may increase the risks of infection/inflammation, as well as tumour growth (serious infections including tuberculosis after tocilizumab use for rheumatoid arthritis), stabilization of HIF in some studies enhances tumour growth, interruption of BMP (particularly BMP-6) may result in calcification of tissues (including peritoneum), and interruption of the binding of hepcidin to ferroportin may enhance iron absorption and mobilization (Sun et al., 2012).

Summary

Iron metabolism is not well described in CKD. Although iron handling is frequently termed iron metabolism, iron itself is not metabolized in a classical sense. Systemic iron homeostasis involves meticulous control of intestinal iron absorption, effective utilization of iron for erythropoiesis, efficient recycling of iron from senescent erythrocytes, and controlled storage of iron by hepatocytes and macrophages. Hepcidin, a peptide hormone produced by the liver, has primary responsibility for modulating iron availability to meet iron needs. The diagnosis of iron deficiency in CKD is an important issue since the laboratory criteria are markedly different from those in persons with relatively normal renal function. In normal subjects, the values of ferritin are within the normal range. These discrepancies in serum ferritin between normal subjects and CKD patients are partly due to the fact that ferritin is an acute phase reactant and CKD is a subclinical inflammatory state. FID may also exist among patients with CKD and should be differentiated from inflammatory block. Despite many years of research, there are no biomarkers considered as 'gold standards' for iron stores or availability, therefore the search for them continues.

References

Anderson, G. J., Frazer, D. M., McKie, A. T., *et al.* (2005). Mechanisms of haem and non-haem iron absorption, lessons from inherited disorders of iron metabolism. *Biometals*, 18, 339–48.

Andrews, N. C. (2005). Molecular control of iron metabolism. *Best Pract Res Clin Hematol*, 18, 159–69.

Andriopoulos, B. Jr., Corradini, E., Xia, Y., *et al.* (2009). BMP6 is a key endogenous regulator of hepcidin expression and iron metabolism. *Nat Genet*, 41, 482–7.

Ashby, D. R., Gale, D. P., Busbridge, M., *et al.* (2009). Plasma hepcidin levels are elevated but responsive to erythropoietin therapy in renal disease. *Kidney Int*, 75, 976–81.

Babitt, J. L., Huang, F. W., Wrighting, D. M., *et al.* (2006). Bone morphogenetic protein signaling by hemojuvelin regulates hepcidin expression. *Nat Genet*, 38, 531–9.

Baynes, R. D. (1996). Assessment of iron status. *Clin Biochem*, 29, 209–15.

Baynes, R. D., Skikne, B. S., and Cook, J. D. (1994). Circulating transferrin receptors and assessment of iron status. *J Nutr Biochem*, 5, 322–30.

Beaumont, C., Beris, P., Beuzard, Y., *et al.* (2009). *Disorders of Erythropoiesis, Erythrocytes and Iron Metabolism*. Genoa: Forum Service Editore.

Berlin, T., Meyer, A., Rotman-Pikielny, P., *et al.* (2011). Soluble transferrin receptor as a diagnostic laboratory test for detection of iron deficiency anemia in hospitalized patients with acute illness. *Israel Med Assoc J*, 13, 96–8.

Bothwell, T. H. (1995). Overview and mechanisms of iron regulation. *Nutr Rev*, 53, 237–45.

Bridges, K. R. and Seligman, P. A. (1995). Disorders of iron metabolism. In R. I. Handin, S. E. Lux, and T. P. Stossel (eds.) *Blood, Principles and Practice of Hematology*, pp. 1433– 72. Philadelphia, PA: Lippincott.

Brissot, P., Ropert, M., Le Lan, C., *et al.* (2012). Non-transferrin bound iron. A key role in iron overload and iron toxicity. *Biochim Biophys Acta*, 1820, 403–10.

Brittenham, G. M. (1995). Disorders of iron metabolism: iron deficiency and overload. In R. Hoffman, E. J. Benz, Jr., S. J. Shattil, *et al.* (eds.) *Hematology Basic Principles and Practice* (2nd ed.), pp. 492–523. New York: Churchill Livingstone.

Carrondo, M. A. (2003) Ferritins, iron uptake and storage from the bacterioferritin viewpoint. *EMBO J*, 22, 1959–68.

Chen, T. T., Li, L., Chung, D. H., *et al.* (2005). TIM-2 is expressed on B cells and in liver and kidney and is a receptor for H-ferritin endocytosis. *J Exp Med*, 202, 955–65.

Cook, J. D. (1982). Clinical evaluation of iron deficiency. *Semin Hematol*, 19, 6–18.

Cook, J. D., Boy, E., Flowers, C. H., *et al.* (2003). The quantitative assessment of body iron. *Blood*, 101, 3359–63.

Das Gupta, A. and Abbi, A. (2003). High serum transferrin receptor level in anemia of chronic disorders indicates coexistent iron deficiency. *Am J Hematol*, 72, 158–61.

Deaglio, S., Capobianco, A., Cali, A., *et al.* (2002). Structural, functional, and tissue distribution analysis of human transferrin receptor-2 by murine monoclonal antibodies and a polyclonal antiserum. *Blood*, 100, 3782–9.

Drüeke, T. B. and Parfrey, P. S. (2012). Summary of the KDIGO guideline on anemia and comment, reading between the (guide) line(s). *Kidney Int*, 82, 952–60.

Dukkipati, R. and Kalantar-Zadeh, K. (2007). Should we limit the ferritin upper threshold to 500 ng/ml in CKD patients? *Nephrol News Issues*, 21, 34–8.

Edwards, C. Q. and Kushner, J. P. (1993). Screening for hemochromatosis. *N Engl J Med*, 328, 1616–20.

Finch, C. A., Bellotti, V., and Stray, S. (1986). Plasma ferritin determination as a diagnostic tool. *West J Med*, 145, 657–63.

Finch, C. A. and Huebers, H. (1982). Perspectives in iron metabolism. *N Engl J Med*, 306, 1520–8.

Fenton, H. J. H. (1894). Oxidation of tartaric acid in presence of iron. *J Chem Soc Trans*, 65, 899–911.

Fernandez-Rodriguez, A. M., Guindeo-Casasus, M. C., Molero-Labarta, T., *et al*. (1993). Diagnosis of iron deficiency in chronic renal failure. *Am J Kidney Dis*, 34, 508–13

Ferguson, B. J., Skikne, B. S., Simpson, K. M., *et al*. (1992). Serum transferrin receptor distinguishes the anemia of chronic disease from IDA. *J Lab Clin Med*, 119, 385–90.

Ganz, T. (2003). Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. *Blood*, 102, 783–8.

Ganz, T. (2006). Molecular pathogenesis of anemia of chronic disease. *Pediatr Blood Cancer*, 46, 554–7.

Geisser, P. (1998). *Iron Therapy with Special Emphasis on Oxidative Stress*. St Gallen: Vifor International Inc.

Haber, F. and Weiss, J. (1932). Über die Katalyse des Hydroperoxydes. *Naturwissenschaften*, 1932.

Handelman, G. J. and Levin, N. W. (2008). Iron and anemia in human biology, a review of mechanisms. *Heart Fail Rev*, 13, 393–404.

Hentze, M. W., Muckenthaler, M. U., Galy, B., *et al*. (2010). Two to tango, regulation of mammalian iron metabolism. *Cell*, 142, 24–38.

Hider, R. C. and Kong, X. L. (2011). Glutathione, a key component of the cytoplasmic labile iron pool. *Biometals*, 24, 1179–87.

Hunter, H. N., Fulton, D. B., Ganz, T., *et al*. (2002). The solution structure of human hepcidin, a peptide-hormone with antimicrobial activity that is involved in iron uptake and hereditary hemochromatosis. *J Biol Chem*, 277, 37597–603.

Jensen, P. D. (2004). Evaluation of iron overload. *Br J Haematol*, 124, 697–711.

Johnson, M. B. and Enns, C. A. (2004). Diferric transferrin regulates transferrin receptor 2 protein stability. *Blood*, 104, 4287–93.

Kautz, L., Meynard, D., Monnier, A., *et al*. (2008). Iron regulates phosphorylation of Smad1/5/8 and gene expression of Bmp6, Smad7, Id1, and Atoh8 in the mouse liver. *Blood*, 112, 1503–9.

Kawabata, H., Nakamaki, T., Ikonomi, P., *et al*. (2001). Expression of transferrin receptor 2 in normal and neoplastic hematopoietic cells. *Blood*, 98, 2714–19.

Krause, A., Neitz, S., Magert, H. J., *et al*. (2000). LEAP-1, a novel highly disulfide-bonded human peptide exhibits antimicrobial activity. *FEBS Lett*, 480, 147–50.

Kroot, J. J., Kemna, E. H., Bansal, S. S., *et al*. (2009). Results of the first international round robin for the quantification of urinary and plasma hepcidin assays, need for standardization. *Haematologica*, 94, 1748–52.

Kulaksiz, H., Theilig, F., Bachmann, S., *et al*. (2005). The iron-regulatory peptide hormone hepcidin, expression and cellular localization in the mammalian kidney. *J Endocrinol*, 184, 361–70.

Lakhal, S., Talbot, N. P., Crosby, A., *et al*. (2009). Regulation of growth differentiation factor 15 expression by intracellular iron. *Blood*, 113, 1555–63.

Lee, E. J., Oh, E. J., Park, Y. J., *et al*. (2002). Soluble transferrin receptor (sTfR), ferritin, and sTfR/log ferritin index in anemic patients with nonhematologic malignancy and chronic inflammation. *Clin Chem*, 48, 1118–21.

Lin, L., Goldberg, Y. P., and Ganz, T. (2005). Competitive regulation of hepcidin mRNA by soluble and cell-associated hemojuvelin. *Blood*, 106, 2884–2809.

Macdougall, I. C., Hutton, R. D., Cavill, I., *et al*. (1989). Poor response to treatment of renal anaemia with erythropoietin corrected by iron given intravenously. *Br Med J*, 299, 157–8.

Macdougall, I. C., Malyszko, J., Hider, R. C., *et al*. (2010). Current status of the measurement of blood hepcidin levels in chronic kidney disease. *Clin J Am Soc Nephrol*, 5, 1681–9.

Malyszko, J., Malyszko, J. S., Kozminski, P., *et al*. (2009). Type of renal replacement therapy and residual renal function may affect prohepcidin and hepcidin. *Ren Fail*, 31, 876–83.

Malyszko, J., Malyszko, J. S., Kozminski, P., *et al*. (2010). Possible relationship between neutrophil gelatinase-associated lipocalin, hepcidin, and inflammation in haemodialysed patients. *Nephron Clin Pract*, 115, c268–75.

Malyszko, J. and Mysliwiec, M. (2007). Hepcidin in anemia and inflammation in chronic kidney disease. *Kidney Blood Press Res*, 30, 15–30.

Mast, A. E., Blinder, M. A., Gronowski, A. M., *et al*. (1998). Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. *Clin Chem*, 44, 45–51.

Meynard, D., Kautz, L., Darnaud, V., *et al*. (2009). Lack of the bone morphogenetic protein BMP6 induces massive iron overload. *Nat Genet*, 41, 478–81.

Munro, H. N. (1986). Back to basics: an evolutionary odyssey with reflections on the nutrition research of tomorrow. *Annu Rev Nutr*, 6, 1–12.

Nemeth, E., Valore, E. V., Territo, M., *et al*. (2003). Hepcidin, a putative mediator of anemia of inflammation, is a type II acute-phase protein. *Blood*, 101, 2461–3.

Nicolas, G., Bennoun, M., Devaux, I., *et al*. (2001). Lack of hepcidine gene expression and severe tissue iron overload in upstream stimulatory factor 2 (USF2) knockout mice. *Proc Natl Acad Sci U S A*, 98, 8780–5.

Nissenson, A. R. (1997). Achieving target hematocrit in dialysis patients: new concepts in iron management. *Am J Kidney Dis*, 30, 907–11.

Papanikolaou, G., Samuels, M. E., Ludwig E. H., *et al*. (2004). Mutations in HFE2 cause iron overload in chromosome 1q-linked juvenile hemochromatosis. *Nat Genet*, 36, 77–82.

Park, C. H., Valore, E. V., Waring, A. J., *et al*. (2001). Hepcidin, a urinary antimicrobial peptide synthesized in the liver. *J Biol Chem*, 276, 7806–10.

Peters, H. P., Rumjon, A., Bansal, S. S., *et al*. (2012). Intra-individual variability of serum hepcidin-25 in haemodialysis patients using mass spectrometry and ELISA. *Nephrol Dial Transplant*, 27, 3923–9.

Philpott, C. C. (2002). Molecular aspects of iron absorption, Insights into the role of HFE in hemochromatosis. *Hepatology*, 35, 993–1001.

Pigeon, C., Ilyin, G., Courselaud, B., *et al*. (2001). A new mouse liver-specific gene, encoding a protein homologous to human antimicrobial peptide hepcidin, is overexpressed during iron overload. *J Biol Chem*, 276, 7811–19.

Rambod, M., Kovesdy, C. P., and Kalantar-Zadeh, K. (2008). Combined high serum ferritin and low iron saturation in hemodialysis patients: the role of inflammation. *Clin J Am Soc Nephrol*, 3, 1691–701.

Ramirez, J. M., Schaad, O., Durual, S., *et al*. (2009). Growth differentiation factor 15 production is necessary for normal erythroid differentiation and is increased in refractory anaemia with ring-sideroblasts. *Br J Haematol*, 144, 251–62.

Rivera, S., Nemeth, E., Gabayan, V., *et al*. (2005). Synthetic hepcidin causes rapid dose-dependent hypoferremia and is concentrated in ferroportin-containing organs. *Blood*, 106, 2196–9.

Robb, A. and Wessling-Resnick, M. (2004). Regulation of transferrin receptor 2 protein levels by transferrin. *Blood*, 104, 4294–9.

Rocha, L. A., Barreto, D. V., Barreto, F. C., *et al*. (2009). Serum ferritin level remains a reliable marker of bone marrow iron stores evaluated by histomorphometry in hemodialysis patients. *Clin J Am Soc Nephrol*, 4, 105–9.

Roy, C. N. and Enns, C. A. (2000). Iron homeostasis, new tales from the crypt. *Blood*, 96, 4020–7.

Sasu, B. J., Cooke, K. S., Arvedson, T. L., *et al*. (2010). Antihepcidin antibody treatment modulates iron metabolism and is effective in a mouse model of inflammation-induced anemia. *Blood*, 115, 3616–24.

Silvestri, L., Pagani, A., Nai, A., *et al.* (2008). The serine protease matriptase-2 (TMPRSS6) inhibits hepcidin activation by cleaving membrane hemojuvelin. *Cell Metab*, 8, 502–11.

Sun, C. C., Vaja, V., Babitt, J. L., *et al.* (2012). Targeting the hepcidin-ferroportin axis to develop new treatment strategies for anemia of chronic disease and anemia of inflammation. *Am J Hematol*, 87, 392–400.

Swinkels, D. W. and Wetzels, J. F. (2008). Hepcidin: a new tool in the management of anaemia in patients with chronic kidney disease? *Nephrol Dial Transplant*, 23, 2450–3.

Tanno, T., Bhanu, N. V., Oneal, P. A., *et al.* (2007). High levels of GDF15 in thalassemia suppress expression of the iron regulatory protein hepcidin. *Nat Med*, 13, 1096–101.

Tessitore, N., Girelli, D., Campostrini, N., *et al*, A. (2010) Hepcidin is not useful as a biomarker for iron needs in haemodialysis patients on maintenance erythropoiesis-stimulating agents. *Nephrol Dial Transplant*, 25: 3996–4002.

Torti, F. M. and Torti, S. V. (2002). Regulation of ferritin genes and protein. *Blood*, 99, 3505–16.

Truksa, J., Gelbart, T., Peng, H., *et al.* (2009). Suppression of the hepcidin-encoding gene Hamp permits iron overload in mice lacking both hemojuvelin and matriptase-2/TMPRSS6. *Br J Haematol*, 147, 571–81.

Van Wyck, D. B., Stivelman, J. C., Ruiz, J., *et al.* (1989). Iron status in patients receiving erythropoietin for dialysis-associated anemia. *Kidney Int*, 35, 712–16.

Viatte, L. and Vaulont, S. (2009). Hepcidin, the iron watcher. *Biochimie*, 91, 1223–8.

Wang, W., Knovich, M. A., Coffman, L. G., *et al.* (2010). Serum ferritin: past, present and future. *Biochim Biophys Acta*, 1800, 760–9.

Wians, F. H., Jr., Urban, J. E., Keffer, J. H., *et al.* (2001). Discriminating between iron deficiency anemia and anemia of chronic disease using traditional indices of iron status vs transferrin receptor concentration. *Am J Clin Pathol*, 115, 112–18.

Worwood, M. (1989). Overview of iron metabolism at a molecular level. *J Intern Med*, 226, 381–91.

Yang, D., Biragyn, A., Hoover, D. M., *et al.* (2004). Multiple roles of antimicrobial defensins, cathelicidins, and eosinophil-derived neurotoxin in host defense. *Annu Rev Immunol*, 22, 181–215.

Zaritsky, J., Young, B., Wang, H. J., *et al.* (2009). Hepcidin, A potential novel biomarker for iron status in chronic kidney disease. *Clin J Am Soc Nephrol*, 4, 1051–6.

Zhang, A. S., Anderson, S. A., Wang, J., *et al.* (2001). Suppression of hepatic hepcidin expression in response to acute iron deprivation is associated with an increase of matriptase-2 protein. *Blood*, 117, 1687–99.

CHAPTER 126

Iron management in renal anaemia

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Introduction

Although erythropoietin is the principal regulator of red cell production, normal erythropoiesis can only occur with an adequate supply of iron to the bone marrow. If this does not occur, then red cells can still be produced, but they contain reduced amounts of haemoglobin since iron is the major component of haem. In the early stages of iron insufficiency, only a small proportion of the youngest red cells will be affected, but as the older populations of red cells become effete, a greater proportion of the total circulating red cell population will have reduced intracellular haemoglobin. Automated blood count analysers can track the evolution of this process. Thus, initially the reticulocyte haemoglobin content will be reduced, and later the haemoglobin content and haemoglobin concentration of the mature red cells will be low. Increasing numbers of red cells are affected. The mean cell haemoglobin content (MCH) and mean cell haemoglobin concentration (MCHC) will become abnormally low. Even later in this process, the volume of the red cells will be affected, and advanced iron deficiency is therefore also associated with a low mean cell volume (MCV) of the red cell population.

Detecting and treating this condition is important since a reduced haemoglobin content in the red cell population will result in an overall decrease in circulating haemoglobin concentration, and this will reduce the oxygen-carrying capacity of the blood. Various laboratory markers of iron status are available (see below), and additional supplemental iron may be given by either the oral or intravenous (IV) route.

Markers of iron status

Since the advent of erythropoiesis-stimulating agent (ESA) therapy, which increased the demand for iron due to the enhanced production of red cells, the need for detecting iron insufficiency became more pertinent. There are quite a number of laboratory parameters of iron status recognized, with variable efficacy and availability (Table 126.1).

The *serum ferritin* is perhaps the most well known and widely available. Normal values in healthy individuals range from a lower level of approximately 20–30 micrograms/L up to an upper limit of around 300 micrograms/L. Levels < 20 micrograms/L indicate unequivocal iron deficiency and reduced total body iron stores, and there is no other explanation to account for this. However, values above this lower threshold do not exclude an inadequate supply to the bone marrow, and there are several possible causes for this, some of them highly relevant to patients with chronic kidney disease (CKD). Thus, serum ferritin is an acute phase reactant, and may be spuriously elevated in conditions where there is underlying infection or inflammation. It is now recognized that patients with CKD, particularly those receiving regular haemodialysis, have a chronic inflammatory state, and thus the serum ferritin levels may be falsely elevated. Liver disease and underlying malignancy may have the same effect. Thus, patients with active liver disease may have ferritin levels in the thousands. Studies in patients with CKD reveal highly variable levels (Fishbane et al., 2009), and levels within the normal laboratory range are known to occur in patients who have obviously reduced iron content in their bone marrow (Stancu et al., 2010). Despite these limitations, measurement of the serum ferritin is widely used, being available in most hospital laboratories, and is easy to perform.

Measurement of the *serum iron* is not a good indicator of iron deficiency, due to the considerable variability in normal measurements. Furthermore, it is not the serum iron per se that is relevant to the diagnosis of iron deficiency, but rather its relationship to the circulating serum transferrin or *total iron binding capacity* (TIBC). This relationship is usually expressed as a percentage, and is known as the *transferrin saturation* (TSAT). In healthy individuals, the transferrin saturation is usually > 20%, and lower values are suggestive of iron deficiency. Similarly, in conditions of iron overload, such as hereditary haemochromatosis, transferrin saturation levels may be in excess of 50%. Values even higher than this are also common shortly after administering IV iron.

The transferrin (or TIBC) levels may be reduced in states of malnutrition, and the diurnal variation of iron also makes the transferrin saturation measurement unreliable as an indicator of iron deficiency. The transferrin saturation is, however, widely available in hospital laboratories, and along with serum ferritin is most widely used in patients with CKD.

Percentage of hypochromic red cells (%HRC) was introduced at around the same time as recombinant human erythropoietin became widely available (Macdougall et al. 1992). Modern-day flow cytometric methods allow the volume and haemoglobin concentration of individual red cells to be accurately calculated, and by 'gating' the red cell population according to size and haemoglobin, it is possible to ascertain if the proportion of circulating red cells with a low intracellular haemoglobin concentration is increasing. Early studies investigating this method used a lower cut-off haemoglobin

Table 126.1 Markers of iron status

Marker	Characteristics
Serum ferritin	Reasonable marker of iron stores, but artificially elevated in the presence of inflammation or liver disease
Transferrin saturation (TSAT)	Subject to considerable diurnal variation; widely used in the United States
Hypochromic red cells	Several studies suggest that this is the most sensitive/specific maker of iron deficiency, but requires to be performed on a fresh blood sample, and requires specific automated blood count analysers which are not widely available
Reticulocyte haemoglobin content (CHr)	Also a fairly sensitive/specific maker of iron deficiency, but requires specific automated blood count analysers which are not widely available
MCV, MCH, MCHC	Abnormalities of these red cell indices will only occur in long-standing iron deficiency, and therefore not a sensitive marker of iron status
Serum transferrin receptor	Used outside the nephrology setting, but not helpful in patients receiving ESA therapy since this parameter will increase in either iron deficiency or enhanced erythropoiesis
Erythrocyte zinc protoporphyrin levels	Largely a research investigation with no practical applicability
Serum hepcidin levels	A novel biomarker of iron status which remains experimental
Bone marrow	Useful investigation, but invasive and not practical for repeat assessments

concentration of 28 g/dL, and in the normal healthy population, this would represent < 2.5% of the total red cell population. If this value increased to > 10% of the red cell population, this was regarded as unequivocally abnormal, and highly suggestive of iron insufficiency. There are, however, two problems with this measurement: firstly, it is not available in many hospital laboratories, and secondly, the sample is required to be analysed shortly after the phlebotomy. Thus, any delay in the sample reaching the haematology laboratory may cause spuriously abnormal results.

Reticulocyte haemoglobin content (CHr) is very similar to the measurement of hypochromic red cells, requiring specialized automated blood count analysers. In this instance, however, the haemoglobin content of the individual reticulocytes is assessed, and values < 29 pg per cell were reported to be indicative of iron insufficiency. Although this laboratory measurement was approved by the US Food and Drug Administration for reimbursement, the test suffers from the same limitations as for the %HRC, namely that the required automated blood count analysers are not widely available. The latest automated blood count analysers have developed other measurements of red cell or reticulocyte morphology, although their utility in the reliable detection of iron deficiency has not been established in robust scientific studies.

The *serum transferrin receptor* (sTfR) is used as a marker of iron deficiency in some clinical scenarios outside the renal setting. Levels of this protein are indeed increased in iron deficiency in an attempt to increase the cellular uptake of iron, but other factors may also affect the circulating levels of sTfR. Notably, any condition in which there is increased erythropoiesis (such as a haemolytic condition in a non-renal population, or with ESA therapy in a renal population) will cause sTfR levels to increase. The measurement is also not readily available in many hospital laboratories, and its utility in detecting iron deficiency in patients with CKD is largely unproven.

Erythrocyte zinc protoporphyrin (ZPP) levels have been suggested as a marker of iron deficiency, largely in non-renal populations. Data in patients with CKD are, however, sparse, and the method is time-consuming and laborious. Most units do not have access to this measurement, and it has little or no role in the detection of iron deficiency in the renal setting.

Red cell indices (such as MCV, MCH, and MCHC) may suggest underlying iron deficiency but, as indicated above, is a late phenomenon in the evolution of this condition. By the time the mean volume and mean haemoglobin concentration of a red cell population is reduced, iron deficiency is in an advanced state. Furthermore, other conditions affecting red cell morphology, such as sickle cell disease and haemoglobinopathies (e.g. thalassaemia) will also cause abnormalities in red cell indices.

Bone marrow stainable iron. It is possible to stain iron in the bone marrow, using reagents such as Prussian blue. Absence of any stainable iron in the bone marrow is strongly indicative of iron deficiency, but this method is clearly invasive and impractical for serial monitoring.

Serum hepcidin. The development of reliable assays for measuring serum hepcidin raised expectations that this laboratory measurement may circumvent many of the problems of the more traditional markers of iron status. This peptide is the major regulator of iron homeostasis (see Chapter 125), and it is possible to measure this molecule in serum using either an immunoassay or mass spectrometry. Immunoassays for hepcidin are now commercially available, but the specificity for biologically-active hepcidin is lacking, and thus the breakdown fragments of hepcidin (hepcidin-22 and hepcidin-20) may also be detected. Mass spectrometric methods are more accurate, but are clearly cumbersome, time-consuming, and costly. Furthermore, a study prospectively evaluating serum hepcidin as a marker of iron insufficiency showed a low sensitivity and specificity for this condition (Tessitore et al., 2010).

Classification of iron deficiency

Iron deficiency may be classified as either *absolute* or *functional*. Absolute iron deficiency is a condition in which the total iron stores are reduced, with a consequent starvation of the bone marrow for iron. Functional iron deficiency is when total body iron stores are normal or increased, but there is an inability to release iron from the stores rapidly enough to provide a ready supply of iron to the bone marrow.

Absolute iron deficiency may result from a low iron intake and/or increased iron losses due to occult or overt bleeding. Functional iron deficiency may be further subclassified into (a) a condition in which erythropoietic activity is increased to a level in which the supplies of iron are unable to keep pace with the requirements of the bone marrow, and (b) a condition in which there is upregulation of hepcidin due to acute or chronic inflammation, effectively locking iron into the cells of the reticuloendothelial system in the liver, spleen, and macrophages. This is further exacerbated

by hepcidin-induced inhibition of dietary or oral iron via the gut enterocytes. In this latter scenario, it may be possible to circumvent this via administration of IV iron.

Detection of iron deficiency

Iron deficiency in patients with CKD is known to be common, due to a combination of low oral intake and increased iron losses (see Chapter 123). Given the critical role of iron in erythropoiesis, it is important to detect this condition early and replace supplemental iron as required.

Many studies have sought to determine the best markers of iron status to achieve this, usually employing a 'gold standard' of a haemoglobin response to the administration of IV iron. Tessitore et al. (2001) compared six of the previously-mentioned iron markers (ferritin, transferrin saturation, hypochromic red cells, reticulocyte haemoglobin content, transferrin receptor, and erythrocyte zinc protoporphyrin). Receptor operator curve (ROC) analyses suggested that a level of hypochromic red cells > 6% yielded the greatest sensitivity/specificity, closely followed by the reticulocyte haemoglobin content. In this study, the serum ferritin and transferrin saturation measurements were not much greater than the line of equality (i.e. the same sensitivity/specificity as tossing a coin). Despite the study, serum ferritin and transferrin saturation have been the most widely used and studied parameters, largely due to their widespread availability.

For serum ferritin, a minimum cut-off of 100 micrograms/L has been suggested for patients with CKD, despite the lower limit of normal in healthy individuals being around 20 micrograms/L. This is thought to be partly due to increased inflammation in the CKD population. There has been much debate about the upper limit of ferritin that excludes iron deficiency, and data from the DRIVE study suggested that some patients with ferritin levels up to 1200 micrograms/L still respond to IV iron. Other than the DRIVE study, there is a paucity of data to support an accurate upper limit of ferritin to exclude iron insufficiency.

In haemodialysis patients, in whom there is an even greater degree of chronic inflammation than in the non-dialysis CKD population, the lower limit of acceptable ferritin to exclude iron deficiency has been reported in various clinical practice guidelines of renal anaemia management to be 200 micrograms/L. In short, in the setting of CKD, avoidance of serum ferritin level below 100 or 200 micrograms/L has been recommended.

The clinical practice guidelines of renal anaemia management also suggest cut-off values for transferrin saturation, hypochromic red cells, and reticulocyte haemoglobin content. For many years, the minimum recommended acceptable level of transferrin saturation was 20%. In line with the evidence base, however, it is clear that some patients with transferrin saturation levels between 20% and 30% may still respond to IV iron, and indeed a randomized controlled trial comparing cut-offs of 20–30% versus 30–40% suggested reduced dosage requirements for recombinant erythropoietin at the higher threshold. The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline on renal anaemia management published in August 2012 suggested that there may be some patients who will derive an increased haemoglobin and/or a reduced ESA dosage requirement with transferrin saturation levels up to 30% (National Kidney Foundation, 2012). Beyond this, the risks of giving supplemental IV iron were thought to outweigh any possible benefits, although robust scientific data in this clinical situation are lacking.

Tessitore et al. (2001) suggested that a measurement of hypochromic red cells above 6% was indicative of a functional iron deficiency, and this cut-off was adopted by the UK NICE anaemia clinical practice guideline (National Institute for Health and Clinical Excellence, 2011). The European Best Practice Guideline, however, used a cut-off of 10%, suggesting that functional iron deficiency was likely with values above this (Locatelli et al., 2013). The studies of reticulocyte haemoglobin content (CHr) suggest that there may be a need for supplemental iron if this measurement is < 29 pg per cell. Data on any of the other markers of iron status mentioned above are too sparse or unreliable to assist in the detection of iron deficiency.

Iron supplementation

Following the detection of overt or suspected iron deficiency, it is important to consider the administration of supplemental iron. This may be given either orally (in tablet or syrup form) or intravenously (as a bolus injection or infusion). In previous days, iron could be given intramuscularly, but the injections were painful, often resulting in brownish discoloration of the skin, and with the risk of producing intramuscular haematomas. Thus, nowadays, only the oral or IV routes are used.

Oral iron

There are many preparations of oral iron available commercially. Traditionally, these have included the iron salts, such as ferrous sulphate, ferrous fumarate, iron succinate, and iron polymaltose. In most countries, ferrous sulphate is the cheapest and most widely available, with most preparations containing around 60–65 mg of elemental iron. This is usually administered two or three times a day, although absorption of iron from the gut is limited, and much of the iron is excreted in the faeces. In conditions in which there is underlying inflammation, hepcidin is upregulated and will further inhibit the absorption of oral iron. Thus, it is generally regarded that oral iron has no role in patients receiving regular haemodialysis, in whom iron absorption is negligible.

Most of the iron salts also cause gastric or colonic irritation, due to a local Fenton reaction in the gut mucosa. The consequence of this is that many patients develop gastrointestinal side effects, such as nausea, vomiting, abdominal pain, bloatedness, constipation, or diarrhoea. For these reasons, many patients do not adhere to therapy, and compliance rates are low.

Absorption of supplemental oral iron is maximal if taken without food, since various foodstuffs will interfere with gut absorption. This will, however, increase the propensity to develop side effects, which can be reduced by taking the oral iron with meals. The latter will, however, result in reduced iron absorption. Absorption of iron from the gut may also be inhibited by the co-administration of various medicinal products, including phosphate binders (widely used, especially in dialysis patients), proton pump inhibitors such as omeprazole, and various antibiotics including ciprofloxacin and tetracycline.

Thus, oral iron supplements have the advantages of being more physiological, cheap, and easier to administer, but have a number of limitations in terms of efficacy and side effects. For these reasons, many physicians choose to use IV iron preparations to supplement their patients.

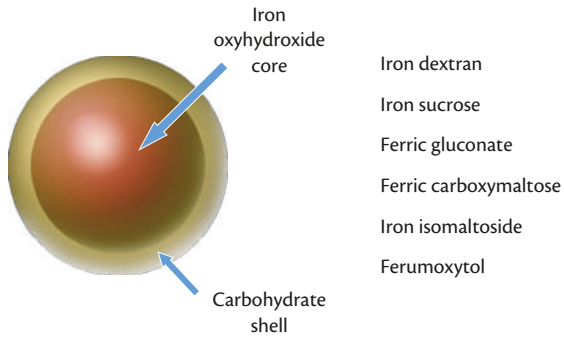

Fig. 126.1 Schematic representation of the structure of intravenous iron compounds, incorporating an iron oxyhydroxide core and a carbohydrate shell.

Intravenous iron

The concept of administering parenteral iron to man was introduced in the 1930s, in a seminal paper published in *The Journal of Clinical Investigation* (Heath et al., 1932). Attempts were made to directly administer iron salts, such as iron oxyhydroxide, directly into the bloodstream, and a number of severe side effects were seen, including abdominal pain and vomiting, skin reactions, and profound haemodynamic effects. At that time, therefore, it was concluded that IV iron was too dangerous to be employed as a therapeutic agent.

In the 1940s and 1950s, however, physical chemists attempted to make 'safer' iron products, and the concept of encasing the iron oxyhydroxide molecule in a carbohydrate shell arose. Early carbohydrates employed were dextran, sucrose, gluconate, and polymaltose. These compounds allowed the iron to be released from the core (Fig. 126.1) of the molecule slowly enough for it to be taken up by circulating transferrin, and thereby avoiding the profound adverse effects of direct administration of iron salts.

Although both iron dextran and iron sucrose products became available in the 1950s, they were not widely used until the advent of recombinant erythropoietin, when suddenly there arose a renewed need for IV iron. Iron dextran released the iron most slowly from the carbohydrate shell, but iron dextran products had their own unique problem, namely anaphylactic reactions caused by pre-formed dextran antibodies. These anaphylactic reactions were life-threatening in many cases, and indeed fatalities occurred. It has been recognized that anaphylaxis is more common with higher-molecular-weight dextrans compared to those of lower molecular weight (LMW), and in recent years LMW iron dextran products have been licensed. There is, however, still some concern that the risk of anaphylaxis with the LMW iron dextrans has not been abolished.

All IV iron preparations, however, may cause injection-related reactions, which are usually haemodynamic and caused by the vasodilatory properties of the iron complex. They may be due to the release of free iron into the circulation, but there is much less evidence for them being immunologically mediated than with the dextran-containing preparations. In most instances, the 'free iron' reactions are mild and self-limiting, and do not generally require hospitalization.

Iron is released more rapidly from iron sucrose and iron gluconate compared to iron dextran, and thus lower maximum doses of these preparations can be administered at any one time (Fig. 126.2). Thus, whereas total dose iron infusions of the dextran-containing preparations may be given up to 3–4 g at one time, the maximum recommended dose of iron sucrose as a bolus is 200 mg, and that of iron gluconate is 125 mg. Higher doses of these products may be given if administered as a slow IV infusion.

In recent years, three new IV iron preparations have become available: ferric carboxymaltose, iron iso-maltoside 1000, and ferumoxytol. All of these preparations benefit from the lack of need for a test dose (required for iron dextran-containing preparations), and may be administered as a larger dose over a shorter period of time.

Ferric carboxymaltose was developed and licensed by Vifor Pharma in Switzerland. This iron compound is able to be administered at a dose of 500 mg over 6 minutes, or 1000 mg as an infusion over 15 minutes. No test dose is required, and this product

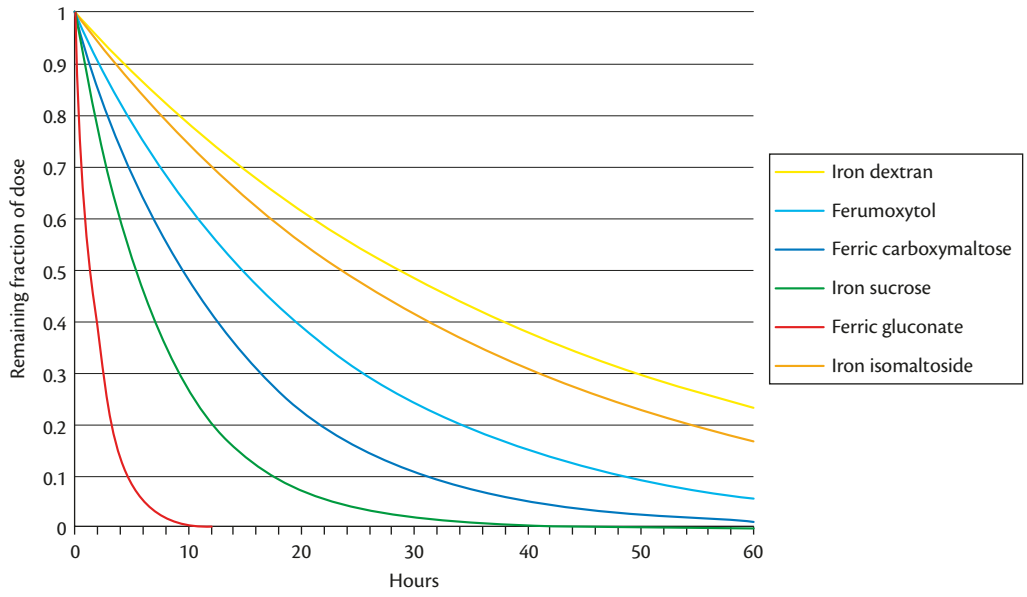

Fig. 126.2 Kinetics of iron release from the six most commonly used intravenous iron compounds worldwide.

has reduced the need for many non-dialysis patients to attend hospital for multiple visits for their 'top-up' of iron. Interestingly, a double-blind placebo-controlled trial of ferric carboxymaltose in heart failure patients showed some short-term beneficial effects, including improved heart failure class, quality-of-life, and physical capacity (Anker et al., 2009).

Iron iso-maltoside 1000 was developed by Pharmacosmos in Denmark, and is currently available in Europe only. Again, the main advantage of this product is that it is possible to administer doses of around 1000 mg as a single administration in < 1 hour. Comparative head-to-head studies of these newer iron products are not available.

Ferumoxytol started out as a magnetic resonance imaging contrast agent, with an administration rate of 510 mg of iron over 17 seconds. It was then developed as an IV iron supplement for treating iron deficiency anaemia, and was licensed as Feraheme® in the United States and Rienso® in Europe. The need to give higher doses of IV iron at a single administration is greater in the non-dialysis than in the haemodialysis population, since the latter are already regularly attending hospital or a dialysis unit several times a week.

All of the IV iron products will supply supplemental iron directly to the circulation, and although IV iron is widely used in dialysis patients, the long-term safety of this practice has never been ascertained. There are theoretical concerns that IV iron administration may exacerbate oxidative stress, promote atherogenesis, and increase cardiovascular toxicity, as well as increase the risk of bacterial or fungal infections, with many laboratory experiments providing supportive evidence. Data from observational studies has been conflicting, with some indicating no concerns (Feldman et al., 2004) and others suggesting a worse outcome with higher doses of iron. However, observational studies of this nature are hugely confounded, in that it is likely that the patients with higher co-morbidities will be given more IV iron. Thus, there is a need for properly conducted randomized controlled trials of IV iron with robust safety endpoints, as has been conducted for the ESAs.

Future of iron management

Ongoing research in this field to facilitate iron management in CKD has focused on a number of strategies. These include attempts to refine the criteria for the administration of supplemental iron. Although the preliminary data with hepcidin as a biomarker for iron insufficiency were disappointing, it may be possible to further refine the utility of hepcidin in guiding the need for iron replacement.

Various attempts have been made to look at alternative means of delivering iron via the oral route, with studies being reported both in the laboratory and the clinical stage of development. It was hypothesized that haem iron may be better absorbed in CKD patients than ferrous sulphate, but a randomized head-to-head study with haem iron versus ferrous sulphate in peritoneal dialysis patients was negative. For haemodialysis patients, a strategy that was developed in the 1990s, and has now completed phase 2 trials, is the administration of iron sodium pyrophosphate in the dialysate, which is then absorbed across the dialysis membrane. Finally, strategies to inhibit hepcidin activity, either by antagonizing the peptide directly, or modulating its action, or indeed inhibiting its synthesis are currently being examined.

Further reading

Bailie, G. R., Hörl, W. H., and Verhoef, J. J. (2011). Differences in spontaneously reported hypersensitivity and serious adverse events for intravenous iron preparations: comparison of Europe and North America. *Arzneimittelforschung*, 61, 267–75.

Barraclough, K. A., Brown, F., Hawley, C. M., *et al.* (2012). A randomized controlled trial of oral heme iron polypeptide versus oral iron supplementation for the treatment of anaemia in peritoneal dialysis patients: HEMATOCRIT trial. *Nephrol Dial Transplant*, 27, 4146–53.

Besarab, A., Amin, N., Ahsan, M., *et al.* (2000). Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients. *J Am Soc Nephrol*, 11, 530–8.

Charytan, C., Qunibi, W., and Bailie, G. R., *et al.* (2005). Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. *Nephron Clin Pract*, 100, c55–62.

Coyne, D. W., Kapoian, T., Suki, W., *et al.* (2007). Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. *J Am Soc Nephrol*, 18, 975–84.

Ganz, T. (2011). Hepcidin and iron regulation, 10 years later. *Blood*, 117, 4425–33.

Geisser, P., Baer, M., and Schaub, E. (1992). Structure/histotoxicity relationship of parenteral iron preparations. *Arzneimittelforschung*, 42, 1439–52.

Gupta, A., Amin, N. B., Besarab, A., *et al.* (1999). Dialysate iron therapy: infusion of soluble ferric pyrophosphate via the dialysate during hemodialysis. *Kidney Int*, 55, 1891–8.

Hamstra, R. D., Block, M. H., and Schocket, A. L. (1980). Intravenous iron dextran in clinical medicine. *JAMA*, 243, 1726–31.

Kalantar-Zadeh, K., Regidor, D. L., McAllister, C. J., *et al.* (2005). Time-dependent associations between iron and mortality in hemodialysis patients. *J Am Soc Nephrol*, 16, 3070–80.

Kapoian, T., O'Mara, N. B., Singh, A. K., *et al.* (2008). Ferric gluconate reduces epoetin requirements in hemodialysis patients with elevated ferritin. *J Am Soc Nephrol*, 19, 372–9.

Macdougall, I. C. (1994). Monitoring of iron status and iron supplementation in patients treated with erythropoietin. *Curr Opin Nephrol Hypertens*, 3, 620–5.

Macdougall, I. C. (1999). Strategies for iron supplementation: oral versus intravenous. *Kidney Int Suppl*, 69, S61–6.

Macdougall, I. C. and Geisser, P. (2013). Use of intravenous iron supplementation in chronic kidney disease: an update. *Iran J Kidney Dis*, 7, 9–22.

Macdougall, I. C., Malyszko, J., Hider, R. C., *et al.* (2010). Current status of the measurement of blood hepcidin levels in chronic kidney disease. *Clin J Am Soc Nephrol*, 5, 1681–9.

Spinowitz, B. S., Kausz, A. T., Baptista, J., *et al.* (2008). Ferumoxytol for treating iron deficiency anemia in CKD. *J Am Soc Nephrol*, 19, 1599–605.

Thomas, D. W., Hinchliffe, R. F., Briggs, C., *et al.* (2013). Guideline for the laboratory diagnosis of functional iron deficiency. *Br J Haematol*, 161, 639–48.

Vaziri, N. D. (2013). Understanding iron: promoting its safe use in patients with chronic kidney failure treated by hemodialysis. *Am J Kidney Dis*, 61, 992–1000.

References

Anker, S. D., Comin Colet, J., Filippatos, G., *et al.* (2009). Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*, 361, 2436–48.

Feldman, H. I., Joffe, M., Robinson, B., *et al.* (2004). Administration of parenteral iron and mortality among hemodialysis patients. *J Am Soc Nephrol*, 15, 1623–32.

Fishbane, S., Pollack, S., Feldman, H.I., *et al.* (2009). Iron indices in chronic kidney disease in the National Health and Nutritional Examination Survey 1988–2004. *Clin J Am Soc Nephrol*, 4, 57–61.

Heath, C. W., Strauss, M. B., and Castle, W. B. (1932). Quantitative aspects of iron deficiency in hypochromic anemia: (The Parenteral Administration of Iron). *J Clin Invest*, 11, 1293–312.

Locatelli, F., Bárány, P., Covic, A., *et al*. (2013). Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. *Nephrol Dial Transplant*, 28(6), 1346–59.

Macdougall, I. C., Cavill, I., Hulme, B., *et al*. (1992). Detection of functional iron deficiency during erythropoietin treatment: a new approach. *BMJ*, 304, 225–6.

National Institute for Health and Clinical Excellence (2011). *Anaemia Management in People with Chronic Kidney Disease*. [Online] [Updated November 2012] <http://guidance.nice.org.uk/CG114>

National Kidney Foundation (2012). KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl*, 2, v–335.

Stancu, S., Bârsan, L., Stanciu, A., *et al*. (2010). Can the response to iron therapy be predicted in anemic nondialysis patients with chronic kidney disease? *Clin J Am Soc Nephrol*, 5, 409–16.

Tessitore, N., Girelli, D., Campostrini, N., *et al*. (2010). Hepcidin is not useful as a biomarker for iron needs in haemodialysis patients on maintenance erythropoiesis-stimulating agents. *Nephrol Dial Transplant*, 25, 3996–4002.

Tessitore, N., Solero, G. P., Lippi, G., *et al*. (2001). The role of iron status markers in predicting response to intravenous iron in haemodialysis patients on maintenance erythropoietin. *Nephrol Dial Transplant*, 16, 1416–23.

CHAPTER 127

Pleiotropic effects of vitamin D

Kaivan Khavandi, Halima Amer,
Sarah Withers, and Behdad Afzali

Introduction

Vitamin D was discovered almost a century ago, and the 'sunshine vitamin' has been in vogue with the scientific community and the general public for over a decade now. Presented by some investigators as the panacea of human disease, others have questioned the therapeutic application of this steroid pro-hormone beyond traditional mineral-bone protecting effects. Epidemiological studies have demonstrated a strong association between vitamin D and kidney and heart disease, with some supplementation studies providing evidence for prevention and intervention of cardiorenal injury. Advances in our understanding of the molecular pathways at work, in particular the discovery of the ubiquitous expression of the vitamin D receptor (VDR) and its immunomodulating effects, has made justification for investigation in nearly every organ system and disease process. Indeed, one might argue that the research community has been overwhelmed by the number of small- and medium-sized studies of vitamin D, in part leading to the ambiguity of research findings, although undoubtedly compounded by the complexity of the underlying basic science, multiple confounding variables, reverse causation bias, challenging laboratory measurements, and confusing nomenclature. Despite an ever-increasing body of epidemiological data in support of the association between vitamin D deficiency and human disease, there remain no adequately powered trials to prove a cause-and-effect relationship to support these observations. The aim of this chapter is to provide a detailed description of the important pathways in the synthesis and metabolism of vitamin D, its biological and physiological roles, how it can be effectively measured in the clinical setting, and to discuss key studies investigating the consequences of vitamin D deficiency and depletion to a variety of target organs, as well as summarizing the results of existing therapeutic 'supplement' strategies.

Vitamin D biology

Vitamin D metabolism

Vitamin D is a fat-soluble steroid pro-hormone integral to the regulation and absorption of calcium and is therefore important in skeletal mineralization and bone metabolism. The nomenclature of vitamin D can be confusing, partly owing to its various forms, both active and inactive, and stages of metabolism and hydroxylation. Vitamin D_2, or ergocalciferol is present in plants and some fish, whilst vitamin D_3, cholecalciferol, is primarily synthesized photochemically from 7-dehydrocholesterol in the skin, following exposure to ultraviolet B radiation in sunlight. Some vitamin D_3 is also absorbed in the intestine from dietary sources such as oily fish and fortified dairy products. Vitamin D metabolites are transported in the circulation by plasma vitamin D-binding protein (Nykjaer et al., 1999). In the liver, these forms of vitamin D undergo hydroxylation by 25-hydroxylase (CYP2R1) and are converted to 25-hydroxyvitamin D (25(OH)D), or calcidiol. In clinical practice, it is conventionally this form of vitamin D which is measured by laboratory assays and therefore the determinant of vitamin D status in the clinical setting (Holick, 2007).

The calcidiol–vitamin D-binding protein complex is transported to the kidneys and following glomerular filtration, enters proximal tubular epithelial cells, where it undergoes megalin-mediated uptake at the brush border. In tubular epithelial cells, calcidiol is further metabolized by the enzyme 25 hydroxyvitamin D-1-α-hydroxylase (CYP27B1), to the active form 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$), or calcitriol (Brannon et al., 2008). CYP27B1 is present in a number of local and distant sites and cells in the body, including the skin, bowels, bone, and brain (Kulie et al., 2009) and regulates circulating concentrations of active vitamin D. Vitamin D can be directly inactivated by the enzyme 1,25-dihydroxyvitamin D_3 24-hydroxylase (CYP24A1) by the addition of another hydroxyl(OH) group at position 24. This results in the generation of $1,24,25(OH)_3$ vitamin D_3 and subsequently 1α-hydroxy-23 carboxy-24,25,26,27-tetranorvitamin D_3, calcitroic acid, the inactive water soluble form of vitamin D which is excreted by the kidney. Although CYP27B1 can be downregulated directly through signalling pathways with vitamin D itself, the regulation of vitamin D is primarily through a network of negative feedback interactions, with calcium, parathyroid hormone (PTH), and especially fibroblast growth factor 23 (FGF23) (Larsson, 2010) playing prominent roles. Some of the complexity of the system is shown in Fig. 127.1.

Vitamin D assays and measurements in the laboratory

Establishing a reliable and uniform means of measuring vitamin D and its various metabolites in the laboratory has been a challenge. PTH, for example, is notoriously tricky to measure accurately, and there are several different assays in current commercial use, giving widely different results (La'ulu and Roberts, 2010). There is a similar situation in the case of the vitamin D assays—$1,25(OH)_2D$ (which has a short half-life of a few minutes) is very laborious to measure, and correspondingly expensive, whereas 25(OH)D—with a much longer half-life of several weeks, acting as a 'whole-body indicator', is widely used for assessing vitamin D status, but is also

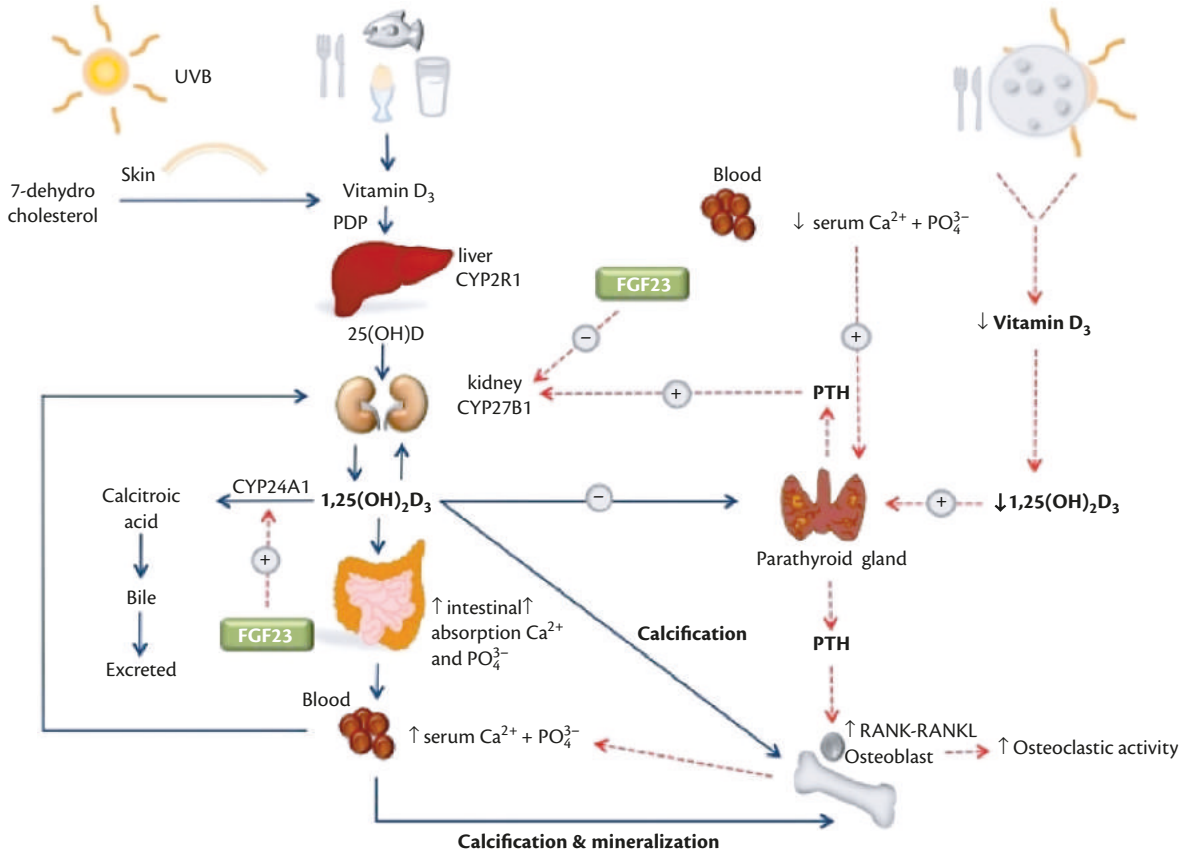

Fig. 127.1 Vitamin D metabolism. Schematic diagram demonstrating the metabolism of vitamin D to its active forms and subsequent negative feedback loops with calcium and parathyroid hormone. Dysregulated homeostasis due to vitamin D deficiency is illustrated on the right hand side of the diagram, with consequent metabolic derangements. 1,25(OH)$_2$D$_3$ = 1,25-dihydroxyvitamin D; 25(OH)D = 25-hydroxyvitamin D; Ca^{2+} = calcium; FGF23 = fibroblast growth factor 23; PDP = plasma vitamin D-binding protein; RANKL = receptor activator of nuclear factor-κ ligand; PO^{3-}_4: phosphate; PTH = parathyroid hormone; UVB = ultraviolet B.

methodologically challenged (Carter, 2011). A dramatic increase in 25(OH)D requests over recent years has prompted many laboratories to consider the use of automated immunoassays. To achieve this higher throughput, these methods have abandoned the traditional solvent extraction of samples and are therefore more prone to non-specific interference. The Vitamin D External Quality Assessment Scheme (DEQAS) has revealed method-related differences in 25(OH)D results, raising concerns about the comparability and accuracy of different assays. One clearly expressed opinion is that all 25(OH)D assays should be monitored by a proficiency testing scheme and the results made available to clinicians and editors of scientific journals (Carter, 2011). Further, most assays measure vitamin D_2 and D_3 (whether mono- or di-hydroxylated) together; only some tandem mass spectrometry assays can reliably separate and measure the two species separately. Clearly this is an area where considerable resource and time must be devoted to ensure widespread adoption of standardization.

Vitamin D, calcium, and parathyroid hormone

Vitamin D has essential roles in the regulation of calcium through reciprocal feedback mechanisms with PTH, plasma phosphorous, and FGF23. Under hypocalcaemic conditions, calcium-sensing cells in the parathyroid gland produce PTH, which is the main inducer of CYP27B1 activity, promoting the conversion of calcidiol to active calcitriol. This simulates PTH receptors on osteoblasts, which then increase osteoclastic activity in bone through enhanced RANK (receptor activator of nuclear factor kappa B (NF-κB))–RANK ligand interaction. The resulting release of calcium into the circulation, combined with the direct effects of active vitamin D, work to inhibit the synthesis and suppress the expression of PTH (Holick, 2005, 2007). Vitamin D stimulates further calcium absorption in the intestine, as well as reabsorption from the distal tubule in the kidneys. Indeed, without vitamin D, only 10–15% of dietary calcium and about 60% of phosphorous is absorbed. The interaction between calcitriol and VDRs increases calcium absorption to 30–40% and phosphorous absorption to approximately 80%. Calcitonin, a hormone produced by the C cells of the thyroid gland, can induce CYP27B1 activity under normocalcaemic conditions where the PTH system is downregulated (Doorenbos et al., 2009; Zhong et al., 2009). Healthy bone depends on a state of constant turnover and remodelling, which is maintained by the homeostasis of calcium, vitamin D and PTH described.

In the face of depleted vitamin D levels, calcium homeostasis is impaired and PTH left unsuppressed, leading to secondary hyperparathyroidism. Increased circulating PTH has damaging effects on skeletal integrity: PTH increases bone turnover by inducing osteoblasts to stimulate the maturation of osteoclasts, which in turn cause osteoporosis (defined as bone mineral density on dual X-ray absorptiometry (DXA) scan ≥ 2.5 standard deviations (SDs)

below mean peak bone mineral density) and osteopenia (defined as bone mineral density on DXA scan between 1 to 2.5 SDs below mean peak bone mineral density) by increased degradation of mineralized collagen matrices, increasing the risk of bone fracture. Deranged renal function contributes to vitamin D deficiency through multiple pathways, including loss of CYP27B1 activity and a decline in the production of active vitamin D, compounded by nutritional vitamin D deficiency/insufficiency. Aberrant vitamin D metabolism, calcium and PTH homeostasis, and osteopenia occur concurrently with drop in overall renal filtration, with PTH and FGF23 levels rising early, when estimated glomerular filtration rate (eGFR) falls below 60mL/min (Levin et al., 2007). High circulating levels of PTH and FGF23, in addition to other phosphatonins, physiologically causes phosphaturia through reduced tubular reabsorption of phosphate and thereby maintain normal serum phosphate levels. In the face of more advanced chronic renal failure, the failing kidney and reduced nephron numbers are unable to compensate for this disparity and failure to excrete sufficient phosphate leads to increased serum phosphate, exacerbating hypocalcaemia. The resultant stimulation of PTH, in addition to increased synthesis of FGF23 by osteocytes, has additional deleterious effects on bone metabolism, as renal hydroxylation of vitamin D is further suppressed, driving progression of secondary hyperparathyroidism. Conversely, over-suppression of PTH is detrimental to bone, as the loss of normal bone turnover results in adynamic bone disease and increases the risk of fracture.

Fibroblast growth factor 23

FGF23 is the most recently identified FGF protein (Shimada et al., 2001). It was initially identified as the causative factor of autosomal dominant hypophosphataemic rickets, which is characterized by hypophosphataemia due to reduced renal reabsorption of phosphate, inappropriately low to normal $1,25(OH)_2D_3$ levels, and rickets/osteomalacia. FGF23 was also identified as an ectopically overproduced phosphaturic factor in tumour-induced osteomalacia (for a comprehensive review, see Larsson, 2010).

Over the last 5 years of clinical and laboratory research, FGF23 has emerged as a negative regulator of circulating phosphate and $1,25(OH)_2D_3$ levels. FGF23 induces phosphaturia through decreased expression and endocytosis of the sodium–phosphate co-transporters Npt2a and Npt2c in the kidney proximal tubule, and directly suppresses renal CYP27B1, leading to decreased conversion of $25(OH)D_3$ to its active metabolite $1,25(OH)_2D_3$. Another mechanism by which FGF23 reduces both $25(OH)D_3$ and $1,25(OH)_2D_3$ levels is stimulation of CYP24A1, enhancing vitamin D degradation.

FGF23 excess is seen in autosomal dominant hypophosphataemic rickets due to activating mutations in the *FGF23* gene, causing FGF23 resistance to proteolytic degradation. Inactivating mutations in the *PHEX* or *DMP-1* genes lead to X-linked hypophosphataemic rickets and autosomal recessive hypophosphataemic rickets, respectively. In contrast, inactivating mutations in *FGF23* or in the *GALNT3* gene, the latter responsible for post-translational O-glycosylation of FGF23, causes tumoural calcinosis, characterized by a reversed biochemical phenotype including hyperphosphataemia, elevated $1,25(OH)_2D_3$ levels, and extensive soft tissue and/or vascular calcification (for review, see Foley et al., 2008, 2009).

The Klotho protein is central to interactions between FGF23 and vitamin D, participating in an inhibitory feedback system resulting in suppression of calcitriol synthesis through regulation of 1α-hydroxylase gene expression (Tsujikawa et al., 2003). Klotho causes modification of the low-affinity FGF receptors (FGF-R1), leading to high affinity receptors through the FGF-R1/Klotho complex (Kurosu et al., 2006; Urakawa et al., 2006; de Borst et al., 2011). FGF23 binds to the FGF-R1-/Klotho complex, resulting in activation of the MAPK cascade, and ERK activation with Egr-1 expression (Kuro-o et al., 1997; Urakawa et al., 2006; Ben-Dov et al., 2007). Oxidative stress has been shown to cause downregulation of renal Klotho (Mitobe et al., 2005) and conversely, free-radical scavenging is able to rescue Klotho expression (Saito et al., 2003). Furthermore, the tumour necrosis factor (TNF) converting enzyme, which is upregulated in vitamin D deficiency (Dusso et al., 2010), and with angiotensin II, has been implicated in cleavage of the extracellular domain of Klotho (Chen et al., 2007). Besides its role as part of the FGF23 receptor complex, the beta-glucuronidase activity of Klotho is important in stabilizing the abundance of the TRPV5 in the apical membrane of the tubular cells (Alexander et al., 2009, Chang et al., 2005). Loss of renal Klotho in chronic kidney disease (CKD) may therefore lead to calcium loss, which in turn promotes vitamin D activation. Over activation of Klotho provides renoprotection in mouse (Haruna et al., 2007) and rat (Wang and Sun, 2009) models of renal damage, through endothelial protection, with beneficial effects on redox and apoptotic processes (Ikushima et al., 2006; Kuro-o, 2008).

Although the classical Klotho–FGF23R complex is needed for organ-specific binding in renal tubules, and the choroid plexus, FGF23 has more recently been shown to have biological effects without activating of Egr-1 (Urakawa et al., 2006), with less specific low affinity FGF23 binding to FGF receptors (Frey et al., 2008; Wang et al., 2008b). High levels of FGF23 suppress activation of vitamin D (Fliser et al., 2007) and FGF23 levels become progressively elevated with worsening stages of CKD (Shimada et al., 2010; Isakova et al., 2011), where Klotho expression is downregulated (Galitzer et al., 2010; Hu et al., 2011). An increasing number of studies now link FGF23 levels with a number of cardiorenal outcomes (Cohen et al., 1991; El-Abbadi and Giachelli, 2007; Voormolen et al., 2007; Gutierrez et al., 2008; Parker et al., 2010a), even after allowing for the already impressive associations with plasma phosphate (Chen et al., 2002; Tonelli et al., 2005). These include atherogenesis (Mirza et al., 2009a), left ventricular (LV) remodelling (Block et al., 1998; Sprague et al., 2003; Mirza et al., 2009b; Kirkpantur et al., 2011), proteinuria (Yilmaz et al., 2010), vascular aging (Ikushima et al., 2006), vascular calcification (Hu et al., 2011), endothelial dysfunction (Saito et al., 1998), and insulin resistance (Yamamoto et al., 2005), which will be discussed in more detail in the relevant sections below. Of greatest interest will be understanding whether the marked reduction in synthesis of vitamin D that is seen with elevated FGF23 levels (Fig. 127.2) has the same effect on mortality and outcomes that we recognize with low or deficient circulating levels of $25(OH)D_3$ or $1,25(OH)_2D_3$ (Wolf et al., 2007).

Vitamin D receptor

It is now known that the VDR, which mediates the biological actions of vitamin D, is not only present in what was traditionally considered relevant organ systems, but instead is ubiquitously expressed throughout the body, including the heart, blood vessels, pancreas, brain, skeletal muscle, immune cells, and kidney (Dusso et al., 2005; Holick, 2006b; Doorenbos et al., 2009). The VDR is a

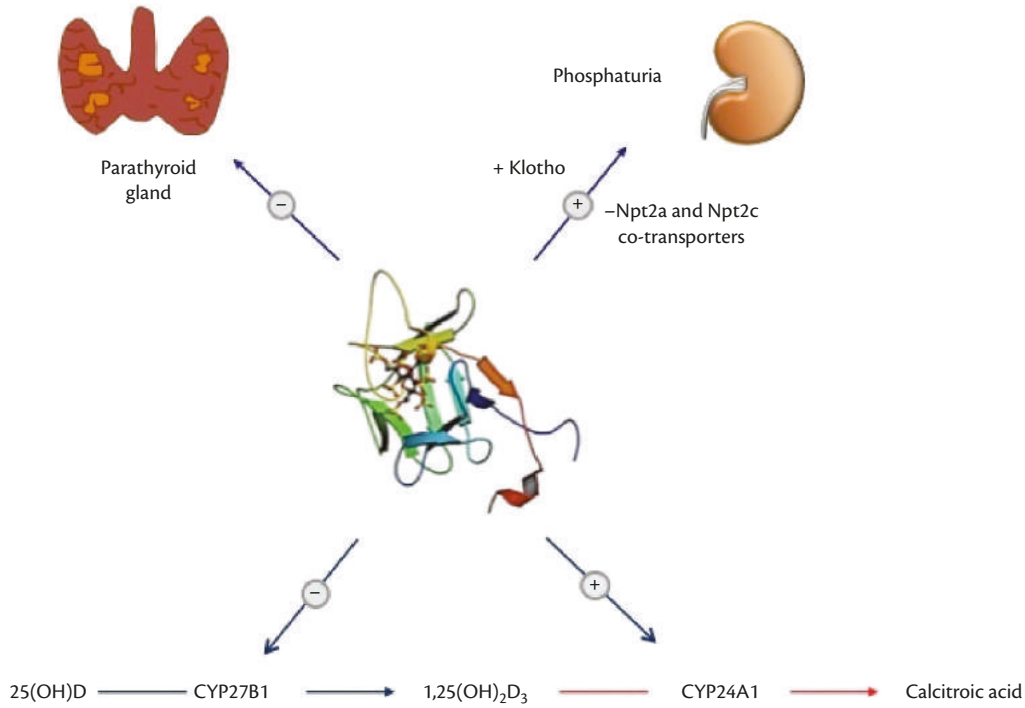

Fig. 127.2 FGF23 in vitamin D biology. Illustration of FGF23 as a negative regulator of vitamin D and summary of interaction with parathyroid gland and kidney. Crystal structure of FGF23 from Goetz et al. (2007).

ligand-activated transcription factor, predominantly located in the nucleus, or in some cells, within lipid rafts of the plasma membrane (caveolae). When bound to $1,25(OH)_2D_3$, the activated receptor recruits transcriptional cofactor molecules, including the retinoid X receptor (RXR), and translocates to vitamin D-response elements (VDREs) in the nucleus of target genes, where it acts on gene promoters to regulate transcription. VDRs located in caveolae can also mediate 'rapid responses' through activation of a number of second messenger pathways, triggering cross-talk with voltage-gated calcium or chloride channels, and thereby modulating the expression of target genes, as well as non-genomic effects (Saleh et al., 2003).

There is now overwhelming evidence that cells expressing the VDR in organs and tissues distant from the parathyroid gland, bone, kidney, and intestine, respond to 1,25 dihydroxyvitamin D exposure with important functional actions. Furthermore, VDR and CYP27B1 single-nucleotide polymorphisms (SNPs) influence the response to vitamin D receptor activators and the vitamin D binding protein, with functional, clinical consequences (Valdivielso and Fernandez, 2006; Hewison, 2012) on vitamin D metabolites (Arnaud and Constans, 1993) and their interaction with supplementation and disease. For a detailed review please see Hewison (2012). These clinical and mechanistic observations have driven research into exploring roles for vitamin D beyond bone metabolism, with the kidney, heart, and vasculature demonstrating particular involvement and interaction with the hormone. The effect of vitamin D and the VDR shall be considered in turn with discussion of its relevance to the related organ systems and disease.

Vitamin D immunobiology

As already discussed, the VDR is almost ubiquitously expressed in human cells, including cells of both the innate and adaptive immune systems. This wide distribution suggests that it has pleiotropic functions in the regulation of immune responses. These immunomodulatory functions include both anti-inflammatory ('regulatory') and some pro-inflammatory effects.

Immune cells, notably T lymphocytes (Sigmundsdottir et al., 2007), monocytes/macrophages (Koeffler et al., 1985; Reichel et al., 1987a, 1987b; Liu et al., 2006; Adams et al., 2009), and dendritic cells (DCs) (Brennan et al., 1987), express not only the VDR but also have the capacity to activate vitamin D through expression of the relevant hydroxylase enzymes (CYP271B and CYP2R1). 25-hydroxylase is basally active, whereas expression of both 1α-hydroxylase and the VDR is induced in immune cells through innate immune signals such as interferon-gamma (IFN-γ) (Reichel et al., 1987a, 1987b; Koeffler et al., 1985) and engagement of pathogen-associated molecular patterns (PAMPs), such as the toll like receptors (TLRs) (see Chapter 128) (Overbergh et al., 2000; Takeda and Akira, 2005; Liu et al., 2006; Stoffels et al., 2006; Adams et al., 2009). During infection/inflammation, both the VDR and 1α-hydroxylase are activated, resulting in the complete activation and signalling machinery of vitamin D. In the immune system, vitamin D has many roles, including cell growth and proliferation, cellular development, movement, cell-to-cell signalling, and cell death, all of which are mediated through direct effects on gene transcription (Baeke et al., 2011). Mechanistically, vitamin D complexed to the VDR modifies signals mediated by a number of intracellular transcription factors that target immune genes. These include NF-κB, AP-1, and NF-AT.

Vitamin D promotes innate immunity through induction of antimicrobial proteins, such as cathelicidin and defensins (Liu et al., 2006). Early work on vitamin D and immunity in the 1980s, whilst investigating the use of cod liver oil in the treatment of tuberculosis

(Grad, 2004), showed that active $1,25(OH)_2D$ reduces proliferation of *Mycobacterium tuberculosis* (MTB) in macrophages, an effect enhanced by IFN-γ (Rook et al., 1986) (which stimulates CYP27B1 in macrophages (Koeffler et al., 1985)). The transcriptional response to MTB has subsequently been shown to include CYP27B1 and the VDR following PAMP-sensing by TLR2/1 (Hewison, 2012, Liu et al., 2006). The monocytic response includes local activation of vitamin D in response to MTB, with $1,25(OH)_2D$ binding to endogenous VDR, supporting an intracrine pathway. The antibiotic protein cathelicidin is a direct transcriptional target for the $1,25(OH)_2D$-VDR complex (Gombart et al., 2005, Wang et al., 2004), and induction of cathelicidin enhances MTB death with monocytes (Liu et al., 2006), a response influenced by T-cell cytokines (Edfeldt et al., 2010). Vitamin D also induces cathelicidin in a number of cell lines, including bronchial epithelial cells (Yim et al., 2007), keratinocytes (Schauber et al., 2007), and myeloid cells (Gombart et al., 2005; Hewison, 2012).

Vitamin D also regulates/modifies adaptive immunity. Treatment with $1,25(OH)_2D$ inhibits dendritic cell (DC) maturation (Griffin et al., 2001), attenuating antigen presenting capacity (Hewison et al., 2003) and promoting a tolerogenic T-cell response (Penna and Adorini, 2000; Adorini et al., 2003). This results in reduced production of inflammatory cytokines such as IFN-γ (Penna and Adorini, 2000; Moro et al., 2008; Ghoreishi et al., 2009), TNF (Cohen-Lahav et al., 2007), interleukin (IL)-8, and IL-12 through both a direct effect on immune cells and indirect modification of antigen presenting cells (APCs). Thus, VDR and CYP27B1 knockout mice develop lymphatic abnormalities secondary to increased numbers of mature dendritic cell (Griffin et al., 2001, Panda et al., 2001) and disordered signalling (Enioutina et al., 2009). In addition, vitamin D modulates T-cell function away from inflammatory phenotypes (Th1 and Th17), promoting, in collaboration with IL-2, development of regulatory T cells (Tregs) and Th2 cells (Adorini, 2002; Adams and Hewison, 2008; Adorini and Penna, 2008; Brown and Slatopolsky, 2008; Joshi et al., 2011), thus regulating cell-mediated inflammatory responses. Indeed, administration of $1,25(OH)_2D$ to renal patients expands Tregs (Barrat et al., 2002), which are discussed in more detail in Chapter 128.

The net effect of vitamin D on the immune system is enhanced innate immunity to pathogens and promotion of adaptive regulatory mechanisms in favour of inflammatory ones (McGregor et al., 2014).

Vitamin D and disease

Vitamin D deficiency and insufficiency

The optimal level of vitamin D remains a subject of contention but levels of 25-hydroxyvitamin D below 20 ng/mL (~ 50nmol/L) are generally accepted as representing deficiency of vitamin D (Lips, 2004; Bischoff-Ferrari et al., 2006; Holick, 2006a, 2007; Doorenbos et al., 2009). Despite the fortification of food with vitamin D, very large numbers of healthy as well as diseased individuals remain deficient. Data from the National Health and Nutrition Examination Survey (NHANES) suggest that levels of serum vitamin D in the US population were reduced between the periods 1988–1994 and 2001–2004 (Ginde et al., 2009). Environmental factors are likely to explain this trend, with increased use of sunscreen (Marwaha et al., 2005) and a sedentary lifestyle with reduced levels of outdoor activity; both of which are associated with reduced vitamin D levels (Doorenbos et al., 2009). Approximately 41–53% of individuals in the United States have calcidiol levels < 28ng/mL (~ 70nmol/L) (Zadshir et al., 2005) and it is estimated that 1 billion individuals are vitamin D deficient worldwide (Holick, 2007), with increased prevalence in elderly cohorts and individuals with CKD, although studies have demonstrated suboptimal levels in up to 50% of adolescents also (Gordon et al., 2004; Sullivan et al., 2005). Furthermore, individuals in countries distant from the equator have reduced vitamin D levels (McKenna, 1992; Vieth, 2004). Of interest, no vitamin D is made in the skin at latitude 52° N (the latitude of London) from October to March because atmospheric ozone filters out ultraviolet B unless the sun is high enough in the sky (Webb et al., 1988). Intrinsic factors such as ethnicity also effect vitamin D levels; Non-Hispanic black people absorb more ultraviolet radiation in the melanin of their skin and therefore require more sun exposure to produce equivalent amounts of vitamin D. Such racial differences in vitamin D exposure and metabolism have been incriminated in varied survival patterns between different racial groups receiving renal replacement therapy (Wolf et al., 2008), and a recent study has suggested that ethnic differences in aortic pulse wave velocity, a measure of arterial distensibility, may be related to vitamin D levels (Rezai et al., 2011).

Vitamin D and target organ damage: overview

It is well recognized that osteoporosis and osteopenia are common in patients with CKD (Pichette et al., 1996; Marcen et al., 2007); as a subset of so-called renal bone disease. The mechanisms leading to bone disease in patients with renal dysfunction are highly complex, and some have been discussed above. In the clinical arena, there is a wealth of evidence from randomized controlled trials and subsequent meta-analyses, that replacing vitamin D in deficient individuals (Bischoff-Ferrari et al., 2009) and those with osteoporosis (Chapuy et al., 1992; Dawson-Hughes et al., 1997; Tang et al., 2007; Avenell et al., 2009) confers strong protective benefits against fractures. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines from the National Kidney Foundation provided a reference text in 2003 addressing mineral and bone disorders in CKD. Initial recommendations advised that patients with any stage of CKD should have vitamin D levels measured annually and supplementation with calcitriol or one of its analogues given to maintain levels at 30 ng/mL (~ 75nmol/L) or higher (Brown, 2001; National Kidney Foundation, 2003; Holick, 2005), to reduce PTH levels and the risk of low bone mineral density and hip fracture (National Kidney Foundation, 2003). Updated guidelines released by in 2009 took a more conservative stance, emphasizing the importance of recognizing rates of progression and trends in abnormal biochemistry, although with lack of clarification on absolute reference levels (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, 2009). For the practising clinician, issues pertaining to screening and monitoring 25-hydroxyvitamin D levels in the CKD and end-stage renal disease (ESRD) population, when to intervene and how to replete levels may remain confusing despite guidelines. The problem is born out of a lack of high-level evidence in the form of randomized controlled trials in these populations. Uncertainty in how best to implement guidance was further reviewed and discussed in a recent European Renal Best Practice statement. Although the purpose of this document was not to provide definitive guidelines, the text did provide some pragmatic consensus on specific issues to aid clinicians in managing and preventing mineral and bone disorders in the CKD population (Goldsmith et al., 2010).

The Institute of Medicine (IOM) advocates 25(OH)D serum levels of 20 ng/mL as sufficient to optimize bone mineral density (BMD) as a marker of skeletal health for most populations in the United States and Canada but concluded that there is currently insufficient trial data to support a role for vitamin D as a health outcome in non-skeletal outcomes, although encouraging further investigation to examine this possibility (Ross et al., 2011). The American Society for Bone and Mineral Research supported the stance of the IOM (Slomski, 2011), whilst others have challenged their conservative position (Heaney and Holick, 2011). The recent guidelines published by the endocrine society recommend supplementation with either vitamin D_2 or vitamin D_3 only for deficient patients, and concluded that there was not sufficient evidence to recommend screening individuals who are not at risk for deficiency or to prescribe vitamin D to attain the non-calcaemic benefit for cardiovascular protection (Holick et al., 2011).

The NHANES III study demonstrated calcidiol levels < 17.8 ng/mL (~ 44 nmol/L) to be associated with a 26% increased risk of all-cause mortality in the general population (Ginde et al., 2009). A systematic review of 35 studies reported a significant risk of mortality and cardiovascular events in individuals with mineral disturbances: data supported a greater mortality risk with elevated phosphate, followed by calcium and then PTH (Covic et al., 2009). Whilst there is increased mortality with PTH levels > 300 ng/L (Kalantar-Zadeh et al., 2006), phosphate levels and total mortality follow a U-shaped curve (Floege et al., 2011). There is also some evidence describing a U-shaped association between 25(OH)D levels and health, with higher levels linked to some rare cancers (Stolzenberg-Solomon et al., 2010), although this finding has not been consistently reproduced.

Supplementation studies with vitamin D have been inconsistent. The Women's Health Initiative (WHI) failed to show any benefit in outcomes of coronary artery calcified plaque burden (Manson et al., 2010) and cerebrovascular disease (Hsia et al., 2007) with moderate doses of calcium and low-dose vitamin D_3 (400 IU daily) supplementation in post-menopausal women over a 7-year follow-up period. The Randomised Evaluation of Calcium or Vitamin D (RECORD) trial (Avenell et al., 2012) investigated 5292 individuals, the majority of whom were women aged at least 70 years, with previous low-trauma fractures. Individuals were randomized to vitamin D_3 (800 IU), calcium (1000 mg), both, or placebo for 24–62 months, with up to 3 years of follow-up after intervention. Intention-to-treat analyses failed to show any significant benefit in vitamin D or calcium supplementation on any of the outcome measures; all-cause mortality, vascular-disease mortality, cancer mortality, and cancer incidence. Post hoc statistical analysis adjusting for compliance did show a trend in favour of reduced mortality with vitamin D, and increased mortality with calcium were accentuated, although the results remained non-significant.

A meta-analysis of 18 trials of vitamin D supplementation in a heterogeneous population demonstrated significant reduction in total mortality (Autier and Gandini, 2007), and this benefit has been reproduced in patients with ESRD (Shoji et al., 2004; Teng et al., 2005; Kalantar-Zadeh et al., 2006; Melamed et al., 2006; Tentori et al., 2006). A recent Cochrane review supported the prognostic role of vitamin D_3 supplementation in elderly, predominantly institution-bound and dependent women. The investigators analysed 50 randomized trials, including 94,148 participants to assess any mortality benefit in vitamin D supplementation (Bjelakovic et al., 2011). Most trials included elderly women (> 70 years) and vitamin D was administered for a median of 2 years. Vitamin D was shown to reduce mortality (relative risk (RR) 0.97, 95% confidence interval (CI) 0.94–1.00). When the different forms of vitamin D were assessed separately, only vitamin D_3 decreased mortality significantly, and not vitamin D_2, alfacalcidol, or calcitriol (although these analyses included smaller number and were therefore at risk of type II errors). Trial sequential analysis found that 161 individuals needed treatment to prevent one death. There was an increased risk of nephrolithiasis (RR 1.17; 95% CI 1.02–1.34) in those treated with vitamin D_3 and calcium combinations, and alfacalcidol and calcitriol increased the risk of hypercalcaemia.

Vitamin D and the kidneys

Epidemiologic data from clinical studies inform us that patients on renal replacement therapy (Wolf et al., 2007) or pre-dialysis, have more severe vitamin D deficiency than those with preserved kidney function (Gonzalez et al., 2004; LaClair et al., 2005; Jean et al., 2008). Cross-sectional studies have reported 78% and 97% of dialysis patients from the United States (Wolf et al., 2007) and Europe (Jean et al., 2008) as vitamin D deficient respectively, as defined by levels < 30 ng/mL (~ 75 nmol/L), with up to 18% (Wolf et al., 2007) severely deficient, with levels < 10 ng/mL (~ 25nmol/L). These figures are consistent with data from patients on peritoneal dialysis (Wang et al., 2008a). This association is not confined to individuals with ESRD and numerous studies have shown a positive correlation between stage of CKD and prevalence of vitamin D deficiency (Levin et al., 2007; Barreto et al., 2009). Furthermore, in patients with CKD, there is evidence that serum levels of active vitamin D are inversely related to the rate of renal decline and mortality (Levin et al., 2007; Inaguma et al., 2008; Ravani et al., 2009). Mechanistically, VDRs are present in healthy kidneys: in proximal and distal tubular epithelial cells (Tan et al., 2008), glomerular parietal epithelial cells (Zhang et al., 2008a), collecting duct cells (Kumar et al., 1994), mesangial cells (Zhang et al., 2007), and podocytes (Zhang et al., 2008a). When these cells are cultured and treated with calcitriol or vitamin D analogues, there is modulation and expression of target genes, suggesting that these receptors are functional. Importantly, hydroxylases within the kidneys facilitate the conversion of calcidiol to calcitriol, supporting an autocrine/paracrine and local relationship between the kidney and vitamin D.

In the clinical arena, these observations have been supported largely by retrospective data, showing that vitamin D supplementation is associated with reduced mortality in patients on dialysis, with a multivariate-adjusted odds ratio survival advantage of 0.60 compared to those untreated (Wolf et al., 2007). Interestingly, the greatest association between vitamin D deficiency and mortality occurs in patients without overt cardiovascular disease, hypertension, or diabetes (Melamed et al., 2008). One might speculate that injury caused by vitamin D deficiency, therefore, precedes and contributes to the development of overt cardiovascular disease. Fig 127.3 summarizes the progression of biochemical abnormalities with declining renal function and associated consequences in mineral bone disease and related cardiovascular complications.

Renin–angiotensin–aldosterone system interactions

Reduced vitamin D levels are associated with reduced renal blood flow in response to angiotensin II, providing indirect support for endogenous Renin–angiotensin–aldosterone system (RAAS) activation in response to vitamin D insufficiency (Forman et al.,

2010). Calcitriol binds to the promoter region of the renin gene, blocking the activity of cyclic AMP response elements (CREs) and thereby causing a 90% downregulation of renal mRNA expression of renin (Li et al., 2002; Yuan et al., 2007). Indeed, renin expression is increased in VDR knockout mice, where RAAS is left unsuppressed in the absence of vitamin D, with resultant phenotypic consequences of hypertension, renal injury (Li et al., 2002; Yuan et al., 2007), and myocardial hypertrophy (Li et al., 2002). Calcitriol has also been shown to inhibit genes encoding the type 1 angiotensin II receptor in a dose-dependent manner in adipocytes (Morris et al., 2005) (although this has not been studied in other cell lines), illustrating the dynamic relationship between vitamin D and the RAAS, with depleted vitamin D levels stimulating PTH release, which also work to inhibit renin. Intervention with calcitriol also decreases plasma renin and angiotensin II levels in haemodialysis patients with secondary hyperparathyroidism (Park et al., 1999; Khavandi et al., 2009). Mechanistic studies have shown that calcitriol binds to the VDR and blocks formation of the CRE–CREB–CBP complexes in the promoter region of the renin gene, thereby reducing its expression (Yuan et al., 2007; Zhang et al., 2010). Calcitriol may also contribute to excretion of urinary acids and calcium through inhibiting HCO_{3-} absorption in the medullary thick ascending limb (Good et al., 2003).

Studies of human renal tissue samples have shown reduced Klotho expression per nephron in CKD (Koh et al., 2001), with increased Klotho expression in response to calcitriol (Tsujikawa et al., 2003).

A number of animal models representing RAAS activation, including the spontaneously hypertensive rate and 5/6 nephrectomy model show downregulation of renal Klotho (Aizawa et al., 1998). Klotho is negatively regulated by angiotensin II through the type 1 (AT_1) receptor, and its effects are completely lost by losartan, but not hydralazine (Mitani et al., 2002; Yoon et al., 2011). Furthermore, restoration of Klotho by gene transfer results in improvements in angiotensin-II induced proteinuria. *In vitro* administration of calcitriol to cultured adrenocortical cells causes reduced aldosterone levels (Lundqvist et al., 2010), and this effect is thought to be primarily driven through renin, rather than directly on aldosterone, as demonstrated by the non-significant elevations in aldosterone levels in VDR-null mice (Simpson et al., 2007). It is likely that any underlying regulatory mechanisms are complex with reciprocal pathways, as evidenced by reduced Klotho expression in the DOCA salt rat model, in which there is RAAS suppression and renal damage (de Borst et al., 2011). It is well recognized that angiotensin II contributes to oxidative stress through the NADPH oxidase system (Griendling et al., 1994) and RAAS inhibition reduces reactive oxygen species (Doran et al., 2007). Salt-restricted mice showed decreased Klotho mRNA and protein expression in a dose-dependent manner in response to ciclosporin-induced renal injury. Treatment with the angiotensin II AT_1 receptor blocker, losartan, was able to rescue Klotho expression with consequent histological improvement in tubulointestinal fibrotic changes and measures of oxidative stress (Yoon et al., 2011).

Proteinuria

Large cross-sectional studies in community-dwelling individuals have demonstrated the increased risk of cardiovascular disease and all-cause mortality with decreasing eGFR (Go et al., 2004; Matsushita et al., 2010). Independent of eGFR, microalbuminuria is a strong predictor of cardiovascular disease, even in ranges considered normal (Gerstein et al., 2001; Remuzzi et al., 2006; Ruggenenti and Remuzzi, 2006). One explanation for this has been that microalbuminuria shares an underlying vascular abnormality predisposing patients to cardiovascular disease (Khavandi et al., 2009; van der Meer et al., 2010). However, it is now recognized that proteinuria also exerts damaging irreversible renal injury and contributes itself to renal decline, inflammation and fibrosis (Abbate et al., 2006). As expected, the NHANES study identified an association between vitamin D deficiency and increased risk of albuminuria (de Boer et al., 2007), although the evidence also suggests that vitamin D may protect against proteinuria (Freundlich et al., 2008) through modulation of the RAAS in cultured juxtaglomerular cells.

It is well established that activation of the RAAS is detrimental to both cardiac and renal function, with proven direct pro-fibrotic effects of aldosterone (Kramer et al., 2007) and renin (Nguyen et al., 2002). Blockade of the RAAS has therefore become established as the mainstay of therapy in patients with CKD. RAAS blockade can, however, be limited by a reactive rise in renin secondary to volume depletion (van Veldhuisen et al., 1998; de Borst et al., 2003), with consequent fibrosis (Hamming et al., 2006). Further blockade of this reactive rise in renin may therefore provide additional benefit in nephroprotection. In the 5/6 nephrectomy rat model, combined treatment with paricalcitol (a synthetic vitamin D analogue, 19-nor-1,25-dihydroxyvitamin D_2) and enalapril provided greater renal benefit than did paricalcitol or enalapril alone (Mizobuchi et al., 2007). Although data from the ONTARGET (Yusuf et al., 2008) study failed to show benefit in the primary composite endpoint of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure, combination therapy with an angiotensin-receptor blocker (ARB) and an angiotensin-converting enzyme inhibitor (ACEI), there was a reduction in the incidence of new micro- or macroalbuminuria, and reduced progression to macroalbuminuria in those with microalbuminuria, compared with individuals treated with monotherapy. This was supported in the CALM study (Mogensen et al., 2000). Although renin inhibitors affect the enzymatic activity of renin, they do not affect production (Batenburg et al., 2008) and therefore vitamin D may have a niche in further inhibition of renin production in patients with CKD, in addition to an ACEI/aldosterone blocker, or in circumstances where traditional pharmacological blockers of RAAS are contraindicated (Zhang et al., 2008b). The anti-inflammatory properties of vitamin D (discussed below) might also add to the value of vitamin D as an adjunct to RAAS blockade, as inflammation is a determinant of resistance to RAAS blockade.

Diabetic nephropathy is the single most frequent cause of ESRD in the Western world (Molitch et al., 2004) and the association between diabetes and cardiovascular and renal disease has not been fully explained (Khavandi et al., 2009), although proteinuria has emerged as a potential unifying marker. In this respect, results of the VITAL trial (de Zeeuw et al., 2010) are particularly intriguing. VITAL randomized type 2 diabetic patients with albuminuria already receiving ACEIs or ARBs to 24 weeks of treatment with placebo and 1 or 2 micrograms/day of paricalcitol. Although the primary outcome of change in urinary albumin-to-creatinine ratio (UACR) did not reach statistical significance, there was evidence of a dose-dependent reduction in proteinuria with paricalcitol, with a dose of 2 micrograms/day resulting in a 20% reduction in UACR

and between-group difference of 18% (P = 0.053). The benefit was lost when paricalcitol was stopped and individuals treated with the lower-dose paricalcitol regimen had similar adverse events profiles to those on placebo, without an increase in traditional complications of hypercalcaemia and hyperphosphataemia (Sprague et al., 2003).

The antiproteinuric effects of vitamin D were also tested by Agarwal et al. (2005), who examined data from three double-blind, randomized, placebo-controlled studies investigating use of paricalcitol for PTH suppression, with up to 24 weeks of follow-up. In patients with CKD stage 3 and 4, with secondary hyperparathyroidism, they showed that oral paricalcitol significantly reduced proteinuria (measured using urine dipstick readings), compared with placebo, with 31% having a reduction and 50% no change in proteinuria, compared to 15% and 62% respectively, in the placebo group. The benefit was observed regardless of diabetes mellitus, hypertension, and importantly, independent of use of RAAS blocking agents, supporting the potential additive antiproteinuric effects of vitamin D. The dosing regimen of paricalcitol varied from 1–2 micrograms daily to a 2–4 micrograms, three times per week regimen, depending on PTH levels and the study.

Podocyte damage has emerged as an important precipitant in CKD, through parenchymal inflammation, tubular injury, and interstitial fibrosis. The Wnt/β-catenin signalling pathway has been shown to play a role in podocyte injury, leading to proteinuria and renal fibrosis (Dai et al., 2009; He et al., 2009). Wnt proteins transmit their signals by interacting with Frizzled receptors, and their co-receptors, members of the low-density lipoprotein (LDL) receptor-related protein 5/6. This triggers downstream signals, resulting in β-catenin dephosphorylation and stabilization, resulting in translocation to the nucleus, where it binds to T cell factor (TCF) and lymphoid enhancer-binding factor, or stimulates the transcription of Wnt target genes. The VDR competes with TCF for β-catenin binding. In an animal model of Adriamycin® nephropathy—characterized by podocyte injury and albuminuria, and later inflammatory and fibrotic changes—paricalcitol has been shown to inhibit Wnt/β-catenin signalling and thereby reduce proteinuria (He et al., 2011). Paricalcitol-treated mice prevented loss of podocyte-specific neprhin, podocin and Wilms tumour 1 (WT1), with reduced glomerulosclerotic lesions. This supports the idea that paricalcitol exerts some of its antiproteinuric effects though podocyte protection.

In an open-label, non-placebo-controlled study, 50 patients with biopsy-proven immunoglobulin A nephropathy and proteinuria (> 0.8 g/day), despite treatment with RAAS blocking agents for at least 3 months, were randomized to receive two doses (0.5 micrograms) of calcitriol per week or no treatment for 48 weeks (Liu et al., 2012). There were significant reductions in proteinuria in the calcitriol-treated group compared with the control group, with percentage change in urinary protein excretion of −19% compared to +21%, respectively. These changes were independent of eGFR and blood pressure, which were not changed. These findings have been supported by other studies (Szeto et al., 2008).

A double-blind, randomized controlled trial of a heterogenous group of 61 patients with varying aetiology and stage of CKD and proteinuria tested the effect of 1 microgram daily paricalcitol on proteinuria (Fishbane et al., 2009). Subjects were followed up for up to 6 months. There was a significant decrease in proteinuria in the paricalcitol group, with changes in mean spot urine protein/creatinine ratios from baseline to last evaluation of +2.9% ± 19.0% in controls and −17.6% ± 47.8% in the paricalcitol group (P = 0.04). There were no changes in eGFR or blood pressure between the two groups.

Vitamin D and cardiovascular disease

Hypertension

A recent systematic review of the relationship between vitamin D levels and arterial hypertension by Pilz et al. concluded that adequate levels of vitamin D are associated with lower arterial blood pressures, and that the antihypertensive effect of vitamin D is greatest in individuals with a combination of both vitamin deficiency and a previous diagnosis of hypertension (Pilz et al., 2009). This was supported by another meta-analysis of three cohorts, where lower 25-hydroxyvitamin D concentrations were associated with incident hypertension, with a relative risk of 1.8. However, meta-analyses of 10 small, observational, and non-controlled trials showed supplementation non-significantly reduced systolic blood pressure (Pittas et al., 2010). Living at higher latitudes is associated with an increased risk of hypertension and cardiovascular disease (Zittermann, 2006) and in a study of patients with hypertension who were exposed to ultraviolet B radiation three times a week for 3 months, 25-hydroxyvitamin D levels increased by approximately 180% and this was associated with normalization of both systolic and diastolic blood pressure. Importantly, this benefit was not observed with ultraviolet A radiation, which has no influence on vitamin D levels (Krause et al., 1998). Although there is evidence supporting the blood pressure lowering quality of vitamin D from a number of other small trials (size varying between 30 and 150 participants) (Pfeifer et al., 2001), there remains a paucity of large trial data and the evidence is inconclusive in evaluating the effect of vitamin D supplementation on arterial blood pressure (Pilz et al., 2009).

A recent placebo-controlled study of high-dose vitamin D supplementation in hypertensive patients in Denmark during winter randomized 130 hypertensive individuals, 92 of whom had low vitamin D levels at baseline (25(OH)D < 80 nmol/L) to a daily oral dose of 75 micrograms of cholecalciferol or placebo. Over a 20-week intervention period, no significant effect on overall 24-hour ambulatory blood pressure was observed, but there were significant reductions in central systolic blood pressure, measured by applanation tonometry, of 6.8 mmHg (P = 0.007). Furthermore, in a subgroup of patients who were vitamin D deficient at the start of the study, there was a borderline significant reduction in diastolic and systolic ABPM of 2.7 mmHg (P = 0.02) and 3.7 mmHg (P = 0.08) respectively. Another study of 114 postmenopausal women with serum 25(OH)D levels between 10 and 60 ng/mL were randomized to 2500 IU of vitamin D_3 or placebo for 4 months (Gepner et al., 2011). During the short follow-up, there was no observed benefit in endothelial function (evaluated using ultrasound brachial artery flow mediated (FMD) dilatation), arterial stiffness (measured using carotid-femoral pulse wave velocity), C-reactive protein (CRP), or blood pressure. The results of the DAYLIGHT study, a double blind trial randomizing 450 participants to 25-hydroxyvitamin D supplementation with the primary endpoint of 24-hour ambulatory blood pressure monitoring are therefore eagerly awaited (Wang, 2011).

Vitamin D and diabetes

A growing body of evidence supports a role for vitamin D in glucose homeostasis and the development of diabetes mellitus: studies

have consistently reported an increased incidence of diabetes mellitus in vitamin D-deficient individuals (Isaia et al., 2001; Chiu et al., 2004; Hypponen and Power, 2006; Pittas et al., 2006; Chonchol and Scragg, 2007) and prevention of vitamin D deficiency in early life is protective against the development of type 1 diabetes (Mathieu et al., 2005; Danescu et al., 2009; Sloka et al., 2010). In animal models of type 1 diabetes, administration of high doses of active vitamin D has been shown to prevent diabetes, through immune regulation (Mathieu et al., 1994), the proposed mechanisms of which include modification of dendritic cell phenotype, lymphocyte proliferation and cytokine production (D'Ambrosio et al., 1998, van Halteren et al., 2002) (discussed in further detail below). VDRs are present in pancreatic β cells, as is the vitamin D-dependent calcium-binding protein, calbindin-D_{28k} (Sooy et al., 1999), which has been shown to be protective against cytokine-mediated beta cell destruction (Rabinovitch et al., 2001). Indeed, mechanistic studies have supported a direct effect of vitamin D on insulin action; pancreatic insulin secretion is inhibited by vitamin D deficiency (Norman et al., 1980) and animal rodent models with VDR knocked out (Zeitz et al., 2003) or with polymorphisms of the VDR (Mathieu et al., 2001, 2004; Palomer et al., 2008), have been associated with dysglycaemia. Insulin receptor numbers also increase after 24 hours of treatment with $1,25(OH)_2D_3$ in U-937 human promonocytic cells (Maestro et al., 2000). In the presence of active vitamin D, isolated beta cells from healthy animals produce insulin in response to a glucose challenge (d'Emden et al., 1989). The role of vitamin D in calcium handling is important for the action of insulin in skeletal muscle and adipose tissue (Milner and Hales, 1967; McCarty and Thomas, 2003). In a population of individuals at high risk of developing diabetes, cholecalciferol treatment was shown to increase disposition index, which reflects insulin action (Mitri et al., 2011).

Investigation of a cohort of 61 patients with type 2 diabetes mellitus and baseline 25(OH)D levels < 100 nmol/L, receiving either placebo or vitamin D_3 (with a random dose of 100,000 or 200,000 IU) (Witham et al., 2010b) found no significant difference in the primary outcome of FMD at 8 or 16 weeks. Systolic blood pressure was significantly lower in both treatment arms at 8 weeks (placebo 146.4 mmHg, 100,000 IU 141.4 mmHg, P = 0.04; 200,000 IU 136.8 mmHg (P = 0.03 vs. placebo)) and brain natriuretic peptide (BNP) was lower at 16 weeks in the 200,000 IU group compared to placebo (placebo 34 pg/mL, 200,000 IU 21 pg/mL, P = 0.02). There was no change in insulin resistance or glycosylated haemoglobin. Recent analysis of the Diabetes Prevention Program (DPP) data—a study originally designed to compare intensive lifestyle modification, metformin, and placebo in preventing diabetes mellitus in patients with 'pre-diabetes' (which included 2039 patients over a mean follow-up period of 3.2 years) showed those individuals in the highest tertile of vitamin D levels, with median concentration of 30.1 ng/mL, had a hazard ratio of 0.74 (95% CI 0.59–0.93) for developing diabetes compared with those in the lowest tertile, who had mean concentration of 12.8 ng/mL. Meta-analysis data have also supported evidence for a relationship between low vitamin D status, calcium, or dairy dietary intake, and prevalence of type 2 diabetes, metabolic syndrome (Ford et al., 2005; Pittas et al., 2007), and obesity (Wortsman et al., 2000; Arunabh et al., 2003). Central to the mechanisms proposed for the observed associations between vitamin D levels, hypertension and diabetes is alterations to RAAS, the molecular mechanisms of which were discussed previously.

Vitamin D and cerebrovascular events

Cross-sectional analyses have shown that hemiplegic patients with acute stroke have significantly reduced calcidiol concentrations compared with healthy controls (Poole et al., 2006) and a number of observational studies have shown vitamin D deficiency to be associated with stroke (Michos and Blumenthal, 2007; Anderson et al., 2010; Pilz et al., 2011). Data from a population-based study showed that elderly persons with low intake of vitamin D and low serum concentrations of calcitriol were at increased risk of future strokes, even after adjusting for confounding factors (Marniemi et al., 2005). Pilz et al. also showed low levels of calcidiol and calcitriol to be independently predictive of fatal strokes in The LUdwigshafen Risk and Cardiovascular Health (LURIC) study (Pilz et al., 2008a) in a cohort with risk factors for cardiovascular disease. Vitamin D supplementation in stroke patients has been shown to reduce osteopenia, fractures, and falls (Sato et al., 1997, 2005) and experimental studies have shown that vitamin D has antithrombotic and neuroprotective effects, with the potential to reduce ischaemic cortical injury in rats (Aihara et al., 2004; Kiraly et al., 2006). The largest prospective study on vitamin D status and stroke (Anderson et al., 2010), the Intermountain Heart Collaborative (IHC), demonstrated a twofold increased risk of incident stroke in patients with low serum 25(OH)D levels. A recent meta-analysis of RCT suggests that there is no significant effect of vitamin D on incidence of strokes (Elamin et al., 2011), although the design of the studies pooled may not have been adequate to perform such an analysis (Muscogiuri et al., 2012).

Vitamin D and ischaemic heart disease

The relationship between vitamin D and cardiovascular disease has been of particular interest over the past four decades. The Tromsø heart study, one of the earliest trials investigating the link between high vitamin D intake and myocardial infarction, initially reported a causative role for vitamin D (Linden, 1974). However, a later study refuted this result (Schmidt-Gayk et al., 1977), and the cardioprotective role of vitamin D was proposed after a positive correlation between levels of 25-$(OH)D_3$ and high density lipoprotein cholesterol levels was established (Auwerx et al., 1992). With the calcium deficiency hypothesis of hypertension (McCarron and Morris, 1987) as its basis, an investigation of the effect of ultraviolet radiation on blood pressure by Krause et al. found a significant drop in both systolic and diastolic values (Krause et al., 1998). These findings have been reproduced in a number of other cross-sectional studies (Pilz et al., 2009; Almirall et al., 2010). Similarly, insufficient vitamin D levels are associated with congestive cardiac failure, possibly through deranged intracellular calcium metabolism (Zittermann et al., 2003). Deficiency of vitamin D has also been found to be associated with increased levels of CRP and other inflammatory markers, additional independent contributors to heart failure (Zittermann, 2006).

A recent meta-analysis of 28 studies incorporating close to 100,000 participants found this figure to be as high as 57% for a cumulative outcome of cardiovascular disease, diabetes, and metabolic syndrome (Parker et al., 2010b). Negative findings published by Hsia et al. (2007) as part of the WHI in 2007 cast uncertainty on the protective role of vitamin D in cardiovascular disease. However, there have been a number of criticisms in response to drawing conclusions from the WHI on the relationship between vitamin D and cardiovascular disease: the primary endpoint of the trial was

evaluation of fracture risk, there was concomitant calcium intervention which was not adjusted for, there was sparse data for baseline vitamin D level and probably most importantly, suboptimal doses of vitamin D replacement were administered. It is therefore difficult to make accurate conclusions on cardiovascular protection from this study. A number of other cohort studies have shown a positive association between vitamin D deficiency and ischaemic heart disease (Giovannucci et al., 2008; Anderson et al., 2010; Bolland et al., 2010). However, pooled data from six randomized controlled trials was unable to show any effect on risk of myocardial infarction from vitamin D supplementation (Elamin et al., 2011) (RR 1.02; 95% CI 0.93–1.13), although these trials may have used sub-optimal dosing regimens of vitamin D also. The VITAL (VITamin D and OmegA-3 TriaL) investigators are addressing some of these shortcomings and currently recruiting 20,000 individuals with the primary endpoint of major cardiovascular events and cancer.

Vitamin D and heart failure

The majority of patients reaching ESRD have abnormalities in LV size and function (Block et al., 2004). Alterations to cardiac function and remodelling occur early in renal dysfunction and progress in concert with reducing eGFR (Levin et al., 1996; Kovesdy et al., 2010). Vitamin D deficiency is associated with congestive cardiac failure (Rostand, 1997) and the role of vitamin D in heart failure has been comprehensively reviewed elsewhere (Covic et al., 2010b). The relationship between the kidney and heart in failure of either organ is reciprocal and mutually detrimental (Ritz, 2009). Activation of an 'adaptive' cascade of neurohormonal pathways eventually leads to maladaptive changes to myocardial structure, fluid and electrolyte homeostasis, atherosclerosis, and blood pressure. The profound role of the RAAS in contributing to the pathology associated with vitamin D deficiency has already been emphasized and is clearly central to the mechanisms responsible for LV abnormalities. The Paricalcitol Capsule Benefits in Renal Failure-Induced Cardiac Morbidity (PRIMO) trial (Thadhani et al., 2012) randomized 227 patients with CKD and left ventricular hypertrophy (LVH) (with preserved LV function) to paricalcitol or placebo over a 48-week period. PTH levels were reduced after just 4 weeks in those individuals in the treatment arm, and levels stabilized over the course of the study. At 48 weeks there was no difference between groups in change of left ventricular mass index (LVMI) on magnetic resonance imaging (MRI), or in diastolic function on echo. Cardiac hospitalizations were slightly lower in the vitamin-D group as compared with the placebo group, and increases in plasma BNP were less marked in the paricalcitol group. Paricalcitol did increase serum creatinine, decrease eGFR, and was associated with a slightly higher number of adverse events, mostly due to hypercalcaemia.

High PTH levels are associated with LVH and increased LVMI in healthy and uraemic populations (Harnett et al., 1988; Saleh et al., 2003). Parathyroidectomy has been shown to reduce LVMI at 6 months (Piovesan et al., 1999) in patients with primary hyperparathyroidism. This occurs in the absence of alterations in blood pressure, supporting the notion that other risk factors drive LVH in hyperparathyroidism. Pilz and Tomaschitz have noted individual case reports of vitamin D-deficient children with dilated cardiomyopathy, suggesting that treatment with vitamin D might replicate these results *in vivo* (Pilz and Tomaschitz, 2009), although vitamin D deficiency rarely occurs in isolation and therefore other causative factors might contribute to the aetiology of cardiac abnormalities in these children. Covic et al. reported that mineral metabolism, along with anaemia and blood pressure represented the most important determinants for changes in LVMI in patients on dialysis (Devlin et al., 1988). Supplementation of calcitriol in individuals undergoing haemodialysis is associated with a decline in renin and angiotensin II levels, with consequent regression of LVH (Piovesan et al., 1999).

Animal studies have provided mechanistic data to explain these observations; in mice with a genetic disruption of the VDR, there are increased levels of plasma angiotensin II and renin mRNA protein levels in the kidney (Goodman et al., 2000), with cardiomyocyte hypertrophy, hypertension and increased levels of atrial natriuretic peptide (ANP), in addition to alterations in extracellular matrix production/deposition and fibrosis (Hujairi et al., 2004). Studies have also provided evidence for alterations in cardiac structure in response to vitamin D, independent of systemic suppression of RAAS (London et al., 2003, 2004), through local autocrine/paracrine actions (Xiang et al., 2005a). Vitamin D acts directly on cardiomyocyte structure and function, causing suppression of renin gene expression (Wang et al., 2008c). Salt-sensitive mice treated with an activated vitamin D analogue show reduced levels of BNP, ANP, and renin, mediated though downregulation of their respective genes (Bodyak et al., 2007). Similarly, vitamin D knockout mice show an increase in cardiomyocyte hypertrophy and renin levels, with the phenotypic consequences of hypertension and LVH (Xiang et al., 2005b). Human studies indicate that VDR polymorphisms may contribute to the development of LVH.

Faul et al. elegantly demonstrated the role of FGF23 in directly inducing LVH (Faul et al., 2011) through a series of human and animal studies. Cellular animal data demonstrated the development of myocyte hypertrophy in response to FGF23, whilst genetic models deficient in Klotho displayed elevated FGF23 levels, with consequent LVH. LVH was dependent on the FGF23 receptor activation of the calcineurin-nuclear factor of activated T cells (NFAT) signalling pathway; a recognized pathway in pathological hypertrophic remodelling (Heineke and Molkentin, 2006). This was independent of Klotho as a co-receptor. The investigators showed that an FGF23 receptor block to the 5/6 nephrectomy rat model of CKD attenuates hypertrophic changes, without significant changes in blood pressure (Faul et al., 2011). Following up the prospective Chronic Renal Insufficiency Cohort (CRIC) of 3070 CKD patients after 1 year, and examining baseline plasma FGF23 levels, prevalence of eccentric and concentric LVH was found to be inversely associated with increasing quartiles of baseline FGF23 ($P < 0.001$) after adjustment for a number of important co-variables, including blood pressure. In a subset of 411 patients without LVH at recruitment, elevated FGF23 at baseline predicted the incidence of LVH during the follow-up over an average of 3 years. Indeed, for every unit increase in FGF23 there was seen a corresponding 4.4-fold increased risk ($P = 0.001$) of LVH (Faul et al., 2011).

In a cohort of 158 patients on long-term haemodialysis, Matias et al. (2010) examined the effect of oral cholecalciferol supplementation on various mineral, inflammatory, and cardiac parameters prospectively over 1 year. Oral cholecalciferol was prescribed once or three times per week, after each haemodialysis session, with regimens varying from 50,000 IU once a week (in those with 25(OH) D levels <15 ng/mL), to 10,000 once a week (levels between 16 and 30 ng/mL) and 2,700 IU three times per week when levels were >30 ng/mL. Although there was no control group, there was a

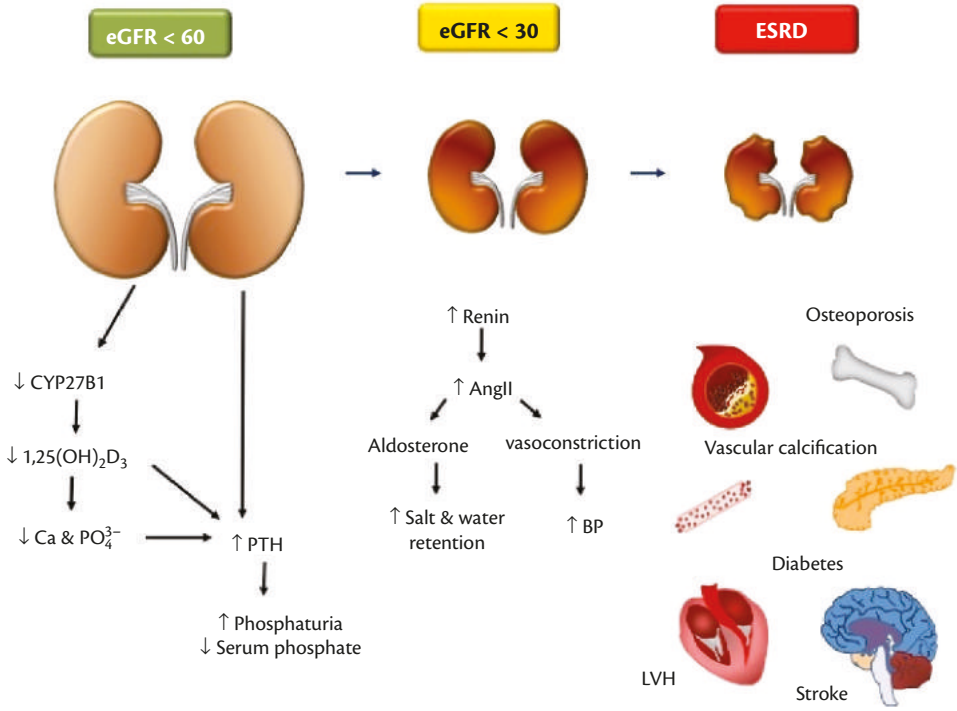

Fig. 127.3 Biochemical abnormalities with declining renal function. Schematic diagram demonstrating progression of biochemical abnormalities with declining renal function and associated consequences in mineral bone disease and related cardiovascular complications.

reduction in serum calcium, phosphate and PTH after cholecalciferol supplementation. There was a reduction in CRP and improvements in albumin levels. Interestingly, BNP levels and LVMI were significantly reduced after cholecalciferol supplementation, and this correlated with the percentage change in 25(OH)D levels, independent of angiotensin blocking agents. There are no large, controlled intervention studies of vitamin D supplementation in heart failure which have shown any functional, structural or haemodynamic benefit (Schleithoff et al., 2006; Witham et al., 2010a), although some other studies have shown a reduction in TNF-α, and BNP (Witte et al., 2005; Muscogiuri et al., 2012).

A cross-sectional study of > 3000 patients found a significant correlation between low levels of both $25(OH)D_3$ and $1,25(OH)_2D_3$, and rates of heart failure and sudden cardiac death (SCD) (Fig. 127.3) (Pilz et al., 2008b). Pilz et al. found that the hazard ratios for death due to heart failure and for SCD were 2.84 (1.20–6.74) and 5.05 (2.13–11.97), respectively, at the 95% CI for patients with severe vitamin D deficiency. These findings were independent of other risk factors, and echo those of Zitterman et al. who found an independent association of high mortality rates in individuals with end-stage heart failure and very low levels of vitamin D (Zittermann and Koerfer, 2008). Drechsler and the 4D investigators confirmed that patients with severe vitamin D deficiency, with 25(OH)D level < 25 nmol/L (~ 10 ng/mL) had a threefold higher risk of SCD compared with those with sufficient 25(OH)D levels, defined as > 75 nmol/L (~ 30 ng/mL) (Drechsler et al., 2010). Measured serum levels of BNP and markers of LVH have been found to correlate negatively with levels of vitamin D (Matias et al., 2010). In conjunction with current understanding of the pathophysiology of heart failure, this association may be due to the effects of vitamin D on immune regulation in addition to its haemodynamic role, as discussed above (Hajjar et al., 2010). Conversely, animal models show that $1,25(OH)_2D_3$ modulates cardiomyocyte contractility via a number of signalling mechanisms, potentiating relaxation and reducing the hypercontractility associated with diastolic heart failure (Green et al., 2006). Prevention of vitamin D deficiency is likely to prove a useful target for reducing incidence of heart failure and SCD.

Vitamin D and vascular biology

Endothelial dysfunction is an early insult in cardiovascular pathophysiology. Vitamin D deficiency has been associated with increased arterial stiffness and endothelial dysfunction, although supplementation studies to reverse these changes have been inconsistent. In 23 healthy subjects, vitamin D deficiency was shown to be associated with impaired brachial artery FMD (Jablonski et al., 2011)—a validated measure of endothelial dysfunction. In a larger study of 554 healthy individuals, serum vitamin D was associated with improved brachial artery FMD (Al Mheid et al., 2011), and these findings have been reproduced in diabetic cohorts (Yiu et al., 2011). Amongst the proposed mechanisms for the endothelial protection conferred by vitamin D are interactions with RAAS, smooth muscle cell remodelling, adhesion molecule expression, and anti-inflammatory changes with cytokines modulation (Muscogiuri et al., 2012). Not all studies, however, have shown positive effects of vitamin D on endothelial health. A trial of 61 diabetic patients randomized to high-dose vitamin D_3 failed to show any improvement in FMD at 8 and 16 weeks, although a blood pressure lowering effect was observed (Witham et al., 2010b). Another small, double-blind, randomized controlled trial of 24 patients piloted the effect of paricalcitol treatment on haemodynamic and biochemical factors (Alborzi et al., 2008): the majority of patients were in CKD stage 3, and those with CKD stage 4, 5, or ESRD were

excluded from the study. All patients were taking an angiotensin blocking agent at time of recruitment. Paricalcitol had no significant beneficial effects on FMD or blood pressure, although there were statistically significant reductions in CRP levels and proteinuria in the treatment group versus placebo. It is possible that there exist ethnic variations in response to vitamin D supplementation, and in a study of African American adults, 60,000 IU per month of oral vitamin D_3 for 16 weeks was shown to improve endothelial function (Harris et al., 2011).

Investigators in Dundee have recently completed a number of clinical studies investigating vitamin D supplementation on cardiovascular health. In a double-blind, placebo-controlled trial of 75 patients with a history of myocardial infarction, patients were randomized to receive 100,000 units of oral vitamin D_3 or placebo at baseline, 2 months, and 4 months (total dose of 300,000 units) (Witham et al., 2013). The primary outcome was endothelial function measured using reactive hyperaemia index on fingertip plethysmography, with 6 months of follow-up. The study failed to show any between-group difference in change in endothelial function, and the only secondary outcome to show a significant difference was decline in CRP, which was greater in the intervention group (−1.3 vs 2.0 mg/L; P = 0.03) compared with placebo. There were no significant differences in blood pressure, total cholesterol, or other serological parameters including TNF-α, BNP, and thrombomodulin. A similar protocol was performed on 58 patients with a history of stroke, and baseline 25(OH)D levels < 75 nmol/L (Witham et al., 2012). Individuals were randomized to 100,000 units of oral vitamin D_2 or placebo at baseline, and various serological tests including lipids, myocardial and inflammatory biomarkers, as well as vascular parameters (endothelial function measured using brachial artery FMD) and blood pressure measured at baseline, 8 weeks, and 16 weeks. The only positive significant difference was FMD at 8 weeks (6.9% vs 3.7%; P = 0.007), but repeat measures at 16 weeks showed no significant change. The investigators proposed that the relatively high average age of participants (67 years) and history of cerebrovascular disease may reflect advanced, established vascular changes, which are more difficult to reverse. It should also be noted that > 80% of individuals were on an angiotensin blocking agent.

Vascular calcification in CKD has been comprehensively reviewed by Covic et al. (2010a). Arterial stiffness has emerged as a powerful predictor of cardiovascular and all-cause mortality in patients with CKD (Blacher et al., 1999), hypertension (Laurent et al., 2001), and healthy individuals in the general population (Willum-Hansen et al., 2006). Dialysis patients have very high calcification scores (Hujairi et al., 2004) and arterial calcification is common in patients with CKD, manifesting early in disease (Goodman et al., 2000). Calcification of arterial intima and media are both independently predictive of all-cause and cardiovascular mortality (London et al., 2003). Low levels of vitamin D are associated with increased vascular stiffness (London et al., 2007) in patients with renal disease. Vascular stiffness is a strong predictor of cardiovascular and all-cause mortality, through increasing afterload, contributing to LVH and reducing coronary perfusion (London et al., 2004). Hyperphosphataemia has been associated with mortality in dialysis and pre-dialysis CKD populations, and this has been postulated as being secondary to vascular calcification (Block et al., 1998; Voormolen et al., 2007). The resulting high serum phosphate levels have been associated with increased carotid intima–media thickness (Kuang et al., 2009), a widely used marker for atherosclerosis. Bone mineral density is reduced with decreasing eGFR (Rix et al., 1999) and there is an inverse relationship between bone mineral density and carotid intima–media thickness (Nakashima et al., 2003), coronary artery calcification (Braun et al., 1996), and increased cardiovascular mortality in CKD patients (Taal et al., 2003) and the general population (Samelson et al., 2004). It has been shown in dialysis and non-dialysis dependent CKD patients that hypercalcaemia is associated with an increased risk of death, possibly due to increased vascular calcification (Block et al., 2004; Kalantar-Zadeh et al., 2006; Kovesdy et al., 2010).

It is known that elevated phosphate induces changes in the phenotype of cultured vascular smooth muscle cells to osteoblast like cells, which can then deposit calcium in the vascular wall (El-Abbadi and Giachelli, 2007). This effect is dependent on a sodium-dependent phosphate co-transporter, Pit-1, that enables entry of phosphate into cells and is upregulated in uraemia and calcified arteries; abnormal function may increase the tendency to calcification (Chen et al., 2002). There is now evidence that elevations in serum phosphate within 'normal' ranges, is associated with increased cardiovascular disease (Dhingra et al., 2007; Foley et al., 2008), notably LVH and vascular calcification (Foley et al., 2009) in community dwelling individuals.

Although original animal studies described the promotion of arterial calcification by high doses of vitamin D (Mertens and Muller, 2010), recent trials on humans suggest the opposite. In a cross-sectional examination of 203 subjects from the Northern Manhattan Study (Carrelli et al., 2011), there was an inverse relationship between 25(OH)D and both intima–media thickness (−0.01 per 10 ng/mL increase; P = 0.05) and maximal carotid plaque thickness (= −0.10 per 10-ng/mL increase; P = 0.03). Another large prospective trial demonstrated that vitamin D levels were associated with increased risk of developing coronary artery calcification, after adjusting for a number of cardiovascular and metabolic covariates. Interestingly, this study showed no correlation between low levels of the vitamin D and prevalence of atherosclerosis (de Boer et al., 2009). Similarly, London et al. reported a positive association between low levels of vitamin D and markers for atherosclerosis in a cross-sectional study of dialysis patients (London et al., 2007). A population-based cohort study suggests that low levels of vitamin D play a role in subclinical atherosclerotic plaque formation (Reis et al., 2009), and vitamin D deficiency is associated with a particularly strong risk of coronary atherosclerosis in CKD cohorts (de Boer et al., 2009). Andrade et al. have shown an association between central arterial stiffness (CAS) as assessed by augmentation index and low 1,25-$(OH)_2D_3$ levels, and have also demonstrated a link between CAS and inflammatory markers such as CRP and certain matrix metalloproteinases (MMP) (Andrade et al., 2008). Although traditionally described as 'non-classical', these actions of vitamin D are regarded increasingly as key to its cardiovascular protective role (Matias et al., 2010).

There is currently inconsistent data on the effect of vitamin D on lipids (Gannage-Yared et al., 2003; Zittermann et al., 2009; Rajpathak et al., 2010). In a group of healthy individuals, serum 25(OH)D levels were inversely associated with serum low-density lipoprotein cholesterol (LDL-c) (Gannage-Yared et al., 2009) in male subjects, independent of body mass index (Chiu et al., 2004). In a supplementation trial in postmenopausal women, there was no associated improvement in lipid profile with calcium and vitamin D supplementation (Gannage-Yared et al., 2003, Rajpathak et al.,

2010). One study found calcium and vitamin D supplementation to be associated with reduced LDL-c levels, but the study design included a parallel weight loss programme (Major et al., 2007). A randomized controlled trial (Rajpathak et al., 2010) of overweight individuals found reductions in triglyceride concentrations but no reduction in LDL-c over a 12-month supplementation period (Zittermann et al., 2009).

The chemokine CCL5/RANTES is a key mediator of atherogenesis and is mediated by expression of the NF-κB cellular inflammatory response regulator. The p65 subunit of the NF-κB protein complex binds to the VDR in proximal tubular epithelial cells *in vitro*, forming an anti-inflammatory complex which prevents the expression of CCL5/RANTES, and thereby modulates atherogenesis in addition to more immediate immune mechanisms. In mesangial cells, vitamin D suppresses the activity of CCL2/MCP-1 through actions on the IκBα subunit of NF-κB (Zhang et al., 2007). Calcitriol has also been shown to suppress NF-κB activity in macrophages and reduce the production of TNF (Cohen-Lahav et al., 2007), which has been implicated in vascular dysfunction and metabolic syndrome (Greenstein et al., 2009).

Vitamin D and immune-mediated pathology

A number of studies support an anti-inflammatory role for vitamin D (Mathieu and Adorini, 2002; Tan et al., 2008), not least murine experiments in which targeted disruption of vitamin D biochemistry (knockouts of the VDR or CYP27B1) increases susceptibility to autoimmune diseases (Adorini and Penna, 2008). This is in keeping with epidemiological studies in humans demonstrating associations between vitamin D insufficiency and autoimmune diseases including type 1 diabetes (Hypponen et al., 2001; Hypponen and Power, 2006), multiple sclerosis (MS) (Smolders et al., 2008), Crohn disease (Lim et al., 2005), systemic lupus erythematosus (Kamen and Aranow, 2008), rheumatoid arthritis (Adorini and Penna, 2008), and Grave disease (Goswami et al., 2009). Indeed, polymorphisms in genes for the VDR and CYP27B1 protect against type 1 diabetes (Ramos-Lopez et al., 2006; Bailey et al., 2007), as previously discussed. Clinically, this translates to an inverse relationship between vitamin D levels and CRP (Matias et al., 2010). The significance of this in the cardiorenal nexus is the strong association between chronic inflammation and both cardiac and renal disease (Vidt, 2006; He et al., 2010), suggesting that vitamin D depletion can enhance cardiovascular risk through both direct effects on the cardiovascular system and indirectly through promotion of chronic inflammation.

It is well recognized that vitamin D is an effective therapeutic tool for certain inflammatory conditions such as psoriasis (Thaci et al., 2001) and that vitamin D repletion is at least a safe manoeuvre in vitamin-deficient human kidney transplant recipients (Courbebaisse et al., 2009). In rats, treatment with active vitamin D results in improved graft survival after kidney transplantation (Redaelli et al., 2002).

Emerging evidence also suggests that vitamin D-mediated upregulation of the natural antimicrobial proteins cathelicidin (CAP) (Wang et al., 2004) (through AP-1 and p38 (Dai et al., 2010)) and β-defensin 4 (DEFB4) (Wang et al., 2004), provides pro-inflammatory functions that are critical to health, although data in support of this assertion is largely circumstantial and poorly characterized. As expected, in a cohort of septic patients in the intensive care unit, serum levels of cathelicidin correlate with vitamin D levels (Jeng et al., 2009). Cathelicidin induction (at least from human keratinocytes) by vitamin D is significantly enhanced by the presence of the highly pro-inflammatory cytokine IL-17 (Peric et al., 2008) and appears to be a critical mediator of immunity against infection: low levels of CAP (and 25(OH)D) are associated with poorer outcomes from sepsis in ITU (Jeng et al., 2009) and higher infection rates in patients with end-stage kidney disease (Gombart et al., 2009).

Vitamin D has been proposed to be important in preventing complications of chronic obstructive pulmonary disease (COPD) (Janssens et al., 2009). Polymorphisms in the VDR have been shown to influence decline in lung function, and the risk of wheezing (Bosse et al., 2009), asthma control and response to steroid therapy in children (Raby et al., 2004) and adults (Raby et al., 2004). Vitamin D upregulation of antimicrobial peptides may protect against viral and bacterial exacerbations in COPD (Celli and Barnes, 2007). COPD is now recognized as a generalized inflammatory state; analogous to the inflammatory environment seen in atherosclerotic cardiovascular disease, and therefore some benefits from vitamin D may be conferred through these pathways (Koli and Keski-Oja, 2000). In the NHANES III data, higher serum 25(OH) D levels were associated with improvement in forced expiratory volume in 1 second (FEV_1) (Black and Scragg, 2005), although baseline vitamin D levels did not influence rate of FEV decline over 6 years of follow-up in the 196 smokers in the Lung Health Study (Kunisaki et al., 2011). A recent randomized trial of intermittent 4-weekly boluses of 100,000 IU of vitamin D_3 or placebo in 182 patients with moderate to severe COPD failed to show any difference in the primary outcome of time to exacerbation over 1 year of follow-up, although a subset of patients with very low baseline 25(OH)D levels (< 10 ng/mL) did see a difference. Secondary outcomes of hospitalization, quality of life, FEV_1 and mortality rates were also unchanged (Lehouck et al., 2012).

Vitamin D has been postulated to have protective effects in multiple sclerosis (MS) (Cantorna et al., 1996; Spach et al., 2004). In a large prospective study of 200,000 women over 30 years, using a comprehensive nutrition questionnaire, the incidence of MS decreased with increasing vitamin D intake (Munger et al., 2004). The large MS genome-wide association study implicated vitamin D genes in synthesis and degradation (Sawcer et al., 2011). A recent study examined the effect of 20,000 IU vitamin per week to standard disease modifying treatment in 66 patients with relapsing-remitting multiple sclerosis (Chataway, 2012; Soilu-Hanninen et al., 2012). There was a non-significant trend in change of the primary outcome of T2 lesion volume on MRI scans between the two groups, with a median increase of 287 mm^3 in the placebo group compared with 83 mm^3 in the vitamin D treated group after 1 year of treatment. There was significant improvement in gadolinium enhancing lesions and a small improvement in the Expanded Disability Status Scale (EDSS) and walking tests. Circulating levels of 25(OH)D have been shown to correspond with Treg activity in patients with MS (Smolders et al., 2008; Royal et al., 2009s) through direct effects on T cells and indirect pathways on antigen presentation to T-cells mediated through local dendritic cell expression of CYP27B1 and intracrine synthesis of $1,25(OH)_2D$.

The Nurses' Health Study sought to examine the association between baseline vitamin D levels and the risk of developing Crohn's Disease (Ananthakrishnan et al., 2012). The study benefited from follow -p data on 72,719 women over 22-years, equating

to 1,492,811 person-years, however, the investigators used a multivariate model to predict 25(OH)D levels from self-reported dietary intake—a prediction tool used and validated in male participants from the Health Professionals Follow-up Study. The study showed that vitamin D sufficient women (predicted 25(OH)D levels ≥ 30 ng/mL) had a 62% lower probability of being diagnosed with Crohn disease compared with those individuals vitamin D deplete (predicted 25(OH)D <20 ng/mL), with a hazard ratio of 0.38 (95% CI 0.15–0.97, p = 0.048). Women in the top 2 quartiles of 25(OH) D levels had an even greater apparent protection from developing Crohn disease, and for each 1ng/mL increase in predicted 25(OH) D levels, there was an associated 6% relative reduction in the risk of developing Crohn disease (multivariate HR, 0.94; 95% CI, 0.89–0.99; p = 0.03).

Serum levels of 25(OH)D < 75 nM are associated with a higher incidence of TB (Wilkinson et al., 2000, Wejse et al., 2009), although causative effects remain uncertain. A dose of 100,000 IU 2.5mg vitamin D_2 suppressed growth of MTB in samples of whole blood *in vitro* (Martineau et al., 2007). Studies using vitamin D supplementation (10,000 IU vitamin D_3 daily) with conventional TB therapy have reduced the time to obtaining a negative acid-fast bacillus (AFB) sputum smear (Nursyam et al., 2006). Two randomized controlled trial of vitamin D_3 (Wejse et al., 2009; Martineau et al., 2011) using three to four doses of 100,000 IU were, however, unable to demonstrate any benefit in clinical outcomes for patients with TB, although one of these trials did not show any elevation in serum 1,25(OH)D levels in the treatment group (Wejse et al., 2009). Sub-analyses did show improvement in time to negative AFB sample in a cohort of TB patients with the Taq1 tt SNP within the VDR gene (Martineau et al., 2007). Vitamin D has been proposed as a potential therapy in other mycobacterial disease, including tuberculoid leprosy (Chaglassian, 1948). Vitamin D deficiency has also been linked with infection and mortality in patients with ESRD (Gombart et al., 2009).

Conclusions

Although vitamin D has been known to medical science for almost a century, it is only in the last 15 -20 years that we have realized that the biological effects of vitamin D extend far beyond the control of calcium metabolism. Recent observational evidence suggests strong links between low vitamin D levels and an impressively wide range of cardiovascular, renal and immune-mediated conditions, including stroke, myocardial infarction, sudden cardiac death, LV mass and function, arterial calcification, hypertension, diabetes, albuminuria, infectious disease, MS, airway disease, and CKD. Predictably therefore interest in this fascinating biological area has mushroomed with a plethora of laboratory, translational, and clinical studies appearing. Despite these efforts, many questions remain unanswered and challenges remain to be overcome, including the current lack of standardization of vitamin D assays, the complexity of the other related biological pathways with which vitamin D and its metabolites interact, and also the many genetic factors affecting the handling and activity of vitamin D in man.

Although there are no definitive renal or cardiovascular guidelines on the subject matter, a number of consensus documents highlight the difficulty in justifying renal supplementation for potential non-skeletal benefits at the current time, in the absence of large, high-quality trial evidence. Interventional studies in several of these therapeutic areas—from large-scale epidemiological 'supplement' strategies to more targeted use of vitamin D analogues—are now beginning to explore whether manipulating vitamin D levels can modify vascular health and prevent cardiorenal diseases: particular interest will be focused on any potential benefit that may accrue from oral vitamin supplementation (cheap and safe) in the battle to prevent malign cardiac and renal outcomes in the millions of subjects with mild-to-moderate CKD.

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References

Abbate, M., Zoja, C., and Remuzzi, G. (2006). How does proteinuria cause progressive renal damage? *J Am Soc Nephrol*, 17, 2974–84.

Adams, J. S. and Hewison, M. (2008). Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. *Nat Clin Pract Endocrinol Metab*, 4, 80–90.

Adams, J. S., Ren, S., Liu, P. T., *et al.* (2009). Vitamin d-directed rheostatic regulation of monocyte antibacterial responses. *J Immunol*, 182, 4289–95.

Adorini, L. (2002). Immunomodulatory effects of vitamin D receptor ligands in autoimmune diseases. *Int Immunopharmacol*, 2, 1017–28.

Adorini, L. and Penna, G. (2008). Control of autoimmune diseases by the vitamin D endocrine system. *Nat Clin Pract Rheumatology*, 4, 404–12.

Adorini, L., Penna, G., Giarratana, N., *et al.* (2003). Tolerogenic dendritic cells induced by vitamin D receptor ligands enhance regulatory T cells inhibiting allograft rejection and autoimmune diseases. *J Cell Biochem*, 88, 227–33.

Agarwal, R., Acharya, M., Tian, J., *et al.* (2005). Antiproteinuric effect of oral paricalcitol in chronic kidney disease. *Kidney Int*, 68, 2823–8.

Aihara, K., Azuma, H., Akaike, M., *et al.* (2004). Disruption of nuclear vitamin D receptor gene causes enhanced thrombogenicity in mice. *J Biol Chem*, 279, 35798–802.

Aizawa, H., Saito, Y., Nakamura, T., *et al.* (1998). Downregulation of the Klotho gene in the kidney under sustained circulatory stress in rats. *Biochem Biophys Res Commun*, 249, 865–71.

Al Mheid, I., Patel, R., Murrow, J., *et al.* (2011). Vitamin D status is associated with arterial stiffness and vascular dysfunction in healthy humans. *J Am Coll Cardiol*, 58, 186–92.

Alborzi, P., Patel, N. A., Peterson, C., *et al.* (2008). Paricalcitol reduces albuminuria and inflammation in chronic kidney disease: a randomized double-blind pilot trial. *Hypertension*, 52, 249–55.

Alexander, R. T., Woudenberg-Vrenken, T. E., Buurman, J., *et al.* (2009). Klotho prevents renal calcium loss. *J Am Soc Nephrol*, 20, 2371–9.

Almirall, J., Vaqueiro, M., Bare, M. L., *et al.* (2010). Association of low serum 25-hydroxyvitamin D levels and high arterial blood pressure in the elderly. *Nephrol Dial Transplant*, 25, 503–9.

Ananthakrishnan, A. N., Khalili, H., Higuchi, L. M., *et al.* (2012). Higher predicted vitamin D status is associated with reduced risk of Crohn's disease. *Gastroenterology*, 142, 482–9.

Anderson, J. L., May, H. T., Horne, B. D., *et al.* (2010). Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. *Am J Cardiol*, 106, 963–8.

Andrade, J., Er, L., Ignaszewski, A., *et al.* (2008). Exploration of association of 1,25-OH2D3 with augmentation index, a composite measure of arterial stiffness. *Clin J Am Soc Nephrol*, 3, 1800–6.

Arnaud, J. and Constans, J. (1993). Affinity differences for vitamin D metabolites associated with the genetic isoforms of the human serum carrier protein (DBP). *Hum Genet*, 92, 183–8.

Arunabh, S., Pollack, S., Yeh, J., *et al.* (2003). Body fat content and 25-hydroxyvitamin D levels in healthy women. *J Clin Endocrinol Metab*, 88, 157–61.

Autier, P. and Gandini, S. (2007). Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med*, 167, 1730–7.

Auwerx, J., Bouillon, R., and Kesteloot, H. (1992). Relation between 25-hydroxyvitamin D3, apolipoprotein A-I, and high density lipoprotein cholesterol. *Arterioscler Thromb*, 12, 671–4.

Avenell, A., Gillespie, W. J., Gillespie, L. D., *et al.* (2009). Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev*, 2, CD000227.

Avenell, A., MacLennan, G. S., Jenkinson, D. J., *et al.* (2012). Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). *J Clin Endocrinol Metab*, 97, 614–22.

Baeke, F., Korf, H., Overbergh, L., *et al.* (2011). The vitamin D analog, TX527, promotes a human CD4+CD25highCD127low regulatory T cell profile and induces a migratory signature specific for homing to sites of inflammation. *J Immunol*, 186, 132–42.

Bailey, R., Cooper, J. D., Zeitels, L., *et al.* (2007). Association of the vitamin D metabolism gene CYP27B1 with type 1 diabetes. *Diabetes*, 56, 2616–21.

Barrat, F. J., Cua, D. J., Boonstra, A., *et al.* (2002). In vitro generation of interleukin 10-producing regulatory CD4(+) T cells is induced by immunosuppressive drugs and inhibited by T helper type 1 (Th1)- and Th2-inducing cytokines. *J Exp Med*, 195, 603–16.

Barreto, D. V., Barreto, F. C., Liabeuf, S., *et al.* (2009). Vitamin D affects survival independently of vascular calcification in chronic kidney disease. *Clin J Am Soc Nephrol*, 4, 1128–35.

Batenburg, W. W., De Bruin, R. J., Van Gool, J. M., *et al.* (2008). Aliskiren-binding increases the half life of renin and prorenin in rat aortic vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol*, 28, 1151–7.

Ben-Dov, I. Z., Galitzer, H., Lavi-Moshayoff, V., *et al.* (2007). The parathyroid is a target organ for FGF23 in rats. *J Clin Invest*, 117, 4003–8.

Bischoff-Ferrari, H. A., Giovannucci, E., Willett, W. C., *et al.* (2006). Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr*, 84, 18–28.

Bischoff-Ferrari, H. A., Willett, W. C., Wong, J. B., *et al.* (2009). Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med*, 169, 551–61.

Bjelakovic, G., Gluud, L. L., Nikolova, D., *et al.* (2011). Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev*, 7, CD007470.

Blacher, J., Guerin, A. P., Pannier, B., *et al.* (1999). Impact of aortic stiffness on survival in end-stage renal disease. *Circulation*, 99, 2434–9.

Black, P. N. and Scragg, R. (2005). Relationship between serum 25-hydroxyvitamin d and pulmonary function in the third national health and nutrition examination survey. *Chest*, 128, 3792–8.

Block, G. A., Hulbert-Shearon, T. E., Levin, N. W., *et al.* (1998). Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*, 31, 607–17.

Block, G. A., Klassen, P. S., Lazarus, J. M., *et al.* (2004). Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*, 15, 2208–18.

Bodyak, N., Ayus, J. C., Achinger, S., *et al.* (2007). Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in Dahl salt-sensitive animals. *Proc Natl Acad Sci U S A*, 104, 16810–15.

Bolland, M. J., Bacon, C. J., Horne, A. M., *et al.* (2010). Vitamin D insufficiency and health outcomes over 5 y in older women. *Am J Clin Nutr*, 91, 82–9.

Bosse, Y., Lemire, M., Poon, A. H., *et al.* (2009). Asthma and genes encoding components of the vitamin D pathway. *Respir Res*, 10, 98.

Brannon, P. M., Yetley, E. A., Bailey, R. L., *et al.* (2008). Overview of the conference 'Vitamin D and Health in the 21st Century: an Update'. *Am J Clin Nutr*, 88, 483S–90S.

Braun, J., Oldendorf, M., Moshage, W., *et al.* (1996). Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. *Am J Kidney Dis*, 27, 394–401.

Brennan, A., Katz, D. R., Nunn, J. D., *et al.* (1987). Dendritic cells from human tissues express receptors for the immunoregulatory vitamin D3 metabolite, dihydroxycholecalciferol. *Immunology*, 61, 457–61.

Brown, A. J. (2001). Therapeutic uses of vitamin D analogues. *Am J Kidney Dis*, 38, S3–19.

Brown, A. J. and Slatopolsky, E. (2008). Vitamin D analogs: therapeutic applications and mechanisms for selectivity. *Mol Aspects Med*, 29, 433–52.

Cantorna, M. T., Hayes, C. E., and Deluca, H. F. (1996). 1,25-Dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. *Proc Natl Acad Sci U S A*, 93, 7861–4.

Carrelli, A. L., Walker, M. D., Lowe, H., *et al.* (2011). Vitamin D deficiency is associated with subclinical carotid atherosclerosis: the Northern Manhattan study. *Stroke*, 42, 2240–5.

Carter, G. D. (2011). Accuracy of 25-hydroxyvitamin D assays: confronting the issues. *Curr Drug Targets*, 12, 19–28.

Celli, B. R. and Barnes, P. J. (2007). Exacerbations of chronic obstructive pulmonary disease. *Eur Respir J*, 29, 1224–38.

Chaglassian, H. T. (1948). Calciferol treatment of leprosy; preliminary report of two cases. *J Invest Dermatol*, 10, 303.

Chang, Q., Hoefs, S., Van Der Kemp, A. W., *et al.* (2005). The beta-glucuronidase klotho hydrolyzes and activates the TRPV5 channel. *Science*, 310, 490–3.

Chapuy, M. C., Arlot, M. E., Duboeuf, F., *et al.* (1992). Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med*, 327, 1637–42.

Chataway, J. (2012). Treating multiple sclerosis with vitamin D. *J Neurol Neurosurg Psychiatry*, 83, 473.

Chen, C. D., Podvin, S., Gillespie, E., *et al.* (2007). Insulin stimulates the cleavage and release of the extracellular domain of Klotho by ADAM10 and ADAM17. *Proc Natl Acad Sci U S A*, 104, 19796–801.

Chen, N. X., O'neill, K. D., Duan, D., *et al.* (2002). Phosphorus and uremic serum up-regulate osteopontin expression in vascular smooth muscle cells. *Kidney Int*, 62, 1724–31.

Chiu, K. C., Chu, A., Go, V. L., *et al.* (2004). Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr*, 79, 820–5.

Chonchol, M. and Scragg, R. (2007). 25-Hydroxyvitamin D, insulin resistance, and kidney function in the Third National Health and Nutrition Examination Survey. *Kidney Int*, 71, 134–9.

Cohen, D., Green, M. S., Block, C., *et al.* (1991). Prospective study of the association between serum antibodies to lipopolysaccharide O antigen and the attack rate of shigellosis. *J Clin Microbiol*, 29, 386–9.

Cohen-Lahav, M., Douvdevani, A., Chaimovitz, C., *et al.* (2007). The anti-inflammatory activity of 1,25-dihydroxyvitamin D3 in macrophages. *J Steroid Biochem Mol Biol*, 103, 558–62.

Courbebaisse, M., Thervet, E., Souberbielle, J. C., *et al.* (2009). Effects of vitamin D supplementation on the calcium-phosphate balance in renal transplant patients. *Kidney Int*, 75, 646–51.

Covic, A., Kanbay, M., Voroneanu, L., *et al.* 2010a. Vascular calcification in chronic kidney disease. *Clin Sci (Lond)*, 119, 111–21.

Covic, A., Kothawala, P., Bernal, M., *et al.* (2009). Systematic review of the evidence underlying the association between mineral metabolism disturbances and risk of all-cause mortality, cardiovascular mortality and cardiovascular events in chronic kidney disease. *Nephrol Dial Transplant*, 24, 1506–23.

Covic, A., Voroneanu, L., and Goldsmith, D. 2010b. The effects of vitamin D therapy on left ventricular structure and function—are these the underlying explanations for improved CKD patient survival? *Nephron Clin Pract*, 116, c187–95.

D'ambrosio, D., Cippitelli, M., Cocciolo, M. G., *et al.* (1998). Inhibition of IL-12 production by 1,25-dihydroxyvitamin D3. Involvement of NF-kappaB downregulation in transcriptional repression of the p40 gene. *J Clin Invest*, 101, 252–62.

D'emden, M. C., Dunlop, M., Larkins, R. G., *et al.* (1989). The in vitro effect of 1 alpha,25-dihydroxyvitamin D3 on insulin production by neonatal rat islets. *Biochem Biophys Res Commun*, 164, 413–18.

Dai, C., Stolz, D. B., Kiss, L. P., *et al.* (2009). Wnt/beta-catenin signaling promotes podocyte dysfunction and albuminuria. *J Am Soc Nephrol*, 20, 1997–2008.

Dai, X., Sayama, K., Tohyama, M., *et al.* (2010). PPARgamma mediates innate immunity by regulating the 1alpha,25-dihydroxyvitamin D3 induced hBD-3 and cathelicidin in human keratinocytes. *J Dermatol Sci*, 60, 179–86.

Danescu, L. G., Levy, S., and Levy, J. (2009). Vitamin D and diabetes mellitus. *Endocrine*, 35, 11–17.

Dawson-Hughes, B., Harris, S. S., Krall, E. A., *et al.* (1997). Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med*, 337, 670–6.

De Boer, I. H., Ioannou, G. N., Kestenbaum, B., *et al.* (2007). 25-Hydroxyvitamin D levels and albuminuria in the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis*, 50, 69–77.

De Boer, I. H., Kestenbaum, B., Shoben, A. B., *et al.* (2009). 25-hydroxyvitamin D levels inversely associate with risk for developing coronary artery calcification. *J Am Soc Nephrol*, 20, 1805–12.

De Borst, M. H., Navis, G., De Boer, R. A., *et al.* (2003). Specific MAP-kinase blockade protects against renal damage in homozygous TGR(mRen2)27 rats. *Lab Invest*, 83, 1761–70.

De Borst, M. H., Vervloet, M. G., Ter Wee, P. M., *et al.* (2011). Cross talk between the renin-angiotensin-aldosterone system and vitamin D-FGF-23-klotho in chronic kidney disease. *J Am Soc Nephrol*, 22, 1603–9.

De Zeeuw, D., Agarwal, R., Amdahl, M., *et al.* (2010). Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. *Lancet*, 376, 1543–51.

Devlin, W. H., Parfrey, P. S., Harnett, J. D., *et al.* (1988). The relationship between hypertension and left ventricular hypertrophy in renal transplant recipients. *Transplant Proc*, 20, 1221–4.

Dhingra, R., Sullivan, L. M., Fox, C. S., *et al.* (2007). Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. *Arch Intern Med*, 167, 879–85.

Doorenbos, C. R., Van Den Born, J., Navis, G., *et al.* (2009). Possible renoprotection by vitamin D in chronic renal disease: beyond mineral metabolism. *Nat Rev Nephrol*, 5, 691–700.

Doran, D. E., Weiss, D., Zhang, Y., *et al.* (2007). Differential effects of AT1 receptor and Ca2+ channel blockade on atherosclerosis, inflammatory gene expression, and production of reactive oxygen species. *Atherosclerosis*, 195, 39–47.

Drechsler, C., Pilz, S., Obermayer-Pietsch, B., *et al.* (2010). Vitamin D deficiency is associated with sudden cardiac death, combined cardiovascular events, and mortality in haemodialysis patients. *Eur Heart J*, 31, 2253–61.

Dusso, A., Arcidiacono, M. V., Yang, J., *et al.* (2010). Vitamin D inhibition of TACE and prevention of renal osteodystrophy and cardiovascular mortality. *J Steroid Biochem Mol Biol*, 121, 193–8.

Dusso, A. S., Brown, A. J., *et al.* (2005). Vitamin D. *Am J Physiol Renal Physiol*, 289, F8–28.

Edfeldt, K., Liu, P. T., Chun, R., *et al.* (2010). T-cell cytokines differentially control human monocyte antimicrobial responses by regulating vitamin D metabolism. *Proc Natl Acad Sci U S A*, 107, 22593–8.

El-Abbadi, M. and Giachelli, C. M. (2007). Mechanisms of vascular calcification. *Adv Chronic Kidney Dis*, 14, 54–66.

Elamin, M. B., Abu Elnour, N. O., Elamin, K. B., *et al.* (2011). Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. *J Clin Endocrinol Metab*, 96, 1931–42.

Enioutina, E. Y., Bareyan, D., and Daynes, R. A. (2009). TLR-induced local metabolism of vitamin D3 plays an important role in the diversification of adaptive immune responses. *J Immunol*, 182, 4296–305.

Faul, C., Amaral, A. P., Oskouei, B., *et al.* (2011). FGF23 induces left ventricular hypertrophy. *J Clin Invest*, 121, 4393–408.

Fishbane, S., Chittineni, H., Packman, M., *et al.* (2009). Oral paricalcitol in the treatment of patients with CKD and proteinuria: a randomized trial. *Am J Kidney Dis*, 54, 647–52.

Fliser, D., Kollerits, B., Neyer, U., *et al.* (2007). Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. *J Am Soc Nephrol*, 18, 2600–8.

Floege, J., Kim, J., Ireland, E., *et al.* (2011). Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. *Nephrol Dial Transplant*, 26(6), 1948–55.

Foley, R. N., Collins, A. J., Herzog, C. A., *et al.* (2009). Serum phosphorus levels associate with coronary atherosclerosis in young adults. *J Am Soc Nephrol*, 20, 397–404.

Foley, R. N., Collins, A. J., Ishani, A., *et al.* (2008). Calcium-phosphate levels and cardiovascular disease in community-dwelling adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J*, 156, 556–63.

Ford, E. S., Ajani, U. A., Mcguire, L. C., *et al.* (2005). Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults. *Diabetes Care*, 28, 1228–30.

Forman, J. P., Williams, J. S., and Fisher, N. D. (2010). Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. *Hypertension*, 55, 1283–8.

Freundlich, M., Quiroz, Y., Zhang, Z., *et al.* (2008). Suppression of renin-angiotensin gene expression in the kidney by paricalcitol. *Kidney Int*, 74, 1394–402.

Frey, N., Frank, D., Lippl, S., *et al.* (2008). Calsarcin-2 deficiency increases exercise capacity in mice through calcineurin/NFAT activation. *J Clin Invest*, 118, 3598–608.

Galitzer, H., Ben-Dov, I. Z., Silver, J., *et al.* (2010). Parathyroid cell resistance to fibroblast growth factor 23 in secondary hyperparathyroidism of chronic kidney disease. *Kidney Int*, 77, 211–8.

Gannage-Yared, M. H., Azoury, M., Mansour, I., *et al.* (2003). Effects of a short-term calcium and vitamin D treatment on serum cytokines, bone markers, insulin and lipid concentrations in healthy post-menopausal women. *J Endocrinol Invest*, 26, 748–53.

Gannage-Yared, M. H., Chedid, R., Khalife, S., *et al.* (2009). Vitamin D in relation to metabolic risk factors, insulin sensitivity and adiponectin in a young Middle-Eastern population. *Eur J Endocrinol*, 160, 965–71.

Gepner, A. D., Ramamurthy, R., Krueger, D. C., *et al.* (2011). A Prospective Randomized Controlled Trial of the Effects of Vitamin D Supplementation on Cardiovascular Disease Risk (Abstract). *Circulation*, 124, A8149.

Gerstein, H. C., Mann, J. F., Yi, Q., *et al.* (2001). Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*, 286, 421–6.

Ghoreishi, M., Bach, P., Obst, J., *et al.* (2009). Expansion of antigen-specific regulatory T cells with the topical vitamin D analog calcipotriol. *J Immunol*, 182, 6071–8.

Ginde, A. A., Scragg, R., Schwartz, R. S., *et al.* (2009). Prospective study of serum 25-hydroxyvitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults. *J Am Geriatr Soc*, 57, 1595–603.

Giovannucci, E., Liu, Y., Hollis, B. W., *et al.* (2008). 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med*, 168, 1174–80.

Go, A. S., Chertow, G. M., Fan, D., *et al.* (2004). Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*, 351, 1296–305.

Goetz, R., Beenken, A., Ibrahimi, O. A., *et al.* (2007). Image from RCSB PDB (http://www.pdb.org) of PDB ID: 2P39. Molecular insights into the klotho-dependent, endocrine mode of action of fibroblast growth factor 19 subfamily members. *Mol Cell Biol*, 27, 3417–28.

Goldsmith, D. J., Covic, A., Fouque, D., *et al.* (2010). Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guidelines: a European Renal Best Practice (ERBP) commentary statement. *Nephrol Dial Transplant*, 25, 3823–31.

Gombart, A. F., Bhan, I., Borregaard, N., *et al.* (2009). Low plasma level of cathelicidin antimicrobial peptide (hCAP18) predicts increased infectious disease mortality in patients undergoing hemodialysis. *Clin Infect Dis*, 48, 418–24.

Gombart, A. F., Borregaard, N., and Koeffler, H. P. (2005). Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. *FASEB J*, 19, 1067–77.

Gonzalez, E. A., Sachdeva, A., Oliver, D. A., *et al.* (2004). Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. *Am J Nephrol*, 24, 503–10.

Good, D. W., George, T., and Watts, B. A., 3rd (2003). Aldosterone potentiates 1,25-dihydroxyvitamin D3 action in renal thick ascending limb via a nongenomic, ERK-dependent pathway. *Am J Physiol Cell Physiol*, 285, C1122–30.

Goodman, W. G., Goldin, J., Kuizon, B. D., *et al.* (2000). Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med*, 342, 1478–83.

Gordon, C. M., Depeter, K. C., Feldman, H. A., *et al.* (2004). Prevalence of vitamin D deficiency among healthy adolescents. *Arch Pediatr Adolesc Med*, 158, 531–7.

Goswami, R., Marwaha, R. K., Gupta, N., *et al.* (2009). Prevalence of vitamin D deficiency and its relationship with thyroid autoimmunity in Asian Indians: a community-based survey. *Br J Nutr*, 102, 382–6.

Grad, R. (2004). Cod and the consumptive: a brief history of cod-liver oil in the treatment of pulmonary tuberculosis. *Pharm Hist*, 46, 106–20.

Green, J. J., Robinson, D. A., Wilson, G. E., *et al.* (2006). Calcitriol modulation of cardiac contractile performance via protein kinase C. *J Mol Cell Cardiol*, 41, 350–9.

Greenstein, A. S., Khavandi, K., Withers, S. B., *et al.* (2009). Local inflammation and hypoxia abolish the protective anticontractile properties of perivascular fat in obese patients. *Circulation*, 119, 1661–70.

Griendling, K. K., Minieri, C. A., Ollerenshaw, J. D., *et al.* (1994). Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. *Circ Res*, 74, 1141–8.

Griffin, M. D., Lutz, W., Phan, V. A., *et al.* (2001). Dendritic cell modulation by 1alpha,25 dihydroxyvitamin D3 and its analogs: a vitamin D receptor-dependent pathway that promotes a persistent state of immaturity in vitro and in vivo. *Proc Natl Acad Sci U S A*, 98, 6800–5.

Gutierrez, O. M., Mannstadt, M., Isakova, T., *et al.* (2008). Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med*, 359, 584–92.

Hajjar, V., Depta, J. P., and Mountis, M. M. (2010). Q: Does vitamin D deficiency play a role in the pathogenesis of chronic heart failure? Do supplements improve survival? *Cleve Clin J Med*, 77, 290–3.

Hamming, I., Navis, G., Kocks, M. J., *et al.* (2006). ACE inhibition has adverse renal effects during dietary sodium restriction in proteinuric and healthy rats. *J Pathol*, 209, 129–39.

Harnett, J. D., Parfrey, P. S., Griffiths, S. M., *et al.* (1988). Left ventricular hypertrophy in end-stage renal disease. *Nephron*, 48, 107–15.

Harris, R. A., Pedersen-White, J., Guo, D. H., *et al.* (2011). Vitamin D3 supplementation for 16 weeks improves flow-mediated dilation in overweight African-American adults. *Am J Hypertens*, 24, 557–62.

Haruna, Y., Kashihara, N., Satoh, M., *et al.* (2007). Amelioration of progressive renal injury by genetic manipulation of Klotho gene. *Proc Natl Acad Sci U S A*, 104, 2331–6.

He, L. P., Tang, X. Y., Ling, W. H., *et al.* (2010). Early C-reactive protein in the prediction of long-term outcomes after acute coronary syndromes: a meta-analysis of longitudinal studies. *Heart*, 96, 339–46.

He, W., Dai, C., Li, Y., *et al.* (2009). Wnt/beta-catenin signaling promotes renal interstitial fibrosis. *J Am Soc Nephrol*, 20, 765–76.

He, W., Kang, Y. S., Dai, C., *et al.* (2011). Blockade of Wnt/beta-catenin signaling by paricalcitol ameliorates proteinuria and kidney injury. *J Am Soc Nephrol*, 22, 90–103.

Heaney, R. P. and Holick, M. F. (2011). Why the IOM recommendations for vitamin D are deficient. *J Bone Miner Res*, 26, 455–7.

Heineke, J. and Molkentin, J. D. (2006). Regulation of cardiac hypertrophy by intracellular signalling pathways. *Nat Rev Mol Cell Biol*, 7, 589–600.

Hewison, M. (2012). An update on vitamin D and human immunity. *Clin Endocrinol (Oxf)*, 76, 315–25.

Hewison, M., Freeman, L., Hughes, S. V., *et al.* (2003). Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells. *J Immunol*, 170, 5382–90.

Holick, M. F. (2005). Vitamin D for health and in chronic kidney disease. *Semin Dial*, 18, 266–75.

Holick, M. F. (2006a). High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc*, 81, 353–73.

Holick, M. F. (2006b). Resurrection of vitamin D deficiency and rickets. *J Clin Invest*, 116, 2062–72.

Holick, M. F. (2007). Vitamin D deficiency. *N Engl J Med*, 357, 266–81.

Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., *et al.* (2011). Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*, 96, 1911–30.

Hsia, J., Heiss, G., Ren, H., *et al.* (2007). Calcium/vitamin D supplementation and cardiovascular events. *Circulation*, 115, 846–54.

Hu, M. C., Shi, M., Zhang, J., *et al.* (2011). Klotho deficiency causes vascular calcification in chronic kidney disease. *J Am Soc Nephrol*, 22, 124–36.

Hujairi, N. M., Afzali, B., and Goldsmith, D. J. (2004). Cardiac calcification in renal patients: what we do and don't know. *Am J Kidney Dis*, 43, 234–43.

Hypponen, E., Laara, E., Reunanen, A., *et al.* (2001). Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet*, 358, 1500–3.

Hypponen, E. and Power, C. (2006). Vitamin D status and glucose homeostasis in the 1958 British birth cohort: the role of obesity. *Diabetes Care*, 29, 2244–6.

Ikushima, M., Rakugi, H., Ishikawa, K., *et al.* (2006). Anti-apoptotic and anti-senescence effects of Klotho on vascular endothelial cells. *Biochem Biophys Res Commun*, 339, 827–32.

Inaguma, D., Nagaya, H., Hara, K., *et al.* (2008). Relationship between serum 1,25-dihydroxyvitamin D and mortality in patients with pre-dialysis chronic kidney disease. *Clin Exp Nephrol*, 12, 126–31.

Isaia, G., Giorgino, R., and Adami, S. (2001). High prevalence of hypovitaminosis D in female type 2 diabetic population. *Diabetes Care*, 24, 1496.

Isakova, T., Wahl, P., Vargas, G. S., *et al.* (2011). Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int*, 79, 1370–8.

Jablonski, K. L., Chonchol, M., Pierce, G. L., *et al.* (2011). 25-Hydroxyvitamin D deficiency is associated with inflammation-linked vascular endothelial dysfunction in middle-aged and older adults. *Hypertension*, 57, 63–9.

Janssens, W., Lehouck, A., Carremans, C., *et al.* (2009). Vitamin D beyond bones in chronic obstructive pulmonary disease: time to act. *Am J Respir Crit Care Med*, 179, 630–6.

Jean, G., Charra, B., and Chazot, C. (2008). Vitamin D deficiency and associated factors in hemodialysis patients. *J Ren Nutr*, 18, 395–9.

Jeng, L., Yamshchikov, A. V., Judd, S. E., *et al.* (2009). Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis. *J Transl Med*, 7, 28.

Joshi, S., Pantalena, L. C., Liu, X. K., *et al.* (2011). 1,25-dihydroxyvitamin D(3) ameliorates Th17 autoimmunity via transcriptional modulation of interleukin-17A. *Mol Cell Biol*, 31, 3653–69.

Kalantar-Zadeh, K., Kuwae, N., Regidor, D. L., *et al.* (2006). Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int*, 70, 771–80.

Kamen, D. and Aranow, C. (2008). Vitamin D in systemic lupus erythematosus. *Curr Opin Rheumatol*, 20, 532–7.

Khavandi, K., Greenstein, A. S., Sonoyama, K., *et al.* (2009). Myogenic tone and small artery remodelling: insight into diabetic nephropathy. *Nephrol Dial Transplant*, 24, 361–9.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009). KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*, S1–130.

Kiraly, S. J., Kiraly, M. A., Hawe, R. D., *et al.* (2006). Vitamin D as a neuroactive substance: review. *Sci World J*, 6, 125–39.

Kirkpantur, A., Balci, M., Gurbuz, O. A., *et al.* (2011). Serum fibroblast growth factor-23 (FGF-23) levels are independently associated with left ventricular mass and myocardial performance index in maintenance haemodialysis patients. *Nephrol Dial Transplant*, 26, 1346–54.

Koeffler, H. P., Reichel, H., Bishop, J. E., *et al.* (1985). Gamma-interferon stimulates production of 1,25-dihydroxyvitamin D3 by normal human macrophages. *Biochem Biophys Res Commun*, 127, 596–603.

Koh, N., Fujimori, T., Nishiguchi, S., *et al.* (2001). Severely reduced production of klotho in human chronic renal failure kidney. *Biochem Biophys Res Commun*, 280, 1015–20.

Koli, K. and Keski-Oja, J. (2000). 1alpha,25-dihydroxyvitamin D3 and its analogues down-regulate cell invasion-associated proteases in cultured malignant cells. *Cell Growth Differ*, 11, 221–9.

Kovesdy, C. P., Kuchmak, O., Lu, J. L., *et al.* (2010). Outcomes associated with serum calcium level in men with non-dialysis-dependent chronic kidney disease. *Clin J Am Soc Nephrol*, 5, 468–76.

Kramer, A. B., Van Der Meulen, E. F., Hamming, I., *et al.* (2007). Effect of combining ACE inhibition with aldosterone blockade on proteinuria and renal damage in experimental nephrosis. *Kidney Int*, 71, 417–24.

Krause, R., Buhring, M., Hopfenmuller, W., *et al.* (1998). Ultraviolet B and blood pressure. *Lancet*, 352, 709–10.

Kuang, D., You, H., Ding, F., *et al.* (2009). Intima-media thickness of the carotid artery and its correlation factors in maintenance hemodialysis patients: a cross-sectional study. *Blood Purif*, 28, 181–6.

Kulie, T., Groff, A., Redmer, J., *et al.* (2009). Vitamin D: an evidence-based review. *J Am Board Fam Med*, 22, 698–706.

Kumar, R., Schaefer, J., Grande, J. P., *et al.* (1994). Immunolocalization of calcitriol receptor, 24-hydroxylase cytochrome P-450, and calbindin D28k in human kidney. *Am J Physiol*, 266, F477–85.

Kunisaki, K. M., Niewoehner, D. E., Singh, R. J., *et al.* (2011). Vitamin D status and longitudinal lung function decline in the Lung Health Study. *Eur Respir J*, 37, 238–43.

Kuro-o, M. (2008). Klotho as a regulator of oxidative stress and senescence. *Biol Chem*, 389, 233–41.

Kuro-o, M., Matsumura, Y., Aizawa, H., *et al.* (1997). Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature*, 390, 45–51.

Kurosu, H., Ogawa, Y., Miyoshi, M., *et al.* (2006). Regulation of fibroblast growth factor-23 signaling by klotho. *J Biol Chem*, 281, 6120–3.

La'ulu, S. L. and Roberts, W. L. (2010). Performance characteristics of six intact parathyroid hormone assays. *Am J Clin Pathol*, 134, 930–8.

Laclair, R. E., Hellman, R. N., Karp, S. L., *et al.* (2005). Prevalence of calcidiol deficiency in CKD: a cross-sectional study across latitudes in the United States. *Am J Kidney Dis*, 45, 1026–33.

Larsson, T. E. (2010). The role of FGF-23 in CKD-MBD and cardiovascular disease: friend or foe? *Nephrol Dial Transplant*, 25, 1376–81.

Laurent, S., Boutouyrie, P., Asmar, R., *et al.* (2001). Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*, 37, 1236–41.

Lehouck, A., Mathieu, C., Carremans, C., *et al.* (2012). High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med*, 156, 105–14.

Levin, A., Bakris, G. L., Molitch, M., *et al.* (2007). Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int*, 71, 31–8.

Levin, A., Singer, J., Thompson, C. R., *et al.* (1996). Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. *Am J Kidney Dis*, 27, 347–54.

Li, Y. C., Kong, J., Wei, M., *et al.* (2002). 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest*, 110, 229–38.

Lim, W. C., Hanauer, S. B., and Li, Y. C. (2005). Mechanisms of disease: vitamin D and inflammatory bowel disease. *Nat Clin Pract Gastroenterol Hepatol*, 2, 308–15.

Linden, V. (1974). Vitamin D and myocardial infarction. *Br Med J*, 3, 647–50.

Lips, P. (2004). Which circulating level of 25-hydroxyvitamin D is appropriate? *J Steroid Biochem Mol Biol*, 89–90, 611–4.

Liu, L. J., Lv, J. C., Shi, S. F., *et al.* (2012). Oral calcitriol for reduction of proteinuria in patients with IgA nephropathy: a randomized controlled trial. *Am J Kidney Dis*, 59, 67–74.

Liu, P. T., Stenger, S., LI, H., *et al.* (2006). Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science*, 311, 1770–3.

London, G. M., Guerin, A. P., Marchais, S. J., *et al.* (2003). Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant*, 18, 1731–40.

London, G. M., Guerin, A. P., Verbeke, F. H., *et al.* (2007). Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency. *J Am Soc Nephrol*, 18, 613–20.

London, G. M., Marchais, S. J., and Guerin, A. P. (2004). Arterial stiffness and function in end-stage renal disease. *Adv Chronic Kidney Dis*, 11, 202–9.

Lundqvist, J., Norlin, M., and Wikvall, K. (2010). 1alpha,25-Dihydroxyvitamin D3 affects hormone production and expression of steroidogenic enzymes in human adrenocortical NCI-H295R cells. *Biochim Biophys Acta*, 1801, 1056–62.

Maestro, B., Campion, J., Davila, N., *et al.* (2000). Stimulation by 1,25-dihydroxyvitamin D3 of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. *Endocr J*, 47, 383–91.

Major, G. C., Alarie, F., Dore, J., *et al.* (2007). Supplementation with calcium + vitamin D enhances the beneficial effect of weight loss on plasma lipid and lipoprotein concentrations. *Am J Clin Nutr*, 85, 54–9.

Manson, J. E., Allison, M. A., Carr, J. J., *et al.* (2010). Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative. *Menopause*, 17, 683–91.

Marcen, R., Caballero, C., Uriol, O., *et al.* (2007). Prevalence of osteoporosis, osteopenia, and vertebral fractures in long-term renal transplant recipients. *Transplant Proc*, 39, 2256–8.

Marniemi, J., Alanen, E., Impivaara, O., *et al.* (2005). Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects. *Nutr Metab Cardiovasc Dis*, 15, 188–97.

Martineau, A. R., Timms, P. M., Bothamley, G. H., *et al.* (2011). High-dose vitamin D(3) during intensive-phase antimicrobial treatment of pulmonary tuberculosis: a double-blind randomised controlled trial. *Lancet*, 377, 242–50.

Martineau, A. R., Wilkinson, R. J., Wilkinson, K. A., *et al.* (2007). A single dose of vitamin D enhances immunity to mycobacteria. *Am J Respir Crit Care Med*, 176, 208–13.

Marwaha, R. K., Tandon, N., Reddy, D. R., *et al.* (2005). Vitamin D and bone mineral density status of healthy schoolchildren in northern India. *Am J Clin Nutr*, 82, 477–82.

Mathieu, C. and Adorini, L. (2002). The coming of age of 1,25-dihydroxyvitamin D(3) analogs as immunomodulatory agents. *Trends Mol Med*, 8, 174–9.

Mathieu, C., Gysemans, C., Giulietti, A., *et al.* (2005). Vitamin D and diabetes. *Diabetologia*, 48, 1247–57.

Mathieu, C., Van Etten, E., Decallonne, B., *et al.* (2004). Vitamin D and 1,25-dihydroxyvitamin D3 as modulators in the immune system. *J Steroid Biochem Mol Biol*, 89–90, 449–52.

Mathieu, C., Van Etten, E., Gysemans, C., *et al.* (2001). In vitro and in vivo analysis of the immune system of vitamin D receptor knockout mice. *J Bone Miner Res*, 16, 2057–65.

Mathieu, C., Waer, M., Laureys, J., *et al.* (1994). Prevention of autoimmune diabetes in NOD mice by 1,25 dihydroxyvitamin D3. *Diabetologia*, 37, 552–8.

Matias, P. J., Jorge, C., Ferreira, C., *et al.* (2010). Cholecalciferol supplementation in hemodialysis patients: effects on mineral metabolism, inflammation, and cardiac dimension parameters. *Clin J Am Soc Nephrol*, 5, 905–11.

Matsushita, K., Van Der Velde, M., Astor, B. C., *et al.* (2010). Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*, 375, 2073–81.

McCarron, D. A. and Morris, C. D. (1987). The calcium deficiency hypothesis of hypertension. *Ann Intern Med*, 107, 919–22.

McCarty, M. F. and Thomas, C. A. (2003). PTH excess may promote weight gain by impeding catecholamine-induced lipolysis-implications for the impact of calcium, vitamin D, and alcohol on body weight. *Med Hypotheses*, 61, 535–42.

McGregor, R., Li, G., Penny, H., *et al.* (2014). Vitamin D in renal transplantation - from biological mechanisms to clinical benefits. *Am J Transplant*, 14(6), 1259–70.

McKenna, M. J. (1992). Differences in vitamin D status between countries in young adults and the elderly. *Am J Med*, 93, 69–77.

Melamed, M. L., Eustace, J. A., Plantinga, L., *et al.* (2006). Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: a longitudinal study. *Kidney Int*, 70, 351–7.

Melamed, M. L., Michos, E. D., Post, W., *et al.* (2008). 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med*, 168, 1629–37.

Mertens, P. R. and Muller, R. (2010). Vitamin D and cardiovascular risk. *Int Urol Nephrol*, 42, 165–71.

Michos, E. D. and Blumenthal, R. S. (2007). Vitamin D supplementation and cardiovascular disease risk. *Circulation*, 115, 827–8.

Milner, R. D. and Hales, C. N. (1967). The role of calcium and magnesium in insulin secretion from rabbit pancreas studied in vitro. *Diabetologia*, 3, 47–9.

Mirza, M. A., Hansen, T., Johansson, L., *et al.* (2009a). Relationship between circulating FGF23 and total body atherosclerosis in the community. *Nephrol Dial Transplant*, 24, 3125–31.

Mirza, M. A., Larsson, A., Melhus, H., *et al.* (2009b). Serum intact FGF23 associate with left ventricular mass, hypertrophy and geometry in an elderly population. *Atherosclerosis*, 207, 546–51.

Mitani, H., Ishizaka, N., Aizawa, T., *et al.* (2002). In vivo klotho gene transfer ameliorates angiotensin II-induced renal damage. *Hypertension*, 39, 838–43.

Mitobe, M., Yoshida, T., Sugiura, H., *et al.* (2005). Oxidative stress decreases klotho expression in a mouse kidney cell line. *Nephron Exp Nephrol*, 101, e67–74.

Mitri, J., Dawson-Hughes, B., Hu, F. B., *et al.* (2011). Effects of vitamin D and calcium supplementation on pancreatic beta cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *Am J Clin Nutr*, 94, 486–94.

Mizobuchi, M., Morrissey, J., Finch, J. L., *et al.* (2007). Combination therapy with an angiotensin-converting enzyme inhibitor and a vitamin D analog suppresses the progression of renal insufficiency in uremic rats. *J Am Soc Nephrol*, 18, 1796–806.

Mogensen, C. E., Neldam, S., Tikkanen, I., *et al.* (2000). Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ*, 321, 1440–4.

Molitch, M. E., Defronzo, R. A., Franz, M. J., *et al.* (2004). Nephropathy in diabetes. *Diabetes Care*, 27 Suppl 1, S79–83.

Moro, J. R., Iwata, M., Von Andriano, U. H., *et al.* (2008). Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol*, 8, 685–98.

Morris, K. L., Zemel, M. B., Morris, K. L., *et al.* (2005). 1,25-dihydroxyvitamin D3 modulation of adipocyte glucocorticoid function. *Obes Res*, 13, 670–7.

Munger, K. L., Zhang, S. M., O'reilly, E., *et al.* (2004). Vitamin D intake and incidence of multiple sclerosis. *Neurology*, 62, 60–5.

Muscogiuri, G., Sorice, G. P., Ajjan, R., *et al.* (2012). Can vitamin D deficiency cause diabetes and cardiovascular diseases? Present evidence and future perspectives. *Nutr Metab Cardiovasc Dis*, 22, 81–7.

Nakashima, A., Yorioka, N., Tanji, C., *et al.* (2003). Bone mineral density may be related to atherosclerosis in hemodialysis patients. *Osteoporos Int*, 14, 369–73.

National Kidney Foundation (2003). K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*, 42, S1–201.

Nguyen, G., Delarue, F., Burckle, C., *et al.* (2002). Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest*, 109, 1417–27.

Norman, A. W., Frankel, J. B., Heldt, A. M., *et al.* (1980). Vitamin D deficiency inhibits pancreatic secretion of insulin. *Science*, 209, 823–5.

Nursyam, E. W., Amin, Z., and Rumende, C. M. (2006). The effect of vitamin D as supplementary treatment in patients with moderately advanced pulmonary tuberculous lesion. *Acta Med Indones*, 38, 3–5.

Nykjaer, A., Dragun, D., Walther, D., *et al.* (1999). An endocytic pathway essential for renal uptake and activation of the steroid 25-(OH) vitamin D3. *Cell*, 96, 507–15.

Overbergh, L., Decallonne, B., Valckx, D., *et al.* (2000). Identification and immune regulation of 25-hydroxyvitamin D-1-alpha-hydroxylase in murine macrophages. *Clin Exp Immunol*, 120, 139–46.

Palomer, X., Gonzalez-Clemente, J. M., Blanco-Vaca, F., *et al.* (2008). Role of vitamin D in the pathogenesis of type 2 diabetes mellitus. *Diabet Obes Metab*, 10, 185–97.

Panda, D. K., Miao, D., Tremblay, M. L., *et al.* (2001). Targeted ablation of the 25-hydroxyvitamin D 1alpha -hydroxylase enzyme: evidence for skeletal, reproductive, and immune dysfunction. *Proc Natl Acad Sci U S A*, 98, 7498–503.

Park, C. W., Oh, Y. S., Shin, Y. S., *et al.* (1999). Intravenous calcitriol regresses myocardial hypertrophy in hemodialysis patients with secondary hyperparathyroidism. *Am J Kidney Dis*, 33, 73–81.

Parker, B. D., Schurgers, L. J., Brandenburg, V. M., *et al.* (2010a). The associations of fibroblast growth factor 23 and uncarboxylated matrix Gla protein with mortality in coronary artery disease: the Heart and Soul Study. *Ann Intern Med*, 152, 640–8.

Parker, J., Hashmi, O., Dutton, D., *et al.* (2010b). Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. *Maturitas*, 65, 225–36.

Penna, G. and Adorini, L. (2000). 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *J Immunol*, 164, 2405–11.

Peric, M., Koglin, S., Kim, S. M., *et al.* (2008). IL-17A enhances vitamin D3-induced expression of cathelicidin antimicrobial peptide in human keratinocytes. *J Immunol*, 181, 8504–12.

Pfeifer, M., Begerow, B., Minne, H. W., *et al.* (2001). Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab*, 86, 1633–7.

Pichette, V., Bonnardeaux, A., Prudhomme, L., *et al.* (1996). Long-term bone loss in kidney transplant recipients: a cross-sectional and longitudinal study. *Am J Kidney Dis*, 28, 105–14.
Pilz, S., Dobnig, H., Fischer, J. E., *et al.* (2008a). Low vitamin d levels predict stroke in patients referred to coronary angiography. *Stroke*, 39, 2611–3.
Pilz, S., Marz, W., Wellnitz, B., *et al.* (2008b). Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. *J Clin Endocrinol Metab*, 93, 3927–35.
Pilz, S. and Tomaschitz, A. (2009). Vitamin D deficiency and myocardial dysfunction. *J Am Coll Cardiol*, 53, 2011; author reply 2012–13.
Pilz, S., Tomaschitz, A., Drechsler, C., *et al.* (2011). Vitamin D supplementation: a promising approach for the prevention and treatment of strokes. *Curr Drug Targets*, 12, 88–96.
Pilz, S., Tomaschitz, A., Ritz, E., *et al.* (2009). Vitamin D status and arterial hypertension: a systematic review. *Nat Rev Cardiol*, 6, 621–30.
Piovesan, A., Molineri, N., Casasso, F., *et al.* (1999). Left ventricular hypertrophy in primary hyperparathyroidism. Effects of successful parathyroidectomy. *Clin Endocrinol (Oxf)*, 50, 321–8.
Pittas, A. G., Chung, M., Trikalinos, T., *et al.* (2010). Systematic review: Vitamin D and cardiometabolic outcomes. *Ann Intern Med*, 152, 307–14.
Pittas, A. G., Dawson-Hughes, B., Li, T., *et al.* (2006). Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care*, 29, 650–6.
Pittas, A. G., Lau, J., Hu, F. B., *et al.* (2007). The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. *J Clin Endocrinol Metab*, 92, 2017–29.
Poole, K. E., Loveridge, N., Barker, P. J., *et al.* (2006). Reduced vitamin D in acute stroke. *Stroke*, 37, 243–5.
Rabinovitch, A., Suarez-Pinzon, W. L., Sooy, K., *et al.* (2001). Expression of calbindin-D(28k) in a pancreatic islet beta-cell line protects against cytokine-induced apoptosis and necrosis. *Endocrinology*, 142, 3649–55.
Raby, B. A., Lazarus, R., Silverman, E. K., *et al.* (2004). Association of vitamin D receptor gene polymorphisms with childhood and adult asthma. *Am J Respir Crit Care Med*, 170, 1057–65.
Rajpathak, S. N., Xue, X., Wassertheil-Smoller, S., *et al.* (2010). Effect of 5 y of calcium plus vitamin D supplementation on change in circulating lipids: results from the Women's Health Initiative. *Am J Clin Nutr*, 91, 894–9.
Ramos-Lopez, E., Jansen, T., Ivaskevicius, V., *et al.* (2006). Protection from type 1 diabetes by vitamin D receptor haplotypes. *Ann N Y Acad Sci*, 1079, 327–34.
Ravani, P., Malberti, F., Tripepi, G., *et al.* (2009). Vitamin D levels and patient outcome in chronic kidney disease. *Kidney Int*, 75, 88–95.
Redaelli, C. A., Wagner, M., Gunter-Duwe, D., *et al.* (2002). 1alpha,25-dihydroxyvitamin D3 shows strong and additive immunomodulatory effects with cyclosporine A in rat renal allotransplants. *Kidney Int*, 61, 288–96.
Reichel, H., Koeffler, H. P., and Norman, A. W. (1987a). Synthesis in vitro of 1,25-dihydroxyvitamin D3 and 24,25-dihydroxyvitamin D3 by interferon-gamma-stimulated normal human bone marrow and alveolar macrophages. *J Biol Chem*, 262, 10931–7.
Reichel, H., Koeffler, H. P., Tobler, A., *et al.* (1987b). 1 alpha,25-Dihydroxyvitamin D3 inhibits gamma-interferon synthesis by normal human peripheral blood lymphocytes. *Proc Natl Acad Sci U S A*, 84, 3385–9.
Reis, J. P., Von Muhlen, D., Michos, E. D., *et al.* (2009). Serum vitamin D, parathyroid hormone levels, and carotid atherosclerosis. *Atherosclerosis*, 207, 585–90.
Remuzzi, G., Benigni, A., and Remuzzi, A. (2006). Mechanisms of progression and regression of renal lesions of chronic nephropathies and diabetes. *J Clin Invest*, 116, 288–96.
Rezai, M. R., Wallace, A. M., Sattar, N., *et al.* (2011). Ethnic differences in aortic pulse wave velocity occur in the descending aorta and may be related to vitamin D. *Hypertension*, 58(2), 247–53.
Ritz, E. (2009). The kidney: both culprit and victim. *Hypertension*, 54, 25–6.
Rix, M., Andreassen, H., Eskildsen, P., *et al.* (1999). Bone mineral density and biochemical markers of bone turnover in patients with predialysis chronic renal failure. *Kidney Int*, 56, 1084–93.
Rook, G. A., Steele, J., Fraher, L., *et al.* (1986). Vitamin D3, gamma interferon, and control of proliferation of Mycobacterium tuberculosis by human monocytes. *Immunology*, 57, 159–63.
Ross, A. C., Manson, J. E., Abrams, S. A., *et al.* (2011). The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab*, 96, 53–8.
Rostand, S. G. (1997). Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension*, 30, 150–6.
Royal, W., 3rd, Mia, Y., Li, H., and Naunton, K. (2009). Peripheral blood regulatory T cell measurements correlate with serum vitamin D levels in patients with multiple sclerosis. *J Neuroimmunol*, 213, 135–41.
Ruggenenti, P. and Remuzzi, G. (2006). Time to abandon microalbuminuria? *Kidney Int*, 70, 1214–22.
Saito, K., Ishizaka, N., Mitani, H., *et al.* (2003). Iron chelation and a free radical scavenger suppress angiotensin II-induced downregulation of klotho, an anti-aging gene, in rat. *FEBS Lett*, 551, 58–62.
Saito, Y., Yamagishi, T., Nakamura, T., *et al.* (1998). Klotho protein protects against endothelial dysfunction. *Biochem Biophys Res Commun*, 248, 324–9.
Saleh, F. N., Schirmer, H., Sundsfjord, J., *et al.* (2003). Parathyroid hormone and left ventricular hypertrophy. *Eur Heart J*, 24, 2054–60.
Samelson, E. J., Kiel, D. P., Broe, K. E., *et al.* (2004). Metacarpal cortical area and risk of coronary heart disease: the Framingham Study. *Am J Epidemiol*, 159, 589–95.
Sato, Y., Iwamoto, J., Kanoko, T., *et al.* (2005). Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. *Cerebrovasc Dis*, 20, 187–92.
Sato, Y., Maruoka, H., and Oizumi, K. (1997). Amelioration of hemiplegia-associated osteopenia more than 4 years after stroke by 1 alpha-hydroxyvitamin D3 and calcium supplementation. *Stroke*, 28, 736–9.
Sawcer, S., Hellenthal, G., Pirinen, M., *et al.* (2011). Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature*, 476, 214–9.
Schauber, J., Dorschner, R. A., Coda, A. B., *et al.* (2007). Injury enhances TLR2 function and antimicrobial peptide expression through a vitamin D-dependent mechanism. *J Clin Invest*, 117, 803–11.
Schleithoff, S. S., Zittermann, A., Tenderich, G., *et al.* (2006). Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr*, 83, 754–9.
Schmidt-Gayk, H., Goossen, J., Lendle, F., *et al.* (1977). Serum 25-hydroxycalciferol in myocardial infarction. *Atherosclerosis*, 26, 55–8.
Shimada, T., Mizutani, S., Muto, T., *et al.* (2001). Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci U S A*, 98, 6500–5.
Shimada, T., Urakawa, I., Isakova, T., *et al.* (2010). Circulating fibroblast growth factor 23 in patients with end-stage renal disease treated by peritoneal dialysis is intact and biologically active. *J Clin Endocrinol Metab*, 95, 578–85.
Shoji, T., Shinohara, K., Kimoto, E., *et al.* (2004). Lower risk for cardiovascular mortality in oral 1alpha-hydroxy vitamin D3 users in a haemodialysis population. *Nephrol Dial Transplant*, 19, 179–84.
Sigmundsdottir, H., Pan, J., Debes, G. F., *et al.* (2007). DCs metabolize sunlight-induced vitamin D3 to 'program' T cell attraction to the epidermal chemokine CCL27. *Nat Immunol*, 8, 285–93.
Simpson, R. U., Hershey, S. H., and Nibbelink, K. A. (2007). Characterization of heart size and blood pressure in the vitamin D receptor knockout mouse. *J Steroid Biochem Mol Biol*, 103, 521–4.
Sloka, S., Grant, M., and Newhook, L. A. (2010). The geospatial relation between UV solar radiation and type 1 diabetes in Newfoundland. *Acta Diabetol*, 47, 73–8.

Slomski, A. (2011). IOM endorses vitamin D, calcium only for bone health, dispels deficiency claims. *JAMA*, 305, 453–4, 456.

Smolders, J., Damoiseaux, J., Menheere, P., *et al.* (2008). Vitamin D as an immune modulator in multiple sclerosis, a review. *J Neuroimmunol*, 194, 7–17.

Soilu-Hanninen, M., Aivo, J., Lindstrom, B. M., *et al.* (2012). A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon beta-1b in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry*, 83, 565–71.

Sooy, K., Schermerhorn, T., Noda, M., *et al.* (1999). Calbindin-D(28k) controls (Ca(2+))(i) and insulin release. Evidence obtained from calbindin-D(28k) knockout mice and beta cell lines. *J Biol Chem*, 274, 34343–9.

Spach, K. M., Pedersen, L. B., Nashold, F. E., *et al.* (2004). Gene expression analysis suggests that 1,25-dihydroxyvitamin D3 reverses experimental autoimmune encephalomyelitis by stimulating inflammatory cell apoptosis. *Physiol Genomics*, 18, 141–51.

Sprague, S. M., Llach, F., Amdahl, M., *et al.* (2003). Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. *Kidney Int*, 63, 1483–90.

Stoffels, K., Overbergh, L., Giulietti, A., *et al.* (2006). Immune regulation of 25-hydroxyvitamin-D3–1alpha-hydroxylase in human monocytes. *J Bone Miner Res*, 21, 37–47.

Stolzenberg-Solomon, R. Z., Jacobs, E. J., Arslan, A. A., *et al.* (2010). Circulating 25-hydroxyvitamin D and risk of pancreatic cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol*, 172, 81–93.

Sullivan, S. S., Rosen, C. J., Halteman, W. A., *et al.* (2005). Adolescent girls in Maine are at risk for vitamin D insufficiency. *J Am Diet Assoc*, 105, 971–4.

Szeto, C. C., Chow, K. M., Kwan, B. C., *et al.* (2008). Oral calcitriol for the treatment of persistent proteinuria in immunoglobulin A nephropathy: an uncontrolled trial. *Am J Kidney Dis*, 51, 724–31.

Taal, M. W., Roe, S., Masud, T., *et al.* (2003). Total hip bone mass predicts survival in chronic hemodialysis patients. *Kidney Int*, 63, 1116–20.

Takeda, K. and Akira, S. (2005). Toll-like receptors in innate immunity. *Int Immunol*, 17, 1–14.

Tan, X., Wen, X., and Liu, Y. (2008). Paricalcitol inhibits renal inflammation by promoting vitamin D receptor-mediated sequestration of NF-kappaB signaling. *J Am Soc Nephrol*, 19, 1741–52.

Tang, B. M., Eslick, G. D., Nowson, C., *et al.* (2007). Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet*, 370, 657–66.

Teng, M., Wolf, M., Ofsthun, M. N., *et al.* (2005). Activated injectable vitamin D and hemodialysis survival: a historical cohort study. *J Am Soc Nephrol*, 16, 1115–25.

Tentori, F., Hunt, W. C., Stidley, C. A., *et al.* (2006). Mortality risk among hemodialysis patients receiving different vitamin D analogs. *Kidney Int*, 70, 1858–65.

Thaci, D., Daiber, W., Boehncke, W. H., *et al.* (2001). Calcipotriol solution for the treatment of scalp psoriasis: evaluation of efficacy, safety and acceptance in 3,396 patients. *Dermatology*, 203, 153–6.

Thadhani, R., Appelbaum, E., Pritchett, Y., *et al.* (2012). Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *JAMA*, 307, 674–84.

Tonelli, M., Sacks, F., Pfeffer, M., *et al.* (2005). Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation*, 112, 2627–33.

Tsujikawa, H., Kurotaki, Y., Fujimori, T., *et al.* (2003). Klotho, a gene related to a syndrome resembling human premature aging, functions in a negative regulatory circuit of vitamin D endocrine system. *Mol Endocrinol*, 17, 2393–403.

Urakawa, I., Yamazaki, Y., Shimada, T., *et al.* (2006). Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*, 444, 770–4.

Valdivielso, J. M. and Fernandez, E. (2006). Vitamin D receptor polymorphisms and diseases. *Clin Chim Acta*, 371, 1–12.

Van Der Meer, I. M., Ruggenenti, P., and Remuzzi, G. (2010). The diabetic CKD patient—a major cardiovascular challenge. *J Ren Care*, 36 Suppl 1, 34–46.

Van Halteren, A. G., Van Etten, E., De Jong, E. C., *et al.* (2002). Redirection of human autoreactive T-cells Upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D(3). *Diabetes*, 51, 2119–25.

Van Veldhuisen, D. J., Genth-Zotz, S., Brouwer, J., *et al.* (1998). High- versus low-dose ACE inhibition in chronic heart failure: a double-blind, placebo-controlled study of imidapril. *J Am Coll Cardiol*, 32, 1811–8.

Vidt, D. G. (2006). Inflammation in renal disease. *Am J Cardiol*, 97, 20A–7A.

Vieth, R. (2004). Why the optimal requirement for Vitamin D3 is probably much higher than what is officially recommended for adults. *J Steroid Biochem Mol Biol*, 89–90, 575–9.

Voormolen, N., Noordzij, M., Grootendorst, D. C., *et al.* (2007). High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. *Nephrol Dial Transplant*, 22, 2909–16.

Wang, A. Y., Lam, C. W., Sanderson, J. E., *et al.* (2008a). Serum 25-hydroxyvitamin D status and cardiovascular outcomes in chronic peritoneal dialysis patients: a 3-y prospective cohort study. *Am J Clin Nutr*, 87, 1631–8.

Wang, H., Yoshiko, Y., Yamamoto, R., *et al.* (2008b). Overexpression of fibroblast growth factor 23 suppresses osteoblast differentiation and matrix mineralization in vitro. *J Bone Miner Res*, 23, 939–48.

Wang, T. J. (2011). *Vitamin D and Myocardial Dysfunction*. Oral presentation at the American College of Cardiology Scientific Sessions.

Wang, T. J., Pencina, M. J., Booth, S. L., *et al.* (2008c). Vitamin D deficiency and risk of cardiovascular disease. *Circulation*, 117, 503–11.

Wang, T. T., Nestel, F. P., Bourdeau, V., *et al.* (2004). Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. *J Immunol*, 173, 2909–12.

Wang, Y. and Sun, Z. (2009). Klotho gene delivery prevents the progression of spontaneous hypertension and renal damage. *Hypertension*, 54, 810–7.

Webb, A. R., Kline, L., and Holick, M. F. (1988). Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *J Clin Endocrinol Metab*, 67, 373–8.

Wejse, C., Gomes, V. F., Rabna, P., *et al.* (2009). Vitamin D as supplementary treatment for tuberculosis: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med*, 179, 843–50.

Wilkinson, R. J., Llewelyn, M., Toossi, Z., *et al.* (2000). Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. *Lancet*, 355, 618–21.

Willum-Hansen, T., Staessen, J. A., Torp-Pedersen, C., *et al.* (2006). Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation*, 113, 664–70.

Witham, M. D., Crighton, L. J., Gillespie, N. D., *et al.* (2010a). The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure: a randomized controlled trial. *Circ Heart Fail*, 3, 195–201.

Witham, M. D., Dove, F. J., Dryburgh, M., *et al.* (2010b). The effect of different doses of vitamin D(3) on markers of vascular health in patients with type 2 diabetes: a randomised controlled trial. *Diabetologia*, 53, 2112–19.

Witham, M. D., Dove, F. J., Khan, F., *et al.* (2013). Effects of vitamin D supplementation on markers of vascular function after myocardial infarction-A randomised controlled trial. *Int J Cardiol*, 167(3), 745–9.

Witham, M. D., Dove, F. J., Sugden, J. A., *et al.* (2012). The effect of vitamin D replacement on markers of vascular health in stroke patients—a randomised controlled trial. *Nutr Metab Cardiovasc Dis*, 22(10), 864–70.

Witte, K. K., Nikitin, N. P., Parker, A. C., *et al.* (2005). The effect of micronutrient supplementation on quality-of-life and left ventricular function in elderly patients with chronic heart failure. *Eur Heart J*, 26, 2238–44.

Wolf, M., Betancourt, J., Chang, Y., *et al.* (2008). Impact of activated vitamin D and race on survival among hemodialysis patients. *J Am Soc Nephrol*, 19, 1379–88.

Wolf, M., Shah, A., Gutierrez, O., *et al.* (2007). Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int*, 72, 1004–13.

Wortsman, J., Matsuoka, L. Y., Chen, T. C., *et al.* (2000). Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr*, 72, 690–3.

Xiang, W., Kong, J., Chen, S., *et al.* (2005a). Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. *Am J Physiol Endocrinol Metab*, 288, E125–32.

Xiang, W., Kong, J., Chen, S. C., *et al.* (2005b). Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. *Am J Physiol Endocrinol Metab*, 288, E125–32.

Yamamoto, M., Clark, J. D., Pastor, J. V., *et al.* (2005). Regulation of oxidative stress by the anti-aging hormone klotho. *J Biol Chem*, 280, 38029–34.

Yilmaz, M. I., Sonmez, A., Saglam, M., *et al.* (2010). FGF-23 and vascular dysfunction in patients with stage 3 and 4 chronic kidney disease. *Kidney Int*, 78, 679–85.

Yim, S., Dhawan, P., Ragunath, C., *et al.* (2007). Induction of cathelicidin in normal and CF bronchial epithelial cells by 1,25-dihydroxyvitamin D(3). *J Cyst Fibros*, 6, 403–10.

Yiu, Y. F., Chan, Y. H., Yiu, K. H., *et al.* (2011). Vitamin D deficiency is associated with depletion of circulating endothelial progenitor cells and endothelial dysfunction in patients with type 2 diabetes. *J Clin Endocrinol Metab*, 96, E830–5.

Yoon, H. E., Ghee, J. Y., Piao, S., *et al.* (2011). Angiotensin II blockade upregulates the expression of Klotho, the anti-ageing gene, in an experimental model of chronic cyclosporine nephropathy. *Nephrol Dial Transplant*, 26, 800–13.

Yuan, W., Pan, W., Kong, J., *et al.* (2007). 1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. *J Biol Chem*, 282, 29821–30.

Yusuf, S., Teo, K. K., Pogue, J., *et al.* (2008). Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*, 358, 1547–59.

Zadshir, A., Tareen, N., Pan, D., *et al.* (2005). The prevalence of hypovitaminosis D among US adults: data from the NHANES III. *Ethn Dis*, 15, S5-97-101.

Zeitz, U., Weber, K., Soegiarto, D. W., *et al.* (2003). Impaired insulin secretory capacity in mice lacking a functional vitamin D receptor. *FASEB J*, 17, 509–11.

Zhang, Y., Kong, J., Deb, D. K., *et al.* (2010). Vitamin D receptor attenuates renal fibrosis by suppressing the renin-angiotensin system. *J Am Soc Nephrol*, 21, 966–73.

Zhang, Z., Sun, L., Wang, Y., *et al.* (2008a). Renoprotective role of the vitamin D receptor in diabetic nephropathy. *Kidney Int*, 73, 163–71.

Zhang, Z., Yuan, W., Sun, L., *et al.* (2007). 1,25-Dihydroxyvitamin D3 targeting of NF-kappaB suppresses high glucose-induced MCP-1 expression in mesangial cells. *Kidney Int*, 72, 193–201.

Zhang, Z., Zhang, Y., Ning, G., *et al.* (2008b). Combination therapy with AT1 blocker and vitamin D analog markedly ameliorates diabetic nephropathy: blockade of compensatory renin increase. *Proc Natl Acad Sci U S A*, 105, 15896–901.

Zhong, Y., Armbrecht, H. J., and Christakos, S. (2009). Calcitonin, a regulator of the 25-hydroxyvitamin D3 1alpha-hydroxylase gene. *J Biol Chem*, 284, 11059–69.

Zittermann, A. (2006). Vitamin D and disease prevention with special reference to cardiovascular disease. *Prog Biophys Mol Biol*, 92, 39–48.

Zittermann, A., Frisch, S., Berthold, H. K., *et al.* (2009). Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. *Am J Clin Nutr*, 89, 1321–7.

Zittermann, A. and Koerfer, R. (2008). Vitamin D in the prevention and treatment of coronary heart disease. *Curr Opin Clin Nutr Metab Care*, 11, 752–7.

Zittermann, A., Schleithoff, S. S., Tenderich, G., *et al.* (2003). Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? *J Am Coll Cardiol*, 41, 105–12.

CHAPTER 128

Immunity

Behdad Afzali and Claudia Kemper

Introduction

Physiological health is critically dependent on balancing the need for immunological responsiveness against foreign pathogens against the requirement to maintain tolerance to self-components, commensal organisms, food-derived innocuous antigens, and semi-allogeneic fetal antigens. Disturbances in this homeostasis are characterized by immunodeficiency, autoimmune disease, fetal loss, and/or chronic inflammation, as shown in Fig. 128.1. Chronic kidney disease (CKD) occupies a unique niche in this model, demonstrating features of both immunodeficiency, readily observed by responses to vaccination in patients with CKD that are poorer than in the general population (Stevens et al., 1984; Kreft et al., 1997) and which become even less pronounced as CKD progresses (DaRoza et al., 2003), and chronic inflammation through immune activation, inferred by chronically raised serum markers of inflammation, such as C-reactive protein, interleukin (IL)-6 and tumour necrosis factor (TNF) (Miyamoto et al., 2011).

These predicates of CKD are independent of chronic inflammatory and immunodeficiency disorders that cause renal failure (e.g. lupus nephritis (Bomback and Appel, 2010), multiple myeloma (Bataille and Harousseau, 1997), and HIV (Douek et al., 2003)) or of consequence/complication of therapy (e.g. immunosuppression for vasculitis (Lode and Schmidt-Ioanas, 2005)). However, defects in the immune system *are* clearly compounded by other factors prevalent in the CKD population, such as advanced age, diabetes mellitus, malnutrition, and abnormalities of other organs that act as portals of entry for pathogens, for example, the lower urinary tract (Powe et al., 1999; Jaar et al., 2000).

The duality of chronic inflammation and immunodeficiency is of particular importance since accelerated cardiovascular disease as a result of chronic inflammation and infective illnesses from immunodeficiency remain the two leading causes of death in patients with CKD.

Numerous defects in both the innate and adaptive immune responses have been described in CKD (Figs 128.2 and 128.3). Although these changes occur concurrently, for convenience and clarity, here they will be discussed in terms of deficiencies causing attenuation of immune responses (immunodeficiency) and acquired immune system changes resulting in chronic inflammation.

The majority of studies of the immune system in CKD have compared healthy individuals against those already on dialysis. Therefore, one infers, but cannot say with confidence, that immune system defects are continuous across progressive CKD (and become explicit when defects accumulate and translate into clinically measurable dysfunction) rather than suddenly occurring at particular thresholds of CKD. Likewise, the immunological changes cannot be conclusively divorced from the physicochemical environment of dialysis. However, as far as possible, the effects of dialysis on the immune system will not be discussed here as these are expounded elsewhere (see Chapters 269–271).

Acquired immunodeficiency

Immunodeficiency in CKD is the result of defects at every level of immune responsiveness to foreign pathogens, including abnormalities of antigen recognition, removal, and presentation, failure of T-cell co-stimulation, depletion and defect of effector T-cell (Teff) subsets, as well as defects in B cells.

Abnormalities in antigen recognition and phagocytosis/removal

Neutrophils, monocytes, and macrophages play a pivotal role in immunological health against bacterial pathogens because they are key to successful recognition and removal of pathogen-associated antigens or self-derived dangerous entities such as apoptotic and necrotic cells. It is not surprising, therefore, that reports of hyporeactivity (Ando et al., 2005), defective phagocytosis (Vanholder and Ringoir, 1993; Vanholder et al., 1993; Anding et al., 2003), impaired cytotoxicity (Prabhakar et al., 1997; Anding et al., 2003), maturation (Lim et al., 2007; Verkade et al., 2007b), and even enhanced apoptosis (Cohen et al., 2001) in these immune cells correlate with bacterial agents as the primary infective source in patients with CKD (Abbott and Agodoa, 2001). Interestingly, decreased function of other innate immune cells such as mast cells and γδ T cells has not been conclusively connected with CKD—the activation state of these cells seems rather increased (Wu et al., 2007; Holdsworth and Summers, 2008). Studies of NK cells in CKD, on the other hand, are still lacking.

The exact mechanisms underlying these functional defects in neutrophils, monocytes, and macrophages in CKD are currently not well understood but several studies suggest that the uraemic environment accompanying CKD may impact on the function of the key danger recognition pathway in innate immune cells, namely the toll-like receptors (TLRs). TLRs are examples of signalling pattern recognition receptors expressed on neutrophils, monocytes, and antigen-presenting cells (APCs) that bind pathogen-associated molecular patterns (PAMPs) and instruct innate effector functions, such as cell degranulation and phagocytosis as well as expression of immune responsive genes, such as T-cell co-stimulatory molecules (e.g. cluster of differentiation (CD)-80 and CD86) and cytokines (Fig. 128.4B). Indeed, the importance of the uraemic environment to at least some of these TLR-related defects is suggested by some

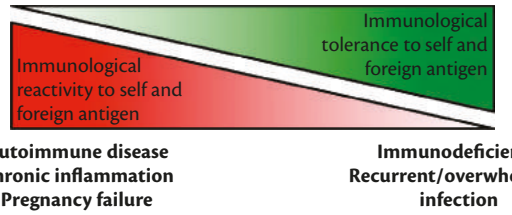

Fig. 128.1 Immune homeostasis and its relationship to disease. The immune system must balance the requirement for response to foreign antigen against the need to maintain tolerance to self-components, commensals, and food-derived and semi-allogeneic fetal antigens. A disturbance of this homeostasis causing excessive immune responsiveness and/or deficiency in tolerogenic mechanisms can result in autoimmune diseases, chronic inflammation, and pregnancy failure. On the other hand, weak immune responsiveness and/or excessive tolerance-inducing machineries may result in immunodeficiency, characterized by recurrent and/or overwhelming infections.

degree of normalization of function in the presence of non-uraemic serum (Lim et al., 2007).

Abnormalities in antigen presentation and T-cell activation

Besides impacting negatively on the direct recognition and removal of antigens by phagocytosis, uraemia also causes a defect in antigen-presenting capacity of key APCs including macrophages and dendritic cells (DCs). These cells are not only an important source of inflammatory cytokines but are also required for effective T-cell activation via presentation of antigen and provision of co-stimulatory signals. There are two types of DCs, myeloid (mDCs) and plasmacytoid (pDCs). The latter orchestrate antiviral immunity, producing type I interferons (e.g. IFN-α) in response to TLR7 and -9 ligands such as CpG-containing DNA, while the former induce T-helper (Th)-1 (and under some circumstances Th2) immunity through production of (predominantly) large quantities of IL-12 in response to TLR3 and -4 ligands. In CKD, not only is there a general reduction in total DC numbers (Hesselink et al., 2005; Verkade et al., 2007b), irrespective of whether subjects are pre- or on dialysis (Hesselink et al., 2005), but the deficiency is manifested more significantly in pDCs than mDCs (Agrawal et al., 2010)—likely explaining the propensity of CKD patients to present with increased inflammatory Th1 responses (see below). Part of this defect is related to impaired maturation of monocytes into DCs, which can be reversed to an extent by non-uraemic serum (Lim et al., 2007). Uraemia not only shifts the balance of mDC versus pDC and related cytokine patterns but also causes a defect in the upregulation of co-stimulatory molecules required for efficient T-cell activation, such as CD80 and CD86 (Girndt et al., 1993, 2001) in macrophages and DCs. Similarly to the initiation of phagocytic function, expression of CD80 and CD86 is regulated by TLRs in these cells. Downregulated TLR expression in both pre-dialysis (Ando et al., 2006b) and dialysis (Kuroki et al., 2007) CKD patients can, therefore partially explain the deficiency in CD80 and CD86 expression on APCs and poor monocyte responses to TLR agonists (Ando et al., 2006a, 2006b) in CKD.

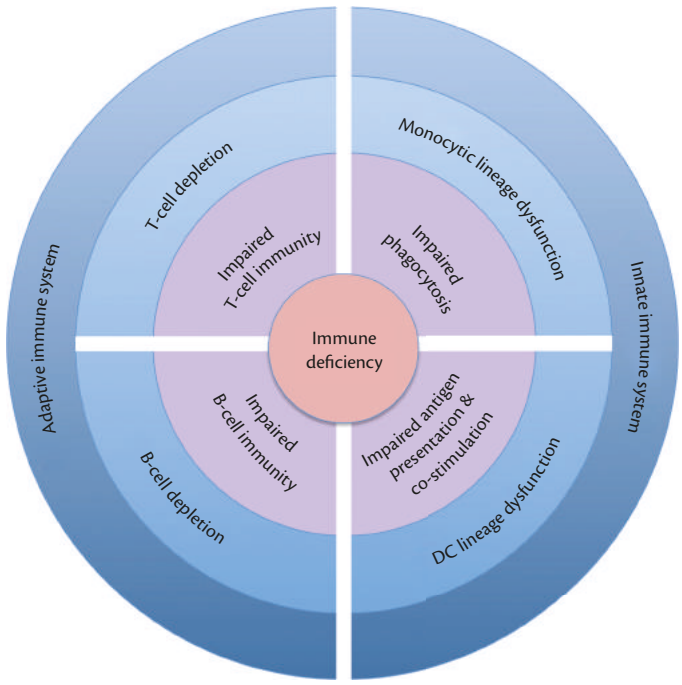

Fig. 128.2 Mechanisms underlying acquired immune deficiency in CKD results in a disturbance of both innate (monocytes and DCs) and adaptive (T and B cells) arms of the immune system, causing attenuation of responses to foreign antigens. The diagram summarizes the key elements affected. DC = dendritic cell.

Depletion and defect of effector T-cell subsets

Defective or altered APC function generally translates into suboptimal T-cell activation or pathological skewing of Teff responses. T cells are critical agents in the maintenance of adaptive immunity and the development of immunological memory. They are divided into subtypes based on function (cytokine expression) (Fig. 128.5) and cell surface/intracellular molecule expression, for example, CD4+ and CD8+. CD4+ cells are further divided into effector (Teff; CD25−) or regulatory (Tregs; CD4+CD25hiCD127loFOXP3+) (Fig. 128.5). The latter are non-redundant in the prevention of autoimmune diseases and candidates for cellular immunotherapy in human diseases and solid organ transplantation (Afzali et al., 2007; Sagoo et al., 2008). Effector cells comprise naïve (CD45RA+) and memory (CD45RO+) subsets, the latter composed of effector memory (CCR7−, displaying immediate effector function on stimulation) and central memory (CCR7+, lacking immediate effector function but generating effector memory T cells on stimulation) types (Sallusto et al., 1999). Homeostatic maintenance of the correct balance between these T-cell subsets is critical in the maintenance of adaptive immunological health, a balance that is disturbed in CKD.

Numerous abnormalities of T cells have been described in CKD. These include a reduction in overall T-cell numbers (Kurz et al., 1986; Deenitchina et al., 1995), including quantitative alteration of lymphocyte subsets (Deenitchina et al., 1995) such as depletion of naïve and central memory Teffs (Yoon et al., 2006). Failure to establish lasting immunological memory to vaccines can, in part, be explained by this depletion of memory Teffs. Since T cells in CKD exhibit an activated state (Meier et al., 2000), T-cell depletion is explained by a markedly enhanced rate of apoptosis in remaining T-cell populations (Matsumoto et al., 1995; Meier et al., 2009). Other significant numerical T-cell perturbations, such as reduction in the relative ratios of CD4+ to CD8+ T cells in CKD (Yoon et al., 2006) are more controversial, since preserved ratios have also been

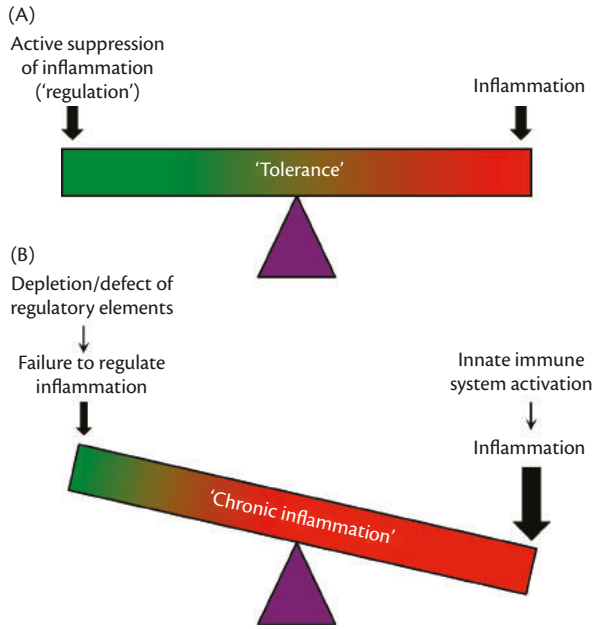

Fig. 128.3 Mechanisms broadly underlying acquired chronic inflammation in CKD.
(A) Under normal circumstances, inflammation generated during homeostatic immune activation, for example, during removal of apoptotic cells generated during normal cell turnover and tissue homeostasis, is counterbalanced ('regulated') by suppressive mechanisms preventing unwanted inflammation. (B) In CKD, this balance is offset by an increase in immune system activation and depletion/defect in regulatory elements, resulting in chronic inflammation.

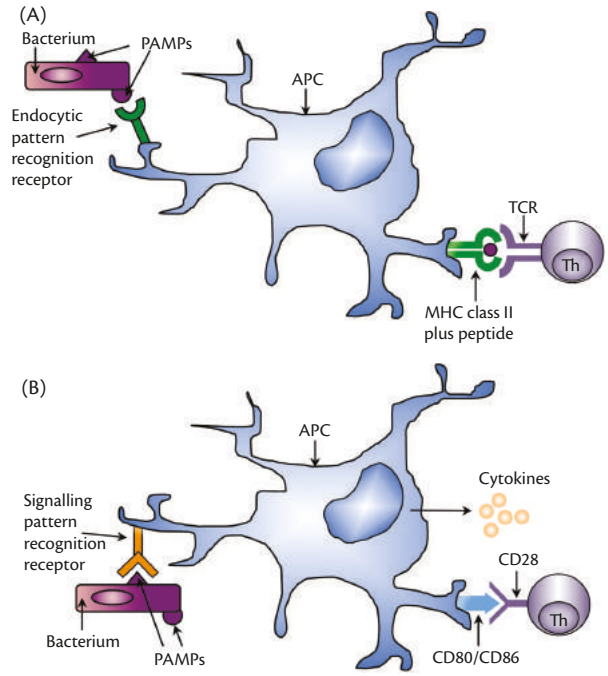

Fig. 128.4 Endocytic and signalling pattern recognition receptors.
Pathogen-associated molecular patterns (PAMPs) can be recognized by either endocytic (A) and/or signalling (B) pattern recognition receptors on antigen-presenting cells. Engagement of the former results in phagocytosis of the pathogen, antigen processing, and presentation in the context of MHC class II. The MHC class II-peptide complex is recognized by cognate T-cell receptors (TCRs), resulting in transduction of a signal from the TCR to downstream elements. Recognition of PAMPs by signalling pattern recognition receptors results in expression of co-stimulatory molecules, such as CD80 and CD86, which engage their receptors, such as CD28, on T cells and secretion of cytokines. Activation of naïve T cells is critically dependent on a TCR signal as well as a co-stimulus, whereas memory T cells are much less dependent on co-stimulation.

reported (Kurz et al., 1986; Deenitchina et al., 1995). The biology of Tregs in CKD is discussed in the 'Regulatory T cell defects in CKD' section.

Functionally, T cells show sluggish and/or defective responsiveness to stimulation (Kurz et al., 1986; Meuer et al., 1987; Cohen et al., 1997; Descamps-Latscha and Herbelin, 1993), which presumably underlies the disturbances of acquired immunity observed in CKD (i.e. high vaccine failure rates and failure of tuberculin skin testing to diagnose latent tuberculosis) (Eleftheriadis et al., 2007). T-cell differentiation also appears to be aberrant, with a propensity to differentiate towards Th1, rather than Th2 (Sester et al., 2000; Ando et al., 2005). These predicates may be the result of failure of T-cell co-stimulation and interaction with APCs (see above), lower expression of the T-cell receptor (TCR)/CD3 complex (Stachowski et al., 1993) (essential for appropriate T-cell activation), as yet unidentified antigen(s) in the CKD milieu, altered monocyte cytokine production (Meuer et al., 1987; Girndt et al., 1998) or a combination of these. Indeed, in patients with CKD, poor monocyte-derived DC function correlates with impaired T-cell responses to vaccines (Verkade et al., 2007a). There is also some evidence to suggest that high parathyroid hormone (PTH) levels in CKD contribute to the T cell hyporesponsiveness observed (Tzanno-Martins et al., 2000).

Defects in B cells

B cells have a repertoire of functionality in the immune system that has only in the recent past been recognized to go beyond antibody production. These include, in addition to antibody production, proliferation, antigen presentation to T cells, cytokine production, and suppressive function. In the uraemic environment, generalized B-cell lymphopenia is the norm (Deenitchina et al., 1995; Fernandez-Fresnedo et al., 2000; Pahl et al., 2010), albeit with the caveat that the circulating environment may not reflect the total body B-cell compartment. Children with CKD appear to have a more significant deficiency in memory B cells (Bouts et al., 2004) than adults, in whom the deficiency is more generalized (Pahl et al., 2010).

Uraemic serum contains elevated levels of key B-cell growth factors, such as IL-17 and B-cell activation factor of the TNF family (BAFF) (Pahl et al., 2010), as their production is significantly stimulated by chronic inflammation and lymphopenia (Mackay et al., 2003), both hallmarks of CKD. However, transitional B cells (see Fig. 128.6) in the uraemic environment exhibit marked reduction in expression of receptors for B-cell growth factors, such as BAFF (Pahl et al., 2010). By extension, there is likely to be an impairment of growth, maturation and differentiation of B cells (Fig. 128.6) in CKD. In addition, B cells in CKD manifest markedly enhanced apoptosis relative to B cells from healthy donors (Fernandez-Fresnedo et al., 2000), so depletion of B-cell numbers may reflect not only a block in differentiation and maturation but also accelerated cell death.

Functionally, defects in T lymphocytes described above likely also have an impact on T-cell-dependent B-cell responses, in particular antibody production against protein antigens. Although

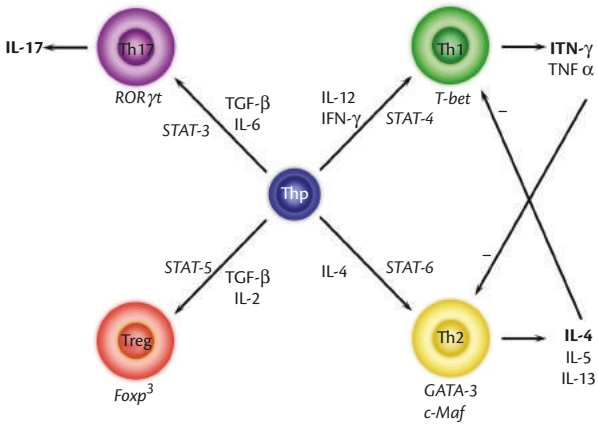

Fig. 128.5 CD4+ helper (Th) cell differentiation, a simplified diagram. Pluripotent Th cells (Thp) are induced to differentiate to different lineages (Th1, Th2, Th17, and Treg), with defined effector functions. These can be distinguished from each other by differentiation pathway (signal transducer and activator of transcription, *STAT* proteins), signature transcription factor expression (italicized in small letters) and dominant cytokine(s) produced. Th1, Th2, and Th17 cells are pro-inflammatory, providing immunity against intracellular pathogens, helminthic infections, and extracellular pathogens respectively, while Tregs suppress immune responses (particularly those mediated by Th1 cells). Please note that the above, linear, model of lineage differentiation is simplified and currently subject to challenge by a more plastic model that proposes less stringent commitment to Th lineages on differentiation.

there are reports of normal serum levels of immunoglobulins in patients on dialysis (Okasha et al., 1997), *in vitro* studies have also shown impaired T-cell-independent B-cell responses and production of immunoglobulin (Ig)-M, IgG, and IgA in these individuals (Raskova et al., 1987; Smogorzewski and Massry, 2001). This deficiency may manifest *in vivo* as deficits in specific subclasses of IgG (Bouts et al., 2000) and may partly be related to elevated levels of intracellular calcium in B cells and high levels of serum PTH in CKD (Smogorzewski and Massry, 2001). When stimulated with a TLR-9 ligand (CpG), uraemic B cells also fail to produce a normal cytokine profile, secreting significantly higher concentrations of the pro-inflammatory cytokine IL-6 and TNF, than healthy control B cells (Pahl et al., 2010).

Chronic inflammation

Strong protective responses are initiated upon pathogen encounter by concerted actions of the innate and adaptive arms of the immune system. However, even in the absence of dangerous microbes, continuous, low-level immune activation is apparent and required for tissue integrity and removal of apoptotic cells. Under normal circumstances, there is a homeostatic balance between pro-inflammatory and anti-inflammatory mechanisms, which prevents the development of autoimmune diseases (Fig. 128.3A). This is perhaps best demonstrated in humans in whom absence/mutations in the transcription factor controlling Treg function (FOXP3) results in death from severe autoimmune disease (Bennett et al., 2001; Baecher-Allan and Hafler, 2006) in the absence of discernible changes in the Teff compartment. Although, as discussed in detail above, CKD patients present with clear manifestations of decreased immune induction, their condition is concurrently also characterized by hallmarks of an over-reactive immune response. This specific combination of immune deregulation in 'both directions' poses an additional layer of complexity in the design of appropriate therapeutic interventions.

Excessive immune system activation in CKD

Chronic inflammation in CKD, inferred from long-term elevations of serum markers, such as C-reactive protein, IL-6 and TNF

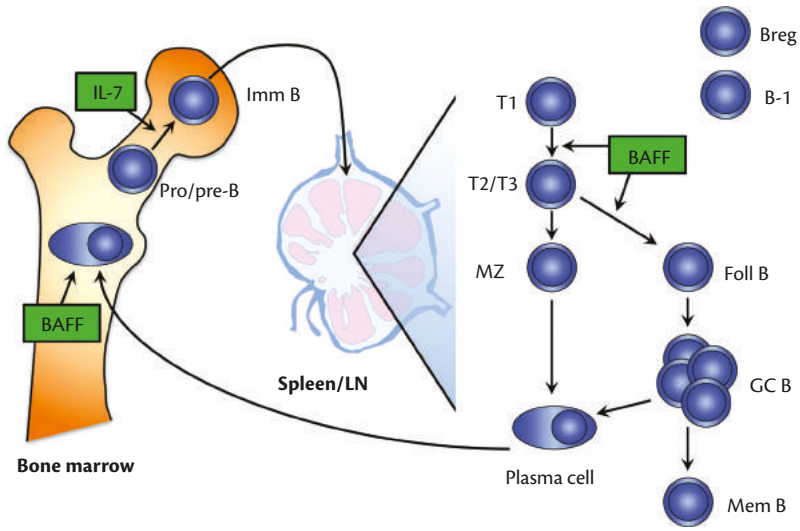

Fig. 128.6 B-cell maturation. B-cell maturation begins in the bone marrow with differentiation of pre-B cells to immature B cells, undergoing a series of gene rearrangement steps to develop unique B-cell receptors (BCRs) before negative selection of autoreactive T cells. A key growth factor for the differentiation of pro- and pre-B cells to immature B cells is interleukin (IL)-7. Immature B cells differentiate further in the spleen initially to transitional zone (T) 1, 2, and 3 B cells before eventually maturing into mature follicular (Foll) and marginal zone (MZ) B cells. During an immune response, mature B cells differentiate into germinal centre (GC) B cells, memory B cells and plasma cells. Plasma cells home preferentially to tissues and bone marrow. Development of T1 to T2/T3 and T2/T3 to follicular B cells as well as persistence of plasma cells in the bone marrow is dependent on the presence of BAFF (B cell activation factor of the TNF family). Regulatory B cells (Bregs) and another population of B cells called B-1 (found in the peritoneum) are two other mature B cell phenotypes whose differentiation is not yet fully understood.

(Miyamoto et al., 2011), is detectable at early stages of CKD and is exacerbated as CKD progresses (Pereira et al., 1994). The pathogenesis of inflammation is by either an increase in immune system activation and/or depletion or defect in regulatory elements (Fig. 128.3B). Further, although it is accepted that many elements of the immune system show heightened activation in CKD, the true difficulty is in discerning whether these changes are the cause or the result of chronic inflammation. For example, soluble levels of CD25 and CD23 (shed from T- and B-cell surfaces, respectively, after activation) are elevated in patients with CKD (Descamps-Latscha et al., 1995), suggesting that there is chronic activation of both T and B cells, but not specifying whether this would be the result or the cause of chronic inflammation. As far as possible, dialysis-specific alterations will not be discussed here (see Chapters 259 and 266).

Monocyte and neutrophil activation

Despite hyporeactivity and poor phagocytic (and antigen-presenting) function (see 'Abnormalities in antigen recognition and phagocytosis/removal'), monocytic and polymorphonuclear (PMN) lineages show significant hyperactivation characteristics in CKD. In particular, they express surface markers, such as integrins (CD11b/CD18 for instance), required for cell-to-cell adhesion and for diapedesis into sites of inflammation (Yoon et al., 2007) and contribute significantly to oxidative stress by producing superoxide and hydrogen peroxide (Yoon et al., 2007). Elevated oxidative stress inhibits the anti-inflammatory properties of high-density lipoprotein (HDL) and increases the pro-inflammatory activity of low-density lipoprotein (LDL), which compounds the dyslipidaemia commonly seen in CKD (Vaziri et al., 2010). While there is general agreement that TLR expression is suppressed on monocytes and PMNs in CKD (Ando et al., 2006b; Kuroki et al., 2007; Koc et al., 2011) and that the responses to TLR ligation are attenuated (Ando et al., 2006a, 2006b), at least one report identified over-expression of TLR2 and -4 (but nor TLR7 and -9) on monocytes and TLR4 on neutrophils and augmented production of the pro-inflammatory cytokines IL-6 and TNF on TLR4 ligation (Gollapudi et al., 2010), suggesting that there may be considerable variation between individuals and/or some relationship between TLR expression and dialysis. Of note, patients with CKD (as early as CKD stage 3) have elevated serum levels of lipopolysaccharide (LPS) (Goncalves et al., 2006; McIntyre et al., 2011). LPS engages a number of receptors on immune cells, including TLR4, CD14, and TLR2 (Yang et al., 1998), resulting in immune cell activation. High levels of LPS in the serum are presumably derived from intestinal bacteria since bowel oedema, caused by fluid overload (contributed to by loss of native urine output in patients on haemodialysis), is a potent risk factor for the permeabilization of the intestines to bacterial translocation (Krack et al., 2005). Although biologically plausible, LPS levels in patients with CKD do not always correlate with the levels of inflammatory markers in the serum (Goncalves et al., 2006), suggesting that chronic inflammation in these individuals is more complex than LPS alone. TLRs are also engaged by self-derived danger signals such as antigens exposed by non-healing injured or dying tissue, possibly explaining continuous activation of the TLR system in the absence of infection. Nevertheless, uraemic serum very clearly promotes adhesion of monocytes from healthy individuals to cultured endothelium (Moradi et al., 2010) providing a plausible link between monocytes, oxidative stress, and atherogenesis in CKD.

Endocytic pattern recognition receptors are expressed on APCs and bind PAMPs to induce phagocytosis, antigen processing, and presentation in the context of major histocompatibility complex (MHC) class II (Fig. 128.4A). In addition to alterations in expression of TLRs, endocytic PAMPs are also altered in CKD. In particular, the macrophage scavenger receptors SR type I (Ando et al., 1996; Konishi et al., 1997) and CD36 (Chmielewski et al., 2005) are both elevated on circulating monocytes, albeit only when patients have been established on dialysis. Since monocytes use these receptors for uptake of oxidized LDL, these observations may also be of relevance when considering the monocyte–oxidative stress–atherogenesis axis in CKD.

Mast cells are also overactive in CKD and contribute significantly to progression of disease; notably, their presence is associated with fibrosis and loss of kidney function (Holdsworth and Summers, 2008).

Hypercytokinaemia

The levels of many cytokines, including IL-6, TNF, IL-12, IFN-γ and IL-10, are significantly elevated in the serum of patients with CKD. Some of this increase is clearly related to chronic immune system activation, particularly of innate cells such as monocytes (see 'Monocyte and neutrophil activation'), but additional non-renal factors, such as congestive cardiac failure (Sharma et al., 2003) and genetic polymorphisms (especially at the IL-6 promoter (Bonafe et al., 2001) also play a part. Other tissues, in particular adipocytes, are also capable of producing IL-6 (Mohamed-Ali et al., 1997), so in renal patients of large body habitus, may contribute significant amounts of pro-inflammatory cytokines to the total body pool (Axelsson et al., 2004).

An inverse linear relationship between the serum concentrations of these cytokines and renal function (Descamps-Latscha et al., 1995; Bolton et al., 2001; Pecoits-Filho et al., 2003) also suggests that the cause of elevation is partly related to failure of renal clearance with worsening renal function. Indeed, in one study, the sole determinant of IL-6 concentration on multiple regression analysis was serum creatinine (Bolton et al., 2001). That failure of renal clearance is a significant contributor to hypercytokinaemia is, additionally, supported by demonstrations in rat models that IL-1β (Poole et al., 1990), and to a lesser extent TNF (Bemelmans et al., 1993), are also removed through renal clearance. If nothing else, this is a compelling reason to persevere with strategies to preserve residual renal function in CKD.

Inflammatory cytokines, such as IL-6 (Pecoits-Filho et al., 2002), and to a lesser extent TNF (Stenvinkel et al., 1999), are linked to increased mortality in patients with CKD (as they are with mortality in the general population (Harris et al., 1999)), through an association with atherogenesis (Huber et al., 1999). However, important caveats need to be considered here. Firstly, it is unclear whether raised levels of inflammatory cytokines cause or are a consequential by-product of endothelial stress and plaque formation. Secondly, serum cytokine levels are poor reflectors of local concentrations at sites of production and may not be indicative of actual cytokine activity, which is dictated by receptor expression, receptor occupancy, intracellular signal transduction, and chromatin structure of target genes. Finally, cytokines function in networks, positively and negatively regulating the expression of other cytokines, so

correlations between serum concentrations of individual cytokines and outcomes might reflect false positive associations based on interaction.

High levels of IL-12 (Sester et al., 2000) and IL-1β reflect the hyperactivation state of the monocyte/macrophage lineage and a predisposition to Th1 and Th17 differentiation in T cells (as illustrated in Fig. 128.5). Strong Th1 responses are also accompanied by elevated IFN-γ levels, which may contribute to excessive tissue injury and prolonged release of self-derived antigens that sustain activation of TLRs (see 'Monocyte and neutrophil activation') or the complement system (see 'Complement activation'). Further, as there is a reciprocal relationship between Th1 and Th2 differentiation (Fig. 128.5), and particularly Th2 cells are required for efficient antibody production against protein antigens, this may explain poor vaccine responses in advancing CKD and clinical improvements in SLE once end-stage renal failure has been reached (Coplon et al., 1983; Cheigh et al., 1990).

Clearly, continuously elevated levels of pro-inflammatory cytokines foster a perpetual cycle of progressive tissue damage and fibrosis that generates a chronic source of danger signals sustaining induction of inflammatory mediators in CKD. However, these patients also present with high amounts of the anti-inflammatory cytokine IL-10 in circulation and the level of IL-10 correlates inversely with inflammatory markers (Morita et al., 1997; Stenvinkel et al., 2005). IL-10 was initially classified as Th2-specific cytokine with strong immunosuppressive properties towards Th1 cells, DCs, and monocytes by inhibiting the production of key inflammatory cytokines, including IL-2, IL-6, IL-12, IFN-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF), and TNF (Moore et al., 2001). It is now clear, though, that IL-10 can also be produced in substantial quantities by several additional immune cell populations: under uraemic conditions, high IL-10 secretion by monocytes and macrophages has been connected with the increased stimulation of these cells by TLRs and complement observed in CKD (Morita et al., 1997). However, and highly relevant here, recent advances in the field suggest that Th1 cells acquiring the ability to co-express IL-10 in addition to IFN-γ upon environmental cues are the biggest source of IL-10 *in vivo* (O'Garra and Vieira, 2007). This co-production of IL-10 is thought to induce a (self-)regulatory state in Th1 cells and may be part of a normal Teff cell 'life cycle' as IL-10 induction has also been observed for all Teff cell subpopulations, including Th17 cells (O'Garra and Vieira, 2007). Thus, the increased Th1 (IFN-γ+/IL-10+) response in CKD, together with heightened monocyte and macrophage activation and impaired renal IL-10 clearance are all probable contributing factors to high levels of circulating IL-10 in CKD. Further, polymorphisms in the *Il10* gene promoter also affect IL-10 production by activated cells (Eskdale and Gallagher, 1995) and CKD patients with the highest levels of IL-10 due to a specific polymorphic sequence show best response to hepatitis B vaccination (Girndt et al., 1995); this is likely due to the fact that IL-10 supports immunoglobulin class switching in B cells (Malisan et al., 1996). Interestingly, the protective effect of high IL-10 levels in CKD may extend beyond that of counter-balancing heightened immune activation and supporting antibody production and maturation. There are indications that IL-10 may also have direct anti-atherogenic properties via inhibition of immune cell diapedesis (Song et al., 1997) and the suppression of matrix metalloprotease (MMPs) activation and superoxide anion production (Niiro et al., 1992; Lacraz et al., 1995), which are required for atherosclerotic plaque rupture. Thus, increasing specifically IL-10 production in CKD patients could be a promising strategy to reset immune balance and actively stabilize plaques.

Complement activation

Besides TLRs, the complement system represents the second major danger recognition and removal system of the immune system (Walport, 2001). The complement system consists of > 30 fluid phase and cell membrane-bound proteins. There are three complement activation pathways—the alternative, the classical, and the lectin pathway—that are activated in a cascade-like fashion upon recognition of danger signals including pathogens, infected cells, malignant cells, and apoptotic or necrotic cells. Activation of the pathways converge on the level of generation of the opsonins C3b and C4b, the generation of the anaphylatoxins C3a and C5a (mediators of the inflammatory reaction), as well as the induction of the terminal lytic pathway, characterized by formation of the membrane attack complex (MAC) and direct killing of targets (Fig. 128.7). Increased systemic and local complement activation with subsequent damage of endothelial and epithelial cells has historically long been connected with acute and chronic kidney disease; complement deposition and activation are well acknowledged as mediators and markers of renal damage in conditions including glomerulonephritis, lupus nephritis, IgA nephropathy, ischaemia reperfusion injury, and atypical haemolytic uraemic syndrome (Berger et al., 2005; Tang and Sheerin, 2009; Vernon and Cook, 2012). Whether complement activation is cause or effect in CKD is currently a matter of discussion and research focus. In part, increased or prolonged complement activation in CKD is observed—similar to the situation described for TLRs (see 'Monocyte and neutrophil activation')—because damaged tissue generates self-derived danger signals that activate complement (Pickering et al., 2000; Brown et al., 2007). In addition, uraemia sustains excessive complement activation because factor D (a factor required for initial activation of the alternative pathway) and complement system-derived acute phase reactants (factor B, mannose-binding protein, and C3 activation fragments) (Fig. 128.7) accumulate due to decreased clearance via the damaged kidney (Deppisch et al., 2001).

However, the recent shift in paradigm, which now also attributes a vital role for complement in immune response contraction and immune homeostasis and not only the induction of inflammatory reactions (see 'Hypercytokinaemia') (Kemper and Atkinson, 2007; Kolev et al., 2014), suggests that complement dysregulation in CKD may also directly contribute to the altered T effector/Treg cell phenotype observed in these patients.

Defective regulatory elements

Many regulatory elements exist in the immune system, including proteins (e.g. IL-10), small RNA species (microRNA), steroid hormones, and immune cells themselves. Two of these are particularly 'hot topics' at present, Tregs and vitamin D. In patients with CKD, both of these show discernible abnormalities and will be discussed here.

Regulatory T-cell defects in CKD

There are several types of regulatory T cells in the immune system. Of these, naturally occurring CD4+CD25hiCD127loFOXP3+ Tregs are thought to be the most important in the prevention of autoimmune diseases and the regulation of excessive immune system

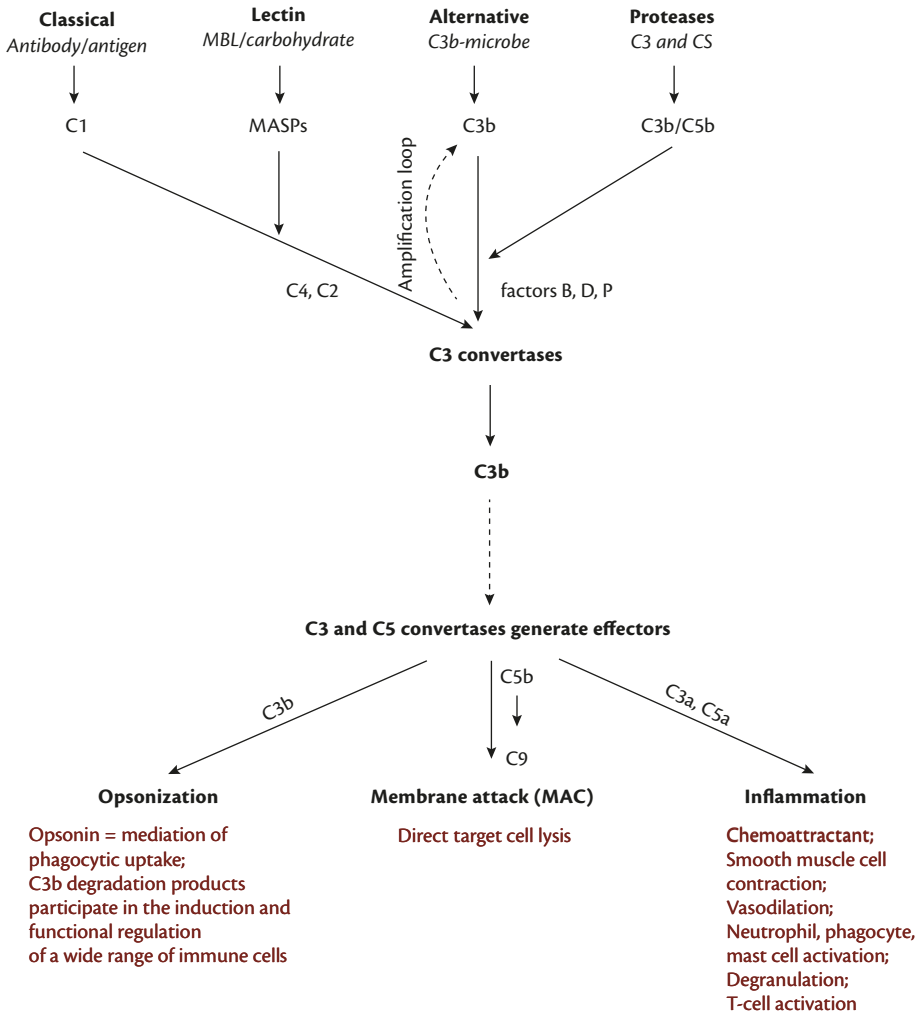

Fig. 128.7 The complement system. Complement activation can be initiated through three cascade-like pathways—the classical, lectin, and alternative pathways—of which all three recognize distinct pathogen- or self-derived danger signals. In addition, complement activation can also be initiated via direct cleavage of C3 (or C5) though proteases such as kallikrin, thrombin, or cathepsins. The deposition of C3b on a target surface then initiates the feedback amplification loop. All activation conditions converge on the level of formation of C3 and C5 convertases. C3 and C5 convertases generate C3b, C5b, and the anaphylatoxins C3a and C5a. These effectors mediate lysis of target cells (MAC formation) or immune adherence and phagocytosis of the pathogen/antigen (C3b and C4b) or function as chemoattractants and activators of immunocompetent cells (C3a and C5a). MAC = membrane attack complex; MBL = mannan-binding lectin; MASP = MBL-associated serine protease

activation during infective illnesses (Afzali et al., 2007). Tregs inhibit activation, proliferation, and cytokine production in Teffs (Thornton and Shevach, 1998; Jonuleit et al., 2001), thus inhibiting immune propagation in response to autoantigens and damping down responses following encounter with pathogen. The mechanism of action of Tregs appears to be multiple, but there is an obligate requirement for cell-to-cell contact or, at least, close proximity between Tregs and target cells (Takahashi et al., 1998; Thornton and Shevach, 1998). Such heterogeneity in function may reflect genuine subpopulations in Tregs, of which emerging data suggests there are several (Miyara et al., 2009; Sakaguchi et al., 2010; Edozie et al., 2014). Tregs can now be enriched/purified from the peripheral circulation and expanded *in vitro* in such a way that they maintain their phenotypic characteristics (Battaglia et al., 2006; Trzonkowski et al., 2009; Tresoldi et al., 2011), making them one of the most viable candidates for trials of cell-based immune therapy (Sagoo et al., 2008) for the induction of transplant tolerance and amelioration of autoimmune diseases.

In CKD, there have been suggestions that Treg populations are diminished, functionally defective, and highly apoptotic (Hendrikx et al., 2009; Meier et al., 2009), possibly as a result of circulating factors in the uraemic environment, such as oxidized LDL (Meier et al., 2009) and Th1-polarizing cytokines, such as IL-12. These observations are important from two perspectives. Firstly, they provide an additional reason for the chronic inflammation seen in CKD, in particular excessive Th1 responses. Secondly, defects in Tregs from patients with CKD effectively diminish the likelihood of successful trials of cell-based therapy. Our own observations and those of our collaborators, that patients with ESRF from non-autoimmune aetiologies have comparable and functionally competent Treg subsets to healthy age- and sex-matched controls (Afzali et al., 2013), are in disagreement with the published literature. The difference may be related to a difference in the patient cohort studied (sex, age, and length of time on HD), the effect of the uraemic environment on Treg longevity and function or the biology of subpopulations of Tregs.

A second population of IL-10-producing regulatory T cells, called Tr1 cells, may also be of interest in CKD. Although high numbers of Tr1 cells are present in patients developing spontaneous tolerance to a kidney or liver allograft (VanBuskirk et al., 2000), an investigation assessing population size and function of Tr1 cells in CKD has not yet been published. However it is practically feasible to purify and expand *ex vivo* fully functional Tr1 cells from uraemic patients (Berglund et al., 2012). This indicates that the Tr1 pool in this patient group is not completely absent, that these cells present with normal function at least upon *in vitro* activation and that their expansion potentially forms a base for adoptive therapy in kidney transplantation.

Vitamin D deficiency

Vitamin D plays an important role in mammalian immunology, irrespective of its role in the maintenance of serum (and, by inference, intracellular) calcium concentrations. The vitamin D receptor (VDR) is ubiquitously expressed on most immune cells (Veldman et al., 2000), including CD4+ and CD8+ lymphocytes and APCs. In contrast to endocrine vitamin D regulation, however, many immune cells also express the enzyme machinery required for vitamin D activation, notably 1α-hydroxylase and 25-hydroxylase (Hewison et al., 2003). 25 hydroxylase is basally active whereas activity of both 1α-hydroxylase and the VDR is mediated by innate immune signals, in particular IFN-γ and PAMPs such as TLR agonists (Overbergh et al., 2000; Stoffels et al., 2006). During infection/inflammation, both the VDR and 1α-hydroxylase are activated, resulting in the complete activation and signalling machinery of vitamin D. In the immune system, vitamin D has many roles, including cell growth and proliferation, cellular development, movement, cell-to-cell signalling and cell death, all of which are mediated through direct effects on gene transcription (Baeke et al., 2011).

The overall effect is a promotion of innate immunity through production of antimicrobial proteins, such as cathelicidin and defensins (Liu et al., 2006), and modulation of adaptive immunity achieved through inhibition of pro-inflammatory effects (e.g. T-cell co-stimulation, production of IL-2, IL-6, IL-12, IL-23, and IFN-γ) and promotion of anti-inflammatory mechanisms (e.g. preferential Treg and Th2 development and activity in place of Th1) (Adams and Hewison, 2008; Adorini and Penna, 2008; Brown and Slatopolsky, 2008). The net effect is enhanced innate immunity to pathogens and promotion of adaptive regulatory mechanisms in favour of inflammatory ones.

A deficiency of vitamin D, as is highly prevalent in the CKD cohort, particularly as a result of dietary restrictions and loss of appetite, results in the two key immune predicates observed in CKD, namely impaired innate immune responsiveness, predisposing to infection, and chronic inflammation. Vitamin D immune biology is discussed in greater depth in Chapter 127 but it is worth mentioning here that in patients on haemodialysis, infectious mortality very strongly correlates with cathelicidin levels, a surrogate marker of vitamin D activity in the innate immune system (Gombart et al., 2009).

Conclusions

Patients with CKD are immunologically unique in demonstrating both a state of chronic inflammation and of immunodeficiency. While these phenomena are easy to observe, and abnormalities in almost all components of the immune system can be measured, it is frustratingly clear that their underlying defective pathways are complex and may potentially not follow a unifying pattern but rather be individual and patient specific. Thus, much needed novel strategies targeted at reversing these abnormalities rely fully on significant progress in our understanding of immune response induction and regulation pathways as well as their respective cross-talk. The collective effort of researchers worldwide to identify aberrant pathways in human immune diseases via genome-wide association studies (GWAS) and substantial progress in complementary technologies such as deep sequencing, chromatin landscape, and proteome analyses even from limited numbers of cells will likely increase the speed of the further functional dissection of the immune network.

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References

Abbott, K. C. and Agodoa, L. Y. (2001). Etiology of bacterial septicemia in chronic dialysis patients in the United States. *Clin Nephrol*, 56, 124–31.

Adams, J. S. and Hewison, M. (2008). Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. *Nat Clin Pract Endocrinol Metab*, 4, 80–90.

Adorini, L. and Penna, G. (2008). Control of autoimmune diseases by the vitamin D endocrine system. *Nature Clin Pract Rheumatol*, 4, 404–12.

Afzali, B., Edozie, F. C., Fazekasova, H., *et al.* (2013). Comparison of regulatory T cells in hemodialysis patients and healthy controls: implications for cell therapy in transplantation. *Clin J Am Soc Nephrol*, 8(8), 1396–405.

Afzali, B., Lombardi, G., Lechler, R. I., *et al.* (2007). The role of T helper 17 (Th17) and regulatory T cells (Treg) in human organ transplantation and autoimmune disease. *Clin Exp Immunol*, 148, 32–46.

Agrawal, S., Gollapudi, P., Elahimehr, R., *et al.* (2010). Effects of end-stage renal disease and haemodialysis on dendritic cell subsets and basal and LPS-stimulated cytokine production. *Nephrol Dial Transplant*, 25, 737–46.

Anding, K., Gross, P., Rost, J. M., *et al.* (2003). The influence of uraemia and haemodialysis on neutrophil phagocytosis and antimicrobial killing. *Nephrol Dial Transplant*, 18, 2067–73.

Ando, M., Lundkvist, I., Bergstrom, J., *et al.* (1996). Enhanced scavenger receptor expression in monocyte-macrophages in dialysis patients. *Kidney Int*, 49, 773–80.

Ando, M., Shibuya, A., Tsuchiya, K., *et al.* (2006a). Reduced capacity of mononuclear cells to synthesize cytokines against an inflammatory stimulus in uremic patients. *Nephron Clin Pract*, 104, c113–19.

Ando, M., Shibuya, A., Tsuchiya, K., *et al.* (2006b). Reduced expression of Toll-like receptor 4 contributes to impaired cytokine response of monocytes in uremic patients. *Kidney Int*, 70, 358–62.

Ando, M., Shibuya, A., Yasuda, M., *et al.* (2005). Impairment of innate cellular response to in vitro stimuli in patients on continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant*, 20, 2497–503.

Axelsson, J., Rashid Qureshi, A., Suliman, M. E., *et al.* (2004). Truncal fat mass as a contributor to inflammation in end-stage renal disease. *Am J Clin Nutr*, 80, 1222–9.

Baecher-Allan, C. and Hafler, D. A. (2006). Human regulatory T cells and their role in autoimmune disease. *Immunol Rev*, 212, 203–16.

Baeke, F., Korf, H., Overbergh, L., *et al.* (2011). The vitamin D analog, TX527, promotes a human CD4+CD25highCD127low regulatory T cell profile and induces a migratory signature specific for homing to sites of inflammation. *J Immunol*, 186, 132–42.

Bataille, R. and Harousseau, J. L. (1997). Multiple myeloma. *N Engl J Med*, 336, 1657–64.

Battaglia, M., Stabilini, A., Migliavacca, B., *et al.* (2006). Rapamycin promotes expansion of functional CD4+CD25+FOXP3+ regulatory T cells of both healthy subjects and type 1 diabetic patients. *J Immunol*, 177, 8338–47.

Bemelmans, M. H., Gouma, D. J., and Buurman, W. A. (1993). Influence of nephrectomy on tumor necrosis factor clearance in a murine model. *J Immunol*, 150, 2007–17.

Bennett, C. L., Christie, J., Ramsdell, F., *et al.* (2001). The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nat Genet*, 27, 20–1.

Berger, S. P., Roos, A., and Daha, M. R. (2005). Complement and the kidney: what the nephrologist needs to know in 2006? *Nephrol Dial Transplant*, 20, 2613–9.

Berglund, D., Korsgren, O., Lorant, T., *et al.* (2012). Isolation, expansion and functional assessment of CD4+CD25+FoxP3+ regulatory T cells and Tr1 cells from uremic patients awaiting kidney transplantation. *Transplant Immunol*, 26, 27–33.

Bolton, C. H., Downs, L. G., Victory, J. G., *et al.* (2001). Endothelial dysfunction in chronic renal failure: roles of lipoprotein oxidation and pro-inflammatory cytokines. *Nephrol Dial Transplant*, 16, 1189–97.

Bomback, A. S., and Appel, G. B. (2010). Updates on the treatment of lupus nephritis. *J Am Soc Nephrol*, 21, 2028–35.

Bonafe, M., Olivieri, F., Cavallone, L., *et al.* (2001). A gender—dependent genetic predisposition to produce high levels of IL-6 is detrimental for longevity. *Eur J Immunol*, 31, 2357–61.

Bouts, A. H., Davin, J. C., Krediet, R. T., *et al.* (2004). Children with chronic renal failure have reduced numbers of memory B cells. *Clin Exp Immunol*, 137, 589–94.

Bouts, A. H., Davin, J. C., Krediet, R. T., *et al.* (2000). Immunoglobulins in chronic renal failure of childhood: effects of dialysis modalities. *Kidney Int*, 58, 629–37.

Brown, A. J. and Slatopolsky, E. (2008). Vitamin D analogs: therapeutic applications and mechanisms for selectivity. *Mol Aspects Med*, 29, 433–52.

Brown, K. M., Sacks, S. H., and Sheerin, N. S. (2007). Mechanisms of disease: the complement system in renal injury—new ways of looking at an old foe. *Nat Clin Pract Nephrol*, 3, 277–86.

Cheigh, J. S., Kim, H., Stenzel, K. H., *et al.* (1990). Systemic lupus erythematosus in patients with end-stage renal disease: long-term follow-up on the prognosis of patients and the evolution of lupus activity. *Am J Kidney Dis*, 16, 189–95.

Chmielewski, M., Bryl, E., Marzec, L., *et al.* (2005). Expression of scavenger receptor CD36 in chronic renal failure patients. *Artif Organs*, 29, 608–14.

Cohen, G., Haag-Weber, M., and Horl, W. H. (1997). Immune dysfunction in uremia. *Kidney Int Suppl*, 62, S79–82.

Cohen, G., Rudnicki, M., and Horl, W. H. (2001). Uremic toxins modulate the spontaneous apoptotic cell death and essential functions of neutrophils. *Kidney Int Suppl*, 78, S48–52.

Coplon, N. S., Diskin, C. J., Petersen, J., *et al.* (1983). The long-term clinical course of systemic lupus erythematosus in end-stage renal disease. *N Engl J Med*, 308, 186–90.

Daroza, G., Loewen, A., Djurdjev, O., *et al.* (2003). Stage of chronic kidney disease predicts seroconversion after hepatitis B immunization: earlier is better. *Am J Kidney Dis*, 42, 1184–92.

Deenitchina, S. S., Ando, T., Okuda, S., *et al.* (1995). Cellular immunity in hemodialysis patients: a quantitative analysis of immune cell subsets by flow cytometry. *Am J Nephrol*, 15, 57–65.

Deppisch, R. M., Beck, W., Goehl, H., *et al.* (2001). Complement components as uremic toxins and their potential role as mediators of microinflammation. *Kidney Int Suppl*, 78, S271–7.

Descamps-Latscha, B. and Herbelin, A. (1993). Long-term dialysis and cellular immunity: a critical survey. *Kidney Int Suppl*, 41, S135–42.

Descamps-Latscha, B., Herbelin, A., Nguyen, A. T., *et al.* (1995). Balance between IL-1 beta, TNF-alpha, and their specific inhibitors in chronic renal failure and maintenance dialysis. Relationships with activation markers of T cells, B cells, and monocytes. *J Immunol*, 154, 882–92.

Douek, D. C., Picker, L. J., and Koup, R. A. (2003). T cell dynamics in HIV-1 infection. *Res Comm Mol Pathol Annu Rev Immunol*, 21, 265–304.

Edozie, F. C., Nova-Lamperti, E. A., Povoleri, G. A., *et al.* (2014). Regulatory T-cell therapy in the induction of transplant tolerance: the issue of subpopulations. *Transplantation*, 98(4), 370–9.

Eleftheriadis, T., Antoniadi, G., Liakopoulos, V., *et al.* (2007). Disturbances of acquired immunity in hemodialysis patients. *Semin Dial*, 20, 440–51.

Eskdale, J. and Gallagher, G. (1995). A polymorphic dinucleotide repeat in the human IL-10 promoter. *Immunogenetics*, 42, 444–5.

Fernandez-Fresnedo, G., Ramos, M. A., Gonzalez-Pardo, M. C., *et al.* (2000). B lymphopenia in uremia is related to an accelerated in vitro apoptosis and dysregulation of Bcl-2. *Nephrol Dial Transplant*, 15, 502–10.

Girndt, M., Kohler, H., Schiedhelm-Weick, E., *et al.* (1993). T cell activation defect in hemodialysis patients: evidence for a role of the B7/CD28 pathway. *Kidney Int*, 44, 359–65.

Girndt, M., Kohler, H., Schiedhelm-Weick, E., *et al.* (1995). Production of interleukin-6, tumor necrosis factor alpha and interleukin-10 in vitro correlates with the clinical immune defect in chronic hemodialysis patients. *Kidney Int*, 47, 559–65.

Girndt, M., Sester, M., Sester, U., *et al.* (2001). Defective expression of B7-2 (CD86) on monocytes of dialysis patients correlates to the uremia-associated immune defect. *Kidney Int*, 59, 1382–9.

Girndt, M., Sester, U., Kaul, H., *et al.* (1998). Production of proinflammatory and regulatory monokines in hemodialysis patients shown at a single-cell level. *J Am Soc Nephrol*, 9, 1689–96.

Gollapudi, P., Yoon, J. W., Gollapudi, S., *et al.* (2010). Leukocyte toll-like receptor expression in end-stage kidney disease. *Am J Nephrol*, 31, 247–54.

Gombart, A. F., Bhan, I., Borregaard, N., *et al.* (2009). Low plasma level of cathelicidin antimicrobial peptide (hCAP18) predicts increased infectious disease mortality in patients undergoing hemodialysis. *Clin Infect Dis*, 48, 418–24.

Goncalves, S., Pecoits-Filho, R., Perreto, S., *et al.* (2006). Associations between renal function, volume status and endotoxaemia in chronic kidney disease patients. *Nephrol Dial Transplant*, 21, 2788–94.

Harris, T. B., Ferrucci, L., Tracy, R. P., *et al.* (1999). Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med*, 106, 506–12.

Hendrikx, T. K., Van Gurp, E. A. F. J., Mol, W. M., *et al.* (2009). End-stage renal failure and regulatory activities of CD4+CD25bright+FoxP3+ T-cells. *Nephrol Dial Transplant*, 24, 1969–78.

Hesselink, D. A., Betjes, M. G., Verkade, M. A., *et al.* (2005). The effects of chronic kidney disease and renal replacement therapy on circulating dendritic cells. *Nephrol Dial Transplant*, 20, 1868–73.

Hewison, M., Freeman, L., Hughes, S. V., *et al.* (2003). Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells. *J Immunol*, 170, 5382–90.

Holdsworth, S. R., and Summers, S. A. (2008). Role of mast cells in progressive renal diseases. *J Am Soc Nephrol*, 19, 2254–61.

Huber, S. A., Sakkinen, P., Conze, D., *et al.* (1999). Interleukin-6 exacerbates early atherosclerosis in mice. *Arterioscler Thromb Vasc Biol*, 19, 2364–7.

Jaar, B. G., Hermann, J. A., Furth, S. L., *et al.* (2000). Septicemia in diabetic hemodialysis patients: comparison of incidence, risk factors, and mortality with nondiabetic hemodialysis patients. *Am J Kidney Dis*, 35, 282–92.

Jonuleit, H., Schmitt, E., Stassen, M., *et al.* (2001). Identification and functional characterization of human CD4(+)CD25(+) T cells with regulatory properties isolated from peripheral blood. *J Exp Med*, 193, 1285–94.
Kemper, C. and Atkinson, J. P. (2007). T-cell regulation: with complements from innate immunity. *Nat Rev Immunol*, 7, 9–18.
Koc, M., Toprak, A., Arikan, H., *et al.* (2011). Toll-like receptor expression in monocytes in patients with chronic kidney disease and haemodialysis: relation with inflammation. *Nephrol Dial Transplant*, 26, 955–63.
Kolev, M., Le Friec, G., and Kemper, C. (2014). Complement—tapping into new sites and effector systems. *Nat Rev Immunol*, 14(12), 811–20.
Konishi, Y., Okamura, M., Konishi, M., *et al.* (1997). Enhanced gene expression of scavenger receptor in peripheral blood monocytes from patients on cuprophane haemodialysis. *Nephrol Dial Transplant*, 12, 1167–72.
Krack, A., Sharma, R., Figulla, H. R., *et al.* (2005). The importance of the gastrointestinal system in the pathogenesis of heart failure. *Eur Heart J*, 26, 2368–74.
Kreft, B., Klouche, M., Kreft, R., *et al.* (1997). Low efficiency of active immunization against diphtheria in chronic hemodialysis patients. *Kidney Int*, 52, 212–6.
Kuroki, Y., Tsuchida, K., Go, I., *et al.* (2007). A study of innate immunity in patients with end-stage renal disease: special reference to toll-like receptor-2 and -4 expression in peripheral blood monocytes of hemodialysis patients. *Int J Mol Med*, 19, 783–90.
Kurz, P., Kohler, H., Meuer, S., *et al.* (1986). Impaired cellular immune responses in chronic renal failure: evidence for a T cell defect. *Kidney Int*, 29, 1209–14.
Lacraz, S., Nicod, L. P., Chicheportiche, R., *et al.* (1995). IL-10 inhibits metalloproteinase and stimulates TIMP-1 production in human mononuclear phagocytes. *J Clin Invest*, 96, 2304–10.
Lim, W. H., Kireta, S., Leedham, E., *et al.* (2007). Uremia impairs monocyte and monocyte-derived dendritic cell function in hemodialysis patients. *Kidney Int*, 72, 1138–48.
Liu, P. T., Stenger, S., Li, H., *et al.* (2006). Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science*, 311, 1770–3.
Lode, H. M., and Schmidt-Ioanas, M. (2005). Vasculitis and infection: effects of immunosuppressive therapy. *Clin Nephrol*, 64, 475–9.
Mackay, F., Schneider, P., Rennert, P., *et al.* (2003). BAFF AND APRIL: a tutorial on B cell survival. *Res Comm Mol Pathol Annu Rev Immunol*, 21, 231–64.
Malisan, F., Briere, F., Bridon, J. M., *et al.* (1996). Interleukin-10 induces immunoglobulin G isotype switch recombination in human CD40-activated naive B lymphocytes. *J Exp Med*, 183, 937–47.
Matsumoto, Y., Shinzato, T., Amano, I., *et al.* (1995). Relationship between susceptibility to apoptosis and Fas expression in peripheral blood T cells from uremic patients: a possible mechanism for lymphopenia in chronic renal failure. *Biochem Biophys Res Commun*, 215, 98–105.
McIntyre, C. W., Harrison, L. E., Eldehni, M. T., *et al.* (2011). Circulating endotoxemia: a novel factor in systemic inflammation and cardiovascular disease in chronic kidney disease. *Clin J Am Soc Nephrol*, 6, 133–41.
Meier, P., Golshayan, D., Blanc, E., *et al.* (2009). Oxidized LDL modulates apoptosis of regulatory T cells in patients with ESRD. *J Am Soc Nephrol*, 20, 1368–84.
Meier, P., Von Fliedner, V., Markert, M., *et al.* (2000). One-year immunological evaluation of chronic hemodialysis in end-stage renal disease patients. *Blood Purif*, 18, 128–37.
Meuer, S. C., Hauer, M., Kurz, P., *et al.* (1987). Selective blockade of the antigen-receptor-mediated pathway of T cell activation in patients with impaired primary immune responses. *J Clin Invest*, 80, 743–9.
Miyamoto, T., Carrero, J. J., and Stenvinkel, P. 2011). Inflammation as a risk factor and target for therapy in chronic kidney disease. *Curr Opin Nephrol Hypertens*, 20, 662–8.
Miyara, M., Yoshioka, Y., Kitoh, A., *et al.* (2009). Functional delineation and differentiation dynamics of human CD4+ T cells expressing the FoxP3 transcription factor. *Immunity*, 30, 899–911.
Mohamed-Ali, V., Goodrick, S., Rawesh, A., *et al.* (1997). Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *J Clin Endocrinol Metab*, 82, 4196–200.
Moore, K. W., De Waal Malefyt, R., Coffman, R. L., *et al.* (2001). Interleukin-10 and the interleukin-10 receptor. *Res Comm Mol Pathol Annu Rev Immunol*, 19, 683–765.
Moradi, H., Ganji, S., Kamanna, V., *et al.* (2010). Increased monocyte adhesion-promoting capacity of plasma in end-stage renal disease—response to antioxidant therapy. *Clin Nephrol*, 74, 273–81.
Morita, Y., Yamamura, M., Kashihara, N., *et al.* (1997). Increased production of interleukin-10 and inflammatory cytokines in blood monocytes of hemodialysis patients. *Res Comm Mol Pathol Pharmacol*, 98, 19–33.
Niiro, H., Otsuka, T., Abe, M., *et al.* (1992). Epstein-Barr virus BCRF1 gene product (viral interleukin 10) inhibits superoxide anion production by human monocytes. *Lymphokine Cytokine Res*, 11, 209–14.
O'Garra, A. and Vieira, P. (2007). T(H)1 cells control themselves by producing interleukin-10. *Nat Rev Immunol*, 7, 425–8.
Okasha, K., Saxena, A., El Bedowey, M. M., *et al.* (1997). Immunoglobulin G subclasses and susceptibility to allosensitization in humans. *Clin Nephrol*, 48, 165–72.
Overbergh, L., Decallonne, B., Valckx, D., *et al.* (2000). Identification and immune regulation of 25-hydroxyvitamin D-1-alpha-hydroxylase in murine macrophages. *Clin Exp Immunol*, 120, 139–46.
Pahl, M. V., Gollapudi, S., Sepassi, L., *et al.* (2010). Effect of end-stage renal disease on B-lymphocyte subpopulations, IL-7, BAFF and BAFF receptor expression. *Nephrol Dial Transplant*, 25, 205–12.
Pecoits-Filho, R., Barany, P., Lindholm, B., *et al.* (2002). Interleukin-6 is an independent predictor of mortality in patients starting dialysis treatment. *Nephrol Dial Transplant*, 17, 1684–8.
Pecoits-Filho, R., Heimburger, O., Barany, P., *et al.* (2003). Associations between circulating inflammatory markers and residual renal function in CRF patients. *Am J Kidney Dis*, 41, 1212–8.
Pereira, B. J., Shapiro, L., King, A. J., *et al.* (1994). Plasma levels of IL-1 beta, TNF alpha and their specific inhibitors in undialyzed chronic renal failure, CAPD and hemodialysis patients. *Kidney Int*, 45, 890–6.
Pickering, M. C., Botto, M., Taylor, P. R., *et al.* (2000). Systemic lupus erythematosus, complement deficiency, and apoptosis. *Adv Immunol*, 76, 227–324.
Poole, S., Bird, T. A., Selkirk, S., *et al.* (1990). Fate of injected interleukin 1 in rats: sequestration and degradation in the kidney. *Cytokine*, 2, 416–22.
Powe, N. R., Jaar, B., Furth, S. L., *et al.* (1999). Septicemia in dialysis patients: incidence, risk factors, and prognosis. *Kidney Int*, 55, 1081–90.
Prabhakar, S. S., Zeballos, G. A., Montoya-Zavala, M., *et al.* (1997). Urea inhibits inducible nitric oxide synthase in macrophage cell line. *Am J Physiol*, 273, C1882–8.
Raskova, J., Ghobrial, I., Czerwinski, D. K., *et al.* (1987). B-cell activation and immunoregulation in end-stage renal disease patients receiving hemodialysis. *Arch Internal Med*, 147, 89–93.
Sagoo, P., Lombardi, G., and Lechler, R. I. (2008). Regulatory T cells as therapeutic cells. *Curr Opin Organ Transplant*, 13, 645–53.
Sakaguchi, S., Miyara, M., Costantino, C. M., *et al.* (2010). FOXP3+ regulatory T cells in the human immune system. *Nat Rev Immunol*, 10, 490–500.
Sallusto, F., Lenig, D., Förster, R., *et al.* (1999). Two subsets of memory T lymphocytes with distinct homing potentials and effector functions. *Nature*, 401, 708–12.
Sester, U., Sester, M., Hauk, M., *et al.* (2000). T-cell activation follows Th1 rather than Th2 pattern in haemodialysis patients. *Nephrol Dial Transplant*, 15, 1217–23.
Sharma, R., Bolger, A. P., Li, W., *et al.* (2003). Elevated circulating levels of inflammatory cytokines and bacterial endotoxin in adults with congenital heart disease. *Am J Cardiol*, 92, 188–93.
Smogorzewski, M., and Massry, S. G. (2001). Defects in B-cell function and metabolism in uremia: role of parathyroid hormone. *Kidney Int Suppl*, 78, S186–9.

Song, S., Ling-Hu, H., Roebuck, K. A., *et al.* (1997). Interleukin-10 inhibits interferon-gamma-induced intercellular adhesion molecule-1 gene transcription in human monocytes. *Blood*, 89, 4461–9.

Stachowski, J., Pollok, M., Burrichter, H., *et al.* (1993). Signalling via the TCR/CD3 antigen receptor complex in uremia is limited by the receptors number. *Nephron*, 64, 369–75.

Stenvinkel, P., Heimburger, O., Paultre, F., *et al.* (1999). Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int*, 55, 1899–911.

Stenvinkel, P., Ketteler, M., Johnson, R. J., *et al.* (2005). IL-10, IL-6, and TNF-alpha: central factors in the altered cytokine network of uremia—the good, the bad, and the ugly. *Kidney Int*, 67, 1216–33.

Stevens, C. E., Alter, H. J., Taylor, P. E., *et al.* (1984). Hepatitis B vaccine in patients receiving hemodialysis. Immunogenicity and efficacy. *N Engl J Med*, 311, 496–501.

Stoffels, K., Overbergh, L., Giulietti, A., *et al.* (2006). Immune regulation of 25-hydroxyvitamin-D3-1alpha-hydroxylase in human monocytes. *J Bone Miner Res*, 21, 37–47.

Takahashi, T., Kuniyasu, Y., Toda, M., *et al.* (1998). Immunologic self-tolerance maintained by CD25+CD4+ naturally anergic and suppressive T cells: induction of autoimmune disease by breaking their anergic/suppressive state. *Int Immunol*, 10, 1969–80.

Tang, Z. and Sheerin, N. (2009). Complement activation and progression of chronic kidney disease. *Hong Kong J Nephrol*, 11, 41–46.

Thornton, A. M., and Shevach, E. M. (1998). CD4+CD25+ immunoregulatory T cells suppress polyclonal T cell activation in vitro by inhibiting interleukin 2 production. *J Exp Med*, 188, 287–96.

Tresoldi, E., Dell'Albani, I., Stabilini, A., *et al.* (2011). Stability of human rapamycin-expanded CD4+CD25+ T regulatory cells. *Haematologica*, 96(9), 1357–65.

Trzonkowski, P., Bieniaszewska, M., Juścińska, J., *et al.* (2009). First-in-man clinical results of the treatment of patients with graft versus host disease with human ex vivo expanded CD4+CD25+CD127- T regulatory cells. *Clin Immunol*, 133, 22–6.

Tzanno-Martins, C., Futata, E., Jorgetti, V., *et al.* (2000). Restoration of impaired T-cell proliferation after parathyroidectomy in hemodialysis patients. *Nephron*, 84, 224–7.

Vanbuskirk, A. M., Burlingham, W. J., Jankowska-Gan, E., *et al.* (2000). Human allograft acceptance is associated with immune regulation. *J Clin Invest*, 106, 145–55.

Vanholder, R., Dell'aquila, R., Jacobs, V., *et al.* (1993). Depressed phagocytosis in hemodialyzed patients: in vivo and in vitro mechanisms. *Nephron*, 63, 409–15.

Vanholder, R., and Ringoir, S. (1993). Infectious morbidity and defects of phagocytic function in end-stage renal disease: a review. *J Am Soc Nephrol*, 3, 1541–54.

Vaziri, N. D., Navab, M., and Fogelman, A. M. (2010). HDL metabolism and activity in chronic kidney disease. *Nat Rev Nephrol*, 6, 287–96.

Veldman, C. M., Cantorna, M. T., and Deluca, H. F. (2000). Expression of 1,25-dihydroxyvitamin D(3) receptor in the immune system. *Arch Biochem Biophys*, 374, 334–8.

Verkade, M. A., Van Druningen, C. J., Op de Hoek, C. T., *et al.* (2007a). Decreased antigen-specific T-cell proliferation by moDC among hepatitis B vaccine non-responders on haemodialysis. *Clin Exp Med*, 7, 65–71.

Verkade, M. A., Van Druningen, C. J., Vaessen, L. M., *et al.* (2007b). Functional impairment of monocyte-derived dendritic cells in patients with severe chronic kidney disease. *Nephrol Dial Transplant*, 22, 128–38.

Vernon, K. A. and Cook, H. T. (2012). Complement in glomerular disease. *Adv Chronic Kidney Dis*, 19, 84–92.

Walport, M. J. (2001). Complement. Second of two parts. *N Engl J Med*, 344, 1140–4.

Wu, H., Wang, Y. M., Wang, Y., *et al.* (2007). Depletion of gammadelta T cells exacerbates murine adriamycin nephropathy. *J Am Soc Nephrol*, 18, 1180–9.

Yang, R. B., Mark, M. R., Gray, A., *et al.* (1998). Toll-like receptor-2 mediates lipopolysaccharide-induced cellular signalling. *Nature*, 395, 284–8.

Yoon, J. W., Gollapudi, S., Pahl, M. V., *et al.* (2006). Naive and central memory T-cell lymphopenia in end-stage renal disease. *Kidney Int*, 70, 371–6.

Yoon, J. W., Pahl, M. V., and Vaziri, N. D. (2007). Spontaneous leukocyte activation and oxygen-free radical generation in end-stage renal disease. *Kidney Int*, 71, 167–72.

CHAPTER 129

The epidemiology of hepatitis viruses in chronic kidney disease

Fabrizio Fabrizi and Michel Jadoul

Introduction

The advanced stages of chronic kidney disease (CKD) are associated with a major increase in the risk for all-cause morbidity and mortality (Go et al., 2004). Of interest, liver damage may contribute to the high rates of hospitalization and mortality in CKD patients. Patients with CKD can develop a variety of acute and chronic diseases of the liver. The most common and serious causes of liver damage in CKD patients remain hepatitis B virus (HBV) and hepatitis C virus (HCV) infection; however, the vast majority of the literature on liver disease in CKD refers to patients on maintenance dialysis or renal transplant recipients. Several studies, mostly small-sized, have however suggested that the prevalence of anti-HCV antibodies is also high among patients with the late stages of non D- CKD, ranging from 2.8% to 20% (Fabrizi et al., 1994; Kumar et al., 1994; Garcia-Valdecasas et al., 1994; Fabrizi et al., 2001; Lopez-Alcorocho et al., 2001; Bergman et al., 2005; Sit et al., 2007; Iwasa et al., 2008). These prevalence figures should be interpreted in the light of the known prevalence of HCV in the general population worldwide, known to be highest in Egypt, intermediate in Asia, the United States, and Southern/Eastern Europe, and lowest in Northern Europe (Lavanchy, 2009).

The features of hepatitis B and C virus infections in CKD, and their treatment, are discussed in Chapters 185 and 186.

Hepatitis C virus and pre-dialysis chronic kidney disease

The importance of HCV as a cause of liver damage in patients with CKD stage 4 has increased with the advent of pre-emptive kidney transplantation: understanding the characteristics of liver disease is important for the evaluation and management of potential renal transplant candidates (Table 129.1). Lemos et al. (2008) assessed the epidemiology and clinical significance of hepatitis C in a large cohort of uraemic patients not yet receiving dialysis in Brazil. Each patient with chronic HCV was matched, in a nested case–control study, with three pre-dialysis controls without viral hepatitis. A total of 1041 patients with a creatinine clearance of 36 ± 18 mL/min were enrolled (49% had CKD stages 4–5). Forty-one (3.9%) patients were anti-HCV positive and, of these, 39 (95%) presented HCV viraemia. A population study conducted in the same region reported an anti-HCV prevalence of 1.4% ($P < 0.001$). When compared to the control group, a larger proportion of patients with chronic HCV presented a history of blood transfusion before 1992 (66.7% vs 10.3%; $P < 0.001$) and of major surgery (53.8% vs 17.1%; $P < 0.001$). Moreover, chronically HCV-infected patients presented significantly higher serum alanine aminotransferase (ALT) levels (1.3 vs 0.4 × ULN; $P < 0.001$). Logistic regression analysis showed that a history of blood transfusion before 1992, intravenous drug abuse and ALT level had an independent and significant association with chronic HCV.

In a prospective, observational study in the United States on 860 maintenance dialysis patients, patients had at dialysis start an anti-HCV positivity rate (14.4%) seven to eight times greater than the estimate for the general population (1.8%) (Alter et al., 1999). In these US inner city units, most of the HCV burden (prevalence 16.8%) was thus acquired prior to starting dialysis, particularly among those who are younger, black, or have a history of drug use (Bergman et al 2005). The authors concluded that risk factors for HCV infection in patients receiving dialysis now may differ substantially from those identified 20 years ago. Transmission of HCV in the haemodialysis setting has clearly decreased because of the virtual elimination of HCV from the blood supply, at least in developed countries, the advent of erythropoiesis-stimulating agents and improved hygienic precautions. Rather, most anti-HCV (+) dialysis patients may have become infected before the initiation of dialysis.

HCV infection results in increased serum aspartate transaminase (AST) and ALT levels. Unfortunately, the diagnostic value of AST/ALT measurement to assess acute or chronic HCV is rather weak in CKD patients. Lower serum aminotransferase values in dialysis patients than in healthy controls have repeatedly been reported (Yasuda et al., 1995). This phenomenon may extend to CKD non-D patients. In a large ($N = 407$) cross-sectional survey of consecutive individuals with a serum creatinine > 2 mg/dL , Fabrizi et al. (2001) reported lower serum aminotransferase activity in comparison with healthy persons. The difference became greater after correction for viral markers (hepatitis B surface antigen (HBsAg) and anti-HCV) and persisted in age-matched comparisons; AST, 17.9 ± 8 vs 20.4 ± 6 IU/L ($P = 0.0001$) and ALT, 17.5 ± 10 vs 21.7 ± 11.3 IU/L ($P = 0.0001$). Although this is a single cross-sectional study, it seems reasonable to state that in patients with or without viral hepatitis, aminotransferase levels are higher in those with normal renal function, probably intermediate in pre-dialysis, and lowest in patients on dialysis. The suspected causes of the lower aminotransferase activity in CKD patients include a reduction in pyridoxal-5′ -phosphate, a coenzyme of

Table 129.1 Hepatitis C in pre-dialysis population: epidemiology

Authors (year)	Prevalence rate	Country
Fabrizi et al. (1994)	14% (44/221)	Italy
Kumar et al. (1994)	6.2% (3/48)	Pakistan
Garcia-Valdecasas et al. (1994)	7.9% (18/226)	Spain
Lopez-Alchoroco et al. (2001)	17% (6/35)	Spain
Bergman et al. (2005)	14.4% (57/396)	United States
Sit et al. (2007)	7% (12/171)	Turkey
Iwasa et al. (2008)	7.3% (29/400)	Japan
Lemos et al. (2008)	3.9% (41/1041)	Brazil

aminotransferase, the presence of ultraviolet-absorbing materials, and high levels of uraemic toxins.

Hepatitis B virus and pre-dialysis chronic kidney disease

As for HCV, the prevalence rates of HBV in pre-dialysis patients are clearly related to their prevalence in the general population of the same regions, with a well-known north-to-south and west-to-east gradient.

Thus, not surprisingly, small reports from India (7%) or Turkey (10.5%) showed high HBsAg positive rates (Salako et al., 2002; Chandra et al., 2004; Sit et al., 2007) whereas the rate of chronic HBsAg seropositive individuals with pre-dialysis CKD from Spain and Italy was between 0% and 3.7% (Lopez-Alcorocho et al., 2001; Fabrizi et al., 2001; Iwasa et al., 2008).

In a large cohort (N = 405) of pre-dialysis patients, the prevalence of HBsAg positivity was 3.7% (Fabrizi et al., 2001), a figure lower than in dialysis (8.7%) but greater than in healthy persons of the same region (0.5%). Multivariate analysis showed an independent and significant association between AST level (P = 0.017) and HBsAg positivity.

Numerous risk factors may predispose pre-dialysis patients to HBV or HCV infections: these include high-risk behaviours (recreational drug use or unsafe sex), prolonged hospitalizations or frequent healthcare utilization potentially increasing nosocomial exposure to infectious agents, impaired immune response from chronic uraemia, and decreased vaccine responsiveness. In addition, HBV may be a significant cause of glomerular disease (and thus CKD), at least in some regions of the world. A recent case series of biopsy-proven membranous nephropathy from China ascribed the disease to HBV in 12% of cases (Zeng et al., 2008). Similarly, HCV has been implicated in the pathogenesis of a fraction of membranoproliferative glomerulonephritis (see Chapter 80).

Hepatitis B virus vaccine in pre-dialysis chronic kidney disease

Uraemic patients not requiring dialysis are now considered an important target population for hepatitis B vaccination. Seroprotection rates in response to HBV vaccine are poor in the haemodialysis compared with the general population (40–70% vs > 95%, respectively). In addition, antibody titres are lower and decline faster over time in dialysis patients (Rangel et al., 2000). Various authors have attempted different regimens to improve seroprotection rates with variable results (El-Reshaid et al., 1994; Marangi et al., 1994; Charest et al., 2000; Labriola and Jadoul, 2010. Numerous *in vivo* and *in vitro* experiments have shown multiple specific deficiencies in the immune response of patients with uraemia, such as diminished interleukin-2 secretion by T lymphocytes, impaired macrophage function, and lowered immunoglobulin production (Girndt and Kohler, 2002). The impaired immune response to HBV vaccination appears to extend to other vaccination types and a number of factors have been implicated; inadequate dialysis, persistent uraemia, anaemia and malnutrition all have been suggested to have an impact on the ability of patients to respond to HBV vaccine (Martin and Friedman, 1995).

Several studies have been conducted regarding the efficacy of vaccination for HBV in pre-dialysis patients and have shown greater seroconversion rates. The largest study (N = 165), conducted by DaRoza et al. (2003), examined seroconversion rates according to CKD stage. Seroprotection rate was 82% (136/165). Multivariate analysis showed that patients with a lower estimated glomerular filtration rate (GFR) were less likely to seroconvert than those with better kidney function, independently of other predictors of response (GFR < 10 mL/min; odds ratio 0.103; 95% CI, 0.027–0.398; P = 0.001).

References

Alter, M., Kruszon-Moran, D., Nainan, O., *et al.* (1999). The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med*, 341, 556–62.

Bergman, S., Accortt, N., Turner, A., *et al.* (2005). Hepatitis C infection is acquired pre-ESRD. *Am J Kidney Dis*, 45, 684–9.

Chandra, M., Khaja, M., Hussain, M., *et al.* (2004). Prevalence of hepatitis B and hepatitis C viral infections in Indian patients with chronic renal failure. *Intervirology*, 47, 374–6.

Charest, A., McDougall, J., and Goldstein, M. (2000). A randomized comparison of intradermal and intramuscular vaccination against hepatitis B virus in incident chronic haemodialysis patients. *Am J Kidney Dis*, 36, 976–82.

DaRoza, G., Loewen, A., Djurdjev, O., *et al.* (2003). Stage of chronic kidney disease predicts seroconversion after hepatitis B immunization: earlier is better. *Am J Kidney Dis*, 42, 1184–92.

El-Reshaid, K., Al Mufti, S., Johny, K., *et al.* (1994). Comparison of two immunization schedules with recombinant hepatitis B vaccine and natural immunity acquired by hepatitis B infection in dialysis patients. *Vaccine*, 12, 223–8.

Fabrizi, F., Marcelli, D., Bacchini, G., *et al.* (1994). Antibodies to hepatitis C virus in chronic renal failure patients on conservative therapy: prevalence, risk factors and relationship to liver disease. *Nephrol Dial Transplant*, 9, 780–4.

Fabrizi, F., Lunghi, G., Finazzi, S., *et al.* (2001). Decreased serum aminotransferase activity in patients with chronic renal failure: Impact on the detection of viral hepatitis. *Am J Kidney Dis*, 38, 1009–15.

Garcia-Valdecasas, J., Bernal, C., Garcia, F., *et al.* (1994). Epidemiology of hepatitis C virus infection in patients with renal disease. *J Am Soc Nephrol*, 5, 186–92.

Girndt, M. and Kohler, H. (2002). Hepatitis B virus infection in haemodialysis patients. *Semin Nephrol*, 22, 340–50.

Go, A., Chertow, G., Fan, D., *et al.* (2004). Chronic kidney disease and the risks of death, cardiovascular events, and hospitalizations. *N Engl J Med*, 351, 1296–305.

Iwasa, Y., Otsubo, S., Suqi, O., *et al.* (2008). Patterns in the prevalence of hepatitis C virus infection at the start of haemodialysis in Japan. *Clin Exp Nephrol*, 12, 53–7.

Kumar, H., Naqvi, S., Ahmed, A., *et al.* (1994). Hepatitis C virus antibodies in haemodialyzed versus non-dialyzed patients. *J Pak Med Assoc*, 44, 28–30.

Labriola, L. and Jadoul, M. (2010). The decades-long fight against HBV transmission to dialysis patients: slow but definite progress. *Nephrol Dial Transplant*, 25, 2047–9

Lavanchy, D. (2009). The global burden of hepatitis C. *Liver Int*, 29 Suppl 1, 74–81.

Lemos, L., Perez, R., Lemos, M., *et al.* (2008). Hepatitis C among pre-dialysis patients: prevalence and characteristics in a large cohort of patients. *Nephron Clin Pract*, 108, c135–40.

Lopez-Alcorocho, J., Barril, G., Ortiz-Movilla, N., *et al.* (2001). Prevalence of hepatitis B, hepatitis C, GB virus C/Hepatitis G and TT viruses in pre-dialysis and haemodialysis patients. *J Med Virol*, 63, 103–7.

Marangi, A., Giordano, R., Montanaro, A., *et al.* (1994). Hepatitis B virus infection in chronic uremia: long-term follow-up of a two-step integrated protocol of vaccination. *Am J Kidney Dis*, 23, 537–42.

Martin, P. and Friedman, L. (1995). Chronic viral hepatitis and the management of chronic renal failure. *Kidney Int*, 47, 1231–41.

Rangel, M., Coronado, V., Euler, G., *et al.* (2000). Vaccine recommendations for patients on chronic dialysis. *Semin Dial*, 13, 101–7.

Salako, B., Ayodele, O., Kadiri, S., *et al.* (2002). Prevalence of hepatitis B and C viruses in pre-dialysis patients with chronic renal failure. *Afr J Med Med Sci*, 31, 311–14.

Sit, D., Kadiroglu, K., Kayabasi, H., *et al.* (2007). Seroprevalence of hepatitis B and C viruses in patients with chronic kidney disease in the pre-dialysis stage at a university hospital in Turkey. *Intervirology*, 50, 133–7.

Yasuda, K., Okuda, K., Endo, N., *et al.* (1995). Hypoaminotransferasemia in patients undergoing long-term haemodialysis: clinical and biochemical appraisal. *Gastroenterology*, 109, 1295–1300.

Zeng, C., Chen, H., Wang, R., *et al.* (2008). Aetiology and clinical characteristics of membranous nephropathy in Chinese patients. *Am J Kidney Dis*, 52, 691–8.

CHAPTER 130

Gastroenterology and renal medicine

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Endoscopic procedures

Endoscopic procedures are widely performed for the investigation of iron deficiency anaemia (IDA) and gastrointestinal (GI) symptoms such as dyspepsia, gastro-oesophageal reflux disease (GORD), change in bowel habit, weight loss, and bleeding.

Patients on anticoagulant therapy should be discussed with the endoscopy department. Short-acting oral hypoglycaemics should be discontinued on the morning of the procedure. Insulin therapy should be omitted and such patients discussed with the endoscopy unit such that they receive a sliding scale and are investigated early during the list.

Oral bowel-cleansing agents

Oral bowel-cleansing agents (OBCAs) are used to purge the bowel prior to endoscopic and radiological examinations. Multiple OBCAs exist and local regimens vary greatly between different endoscopy units. The 2009 NHS National Patient Safety Agency report on OBCAs highlighted one death and 218 patient safety incidents relating to OBCA use. As a result, recommendations were made to reduce the risks associated with OBCA administration. Hypovolaemia should be corrected prior to administration and patients should adhere to a low-fibre diet pre procedure. Polyethylene glycol agents have been found to be the safest in chronic kidney disease (CKD). Recent evidence suggests a split bowel preparation regimen given within 24 hours is most effective (Hassan et al., 2013). Regular medications should be checked as drug absorption may be impaired during OBCA administration. This is particularly important for patients such as renal transplant recipients who may require admission for intravenous immunosuppressant medication during OBCA administration. Where possible, nephrotoxic drugs including angiotensin-converting enzyme inhibitors (ACEIs), diuretics and non-steroidal anti-inflammatory drugs (NSAIDs) should be discontinued during OBCA administration and reinstated 72 hours post procedure (Connor et al., 2012). Oral iron should be discontinued at least 5 days prior to endoscopy to improve colonoscopy quality.

Table 130.1 shows the common characteristics and contraindications of various available OBCAs (Connor et al., 2012).

OBCAs are contraindicated in bowel obstruction, perforation, ileus, severe inflammatory bowel disease (IBD), and the presence of an ileostomy. Complications can occur with any OBCA and include acute phosphate nephropathy, hypovolaemia, hypokalaemia, hypo-/hypernatraemia, and hypermagnesaemia.

In patients undergoing chronic haemodialysis and receiving an OBCA, there is a risk of dialysis access thrombosis where intravascular depletion may cause hypotension. Care should be taken to ensure that dialysis and concurrent OBCA administration does not result in profound hypovolaemia. Conversely, anuric patients taking polyethylene glycol preparations and significant oral intake may become fluid overloaded. Dialysis sessions should be coordinated with the timing of OBCA administration and it is strongly recommended that dialysis and renal transplant patients have planned admissions for careful immunosuppressant drug monitoring and fluid management.

Polypectomy

Polypectomy is generally safe, though it is advised that patients who undergo polypectomies of > 1 cm should be monitored closely for post-procedure bleeding. Additionally, they should undergo heparin-free dialysis at their next session.

There have been multiple case reports of peritonitis following colonoscopy ± polypectomy in continuous ambulatory peritoneal dialysis (CAPD) patients. These cases appear to have a favourable outcome following antimicrobial treatment. A recent retrospective study found the peritonitis risk following colonoscopy without antibiotic prophylaxis to be 6.3%; however, prophylactic antibiotics did not show a statistically significant reduction in peritonitis. Current advice is that CAPD patients should drain their dialysate prior to colonoscopy ± polypectomy and be considered for intravenous prophylactic antibiotics (Piraino et al., 2011).

Endoscopic retrograde cholangiopancreatography, sphincterotomy, and dialysis

Patients who undergo an endoscopic retrograde cholangiopancreatography (ERCP) may have a sphincterotomy performed whereby a small cut is made in the sphincter of Oddi to widen its lumen. It is indicated for patients where drainage of the biliary system is required such as in obstructive gallstone disease. Post-sphincterotomy bleeding is a risk which is exacerbated by coagulopathy and anticoagulation therapy (Ferreira and Baron, 2007). It is advised that anticoagulants not be prescribed for 72

Table 130.1 Comparison of oral bowel cleansing agents (OBCA): characteristics and contraindications

OBCA	Advantages	Tolerability and ease of use	Low-residue diet advised prior to dosing?	Specific complications?	Specific contraindications?
Picolax® or Citrafleet® (sodium picosulphate and magnesium citrate)	Produces lowest watery residue Potentially advantageous for radiological investigation	Powder reconstituted with a low volume of water	Yes	Higher risk of hyponatraemia (if excess water ingestion) Risk of hypermagnesaemia in CKD Relatively contraindicated in CKD stages 4 and 5	Evaluate patient if hypovolaemia present
Citramag® (magnesium carbonate and citric acid)	Produces low watery residue	Powder reconstituted with a low volume of water	Yes	Higher risk of hyponatraemia (if excessive water ingestion) Risk of hypermagnesaemia in CKD Relatively contraindicated in CKD stages 4 and 5	Evaluate patient if hypovolaemia present
Klean Prep® (polyethylene glycol)	Less likely to cause hypovolaemia. Can be used in renal impairment, cirrhosis and ascites.	Powder reconstituted with high volume of water (up to 4 L)	Yes	Lowest risk of provoking hypovolaemia/hyponatraemia	
Moviprep® (polyethylene glycol)	Less likely to cause hypovolaemia Bowel preparation completed within 12 hours Can be used in renal impairment, cirrhosis and ascites	Powder reconstituted with moderate volume of water (~ 2 L)	Yes	Lowest risk of provoking hypovolaemia/hyponatraemia	G6PD deficiency
Fleet Phosphosoda® (sodium phosphate)	Well tolerated	Low-volume liquid mixed with low volume of water	No. Avoid solid food	Acute phosphate nephropathy Hypocalcaemia resulting from hyperphosphataemia Highest risk of hypovolaemia	Hypovolaemia eGFR < 60 mL/min Hepatic cirrhosis Heart failure Hypertension Renin–angiotensin blockade

hours post procedure and patients should undergo heparin-free dialysis at their next session.

Patients undergoing procedures with a high risk of bacteraemia (e.g. ERCP of an obstructed biliary system) should receive prophylactic antibiotics to reduce the chance of procedure-related sepsis. Also, patients taking immunosuppression medication or with severe neutropenia ($< 0.5 \times 10^9$/L) should be discussed with local microbiology services for prophylactic antibiotics as they are at increased risk of post-procedure bacteraemia (Allison et al., 2009).

Colorectal cancer detection in renal transplant patients

Recently, the risk of colorectal cancer in the renal transplant recipient population has been found to be roughly twice that as compared to the general population. They appear to develop colorectal cancers earlier and have a poorer prognosis probably due to increased tumour aggressiveness and a reduced immunological response. Current guidelines suggest faecal occult blood testing for renal transplant patients from the age of 50; however, consideration should be given to screening patients earlier allowing for prevention (Blaker and Goldsmith, 2012).

Gastrointestinal haemorrhage

The most frequent cause for upper GI bleeding is chronic peptic ulceration. In a series of CKD patients with upper GI bleeding, 37%, 23%, and 13% of cases were caused by gastric ulceration, duodenal ulceration, and angiodysplasias respectively (Feldman et al., 2011). Fig. 130.1 shows the commonest causes of upper GI bleeding (Kumar and Clark, 2002).

The Glasgow–Blatchford Score or Rockall score can be used for risk assessment and stratification of upper GI bleeding prior to endoscopy (Stanley et al., 2009) and the Rockall score can specifically be used post procedure. Table 130.2 shows the pre- and post-endoscopy Rockall scoring system (Rockall et al., 1996). The scoring system illustrates which factors are associated with a high risk of rebleeding or death. Specifically, these scoring systems highlight that renal failure confers a greater risk of morbidity and mortality and these patients should be stabilized and scoped early.

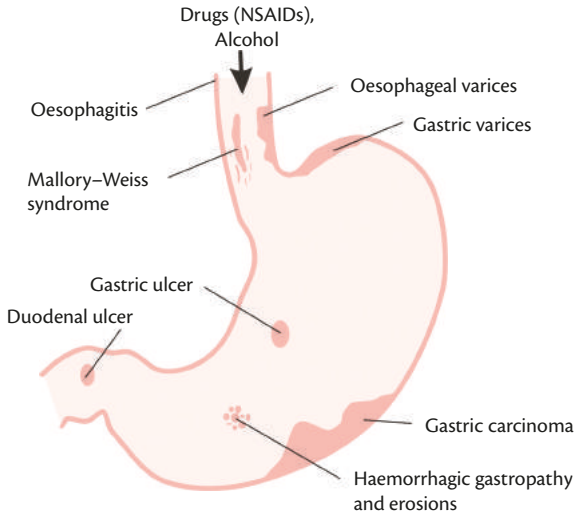


Fig. 130.1 Common causes of upper GI bleeding.

Initial measures should be carried out including circulatory stabilization and resuscitation with intravenous fluids and blood if necessary. Endoscopy should ideally be performed within 24 hours of presentation. Delayed gastric emptying is common in CKD (Feldman et al., 2011) and endoscopic views may be improved by the administration of prokinetics such as metoclopramide prior to the procedure. Figure 130.2 shows a bleeding gastric ulcer found at gastroscopy which was injected with adrenaline to achieve haemostasis.

Massive lower GI bleeding is rare. Patients should be initially fluid resuscitated as per upper GI bleeding management. Bleeding patients should be discussed with gastroenterologists and surgical teams to decide on investigation with endoscopy or less commonly, angiography. Fig. 130.2 shows the common causes for lower GI bleeding (Kumar and Clark, 2002).

Recent studies have shown that mortality in haemodialysis patients with upper GI bleeding is high. Angiodysplastic lesions are more likely to bleed in CKD patients and this may be related to uraemic platelet dysfunction (Feldman et al., 2011). The synthetic vasopressin analogue, desmopressin, has been shown to decrease bleeding tendency in uraemic patients (Hedges et al., 2007); however, great caution should be taken with its use as it has also been shown to be potentially cardiotoxic with case reports of cardiac arrest following administration (Pape et al., 2013).

Proton pump inhibitors (PPIs) are widely prescribed for functional dyspepsia, GORD, and for the treatment of GI bleeding. A recent series of 210 renal biopsies for declining renal function revealed acute interstitial nephritis in 2.86% of cases in which there was a temporal relation with PPI use (Ray et al., 2010). This suggests that PPIs are a rare but important cause of acute kidney injury.

Investigation of anaemia

The commonest cause of anaemia is iron deficiency affecting 30% of the world's population and anaemia is a common cause for referral to gastroenterology. Anaemia is often seen in CKD and as kidney function declines it increases in prevalence and severity and is a risk factor associated with worse prognosis. Erythropoiesis and iron homeostasis are impaired in CKD leading to anaemia.

Occult GI tract blood loss is the most common cause of iron-deficiency anaemia (IDA) in adult men and postmenopausal women and prompts urgent investigation with upper and lower endoscopy. Table 130.3 shows the pathological contributors to IDA in the United Kingdom with prevalence as percentage of total (Goddard et al., 2011).

All IDA patients should be screened for coeliac disease. If the upper and lower GI tracts are normal, then iron therapy should be given. Parenteral iron is indicated for those intolerant of oral preparations and blood transfusions should be given to those at risk of cardiovascular instability. In persistent IDA, video capsule

Table 130.2 The Rockall scoring system for assessing risk of re-bleeding or death pre- and post-endoscopy. Note the high score attached to renal failure

		Score		
Variable	**0**	**1**	**2**	**3**
Age (pre-endoscopy)	< 60 years	60–79 years	> 80 years	
Shock (pre-endoscopy)	No shock (SBP > 100, HR < 100)	Tachycardia (SBP > 100, HR > 100)	Hypotension (SBP < 100)	
Comorbidity (pre-endoscopy)	No major comorbidity		Cardiac failure, ischaemic heart disease, any major comorbidity	Renal failure, liver failure, disseminated malignancy
Diagnosis (post-endoscopy)	Mallory–Weiss tear, no lesion identified and no stigmata of recent haemorrhage	All other diagnoses	Malignancy of upper GI tract	
Major stigmata of recent haemorrhage (post-endoscopy)	None, or dark spot only		Blood in upper GI tract, adherent clot, visible or spurting vessel	

HR = heart rate; SBP = systolic blood pressure.

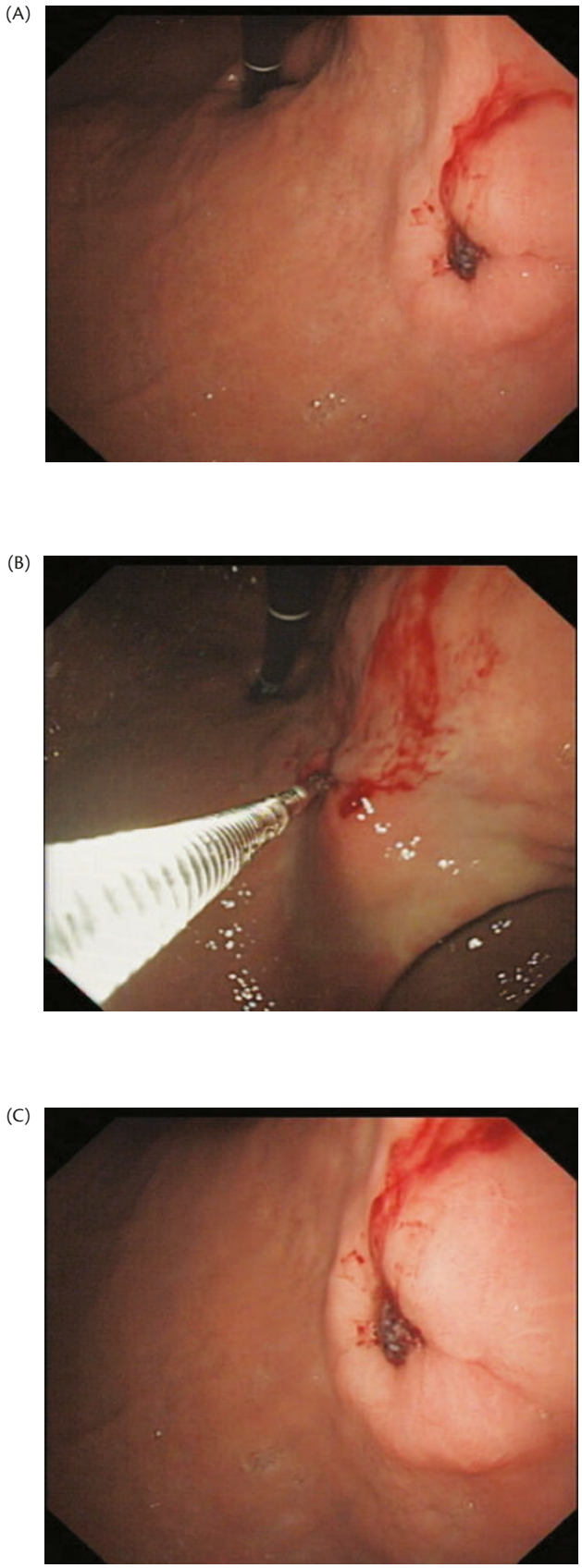


Fig. 130.2 Bleeding gastric ulcer before (A), during (B), and after injection with adrenaline.

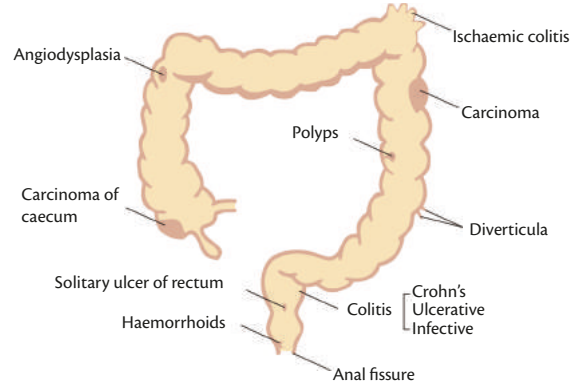


Fig. 130.3 Common causes of lower GI bleeding (Kumar and Clark, 2002).

endoscopy should be initially considered to investigate small bowel causes of GI blood loss.

Nutrition and the refeeding syndrome

First described in American prisoners of war in Japan during World War II, people are at risk of the refeeding syndrome when high calorie nutrition is introduced into their diet following a prolonged period of starvation. This results in a rapid rise of insulin production which leads to an increased cellular uptake of glucose, fluids, and electrolytes. Hypophosphataemia, hypomagnesaemia, hypoglycaemia, hypokalaemia, and other severe electrolyte imbalances may occur, which can result in life-threatening cardiac arrhythmias and respiratory depression (Marinella, 2011).

Renal patients usually require careful monitoring of their fluid status and electrolytes and renal physicians should be alert to look for features of the refeeding syndrome in malnourished patients. At-risk patients should be referred to a gastroenterology and nutrition team for multidisciplinary management. Fluids, electrolytes, and vitamins should be replaced and nutrition should be introduced gradually into the diet with careful monitoring.

Inflammatory bowel disease

Crohn's disease (CD) is a chronic inflammatory condition of the GI tract typically involving the colon and ileum. Possible complications of the disease include abdominal and genitourinary fistulas. Population studies have shown that 50% of CD patients develop fistulas after 20 years (Schwartz et al., 2002). These patients invariably require aggressive immunosuppressant treatment and have a 75% risk of surgery during their lifetime (Mowat et al., 2011). They should be referred for discussion in an IBD and surgical multidisciplinary forum.

5-Aminosalicylic acid drugs

5-Aminosalicylic acid (5-ASA) drugs are widely used as effective first-line treatment in ulcerative colitis and may have some modest benefit in CD. They are generally safe, however, they have been rarely associated with nephrotoxicity (including interstitial nephritis and the nephritic syndrome). This appears to idiosyncratic and partly dose related (Muller et al., 2005). Guidelines suggest annual measurement of serum creatinine (Mowat et al.,

Table 130.3 Causes of iron deficiency in the UK general population (Goddard et al., 2011)

Contributor	Prevalence
Occult GI blood loss	
Common	
Aspirin/NSAID use	10–15%
Colonic carcinoma	5–10%
Gastric carcinoma	5%
Benign gastric ulceration	5%
Angiodysplasia	5%
Uncommon	
Oesophagitis	2–4%
Oesophageal carcinoma	1–2%
Gastric antral vascular ectasia	1–2%
Small bowel tumours	1–2%
Cameron ulcer in large hiatus hernia	< 1%
Ampullary carcinoma	< 1%
Ancylostoma duodenale	< 1%
Malabsorption	
Common	
Coeliac disease	4–6%
Gastrectomy	< 5%
Helicobacter pylori colonization	< 5%
Uncommon	
Gut resection	< 1%
Bacterial overgrowth	< 1%
Non-GI blood loss	
Common	
Menstruation	20–30%
Blood donation	5%
Uncommon	
Haematuria	1%
Epistaxis	< 1%

2011) although a recent survey has shown that less than two-thirds of patients are screened for renal disease prior to treatment initiation (Zallot et al., 2013). We recommend that all patients who receive 5-ASA treatment are screened for pre-existing renal disease and have 6–12-monthly monitoring of their renal function. The 5-ASA should be discontinued if renal function deteriorates (Mowat et al., 2011) and usually returns to normal upon cessation of the offending 5-ASA. Corticosteroids have been successfully used to treat a case of refractory sulfasalazine-related renal failure (Alivanis et al., 2010).

Immunosuppressant medication in inflammatory bowel disease

Patients with IBD are usually treated with immunosuppressant medication, often in combination. Particular care must be taken for the renal transplant and IBD population, in whom these drugs confer an increased risk of opportunistic infections and cancer. All IBD patients should be screened for opportunistic infections prior to immunosuppressant use and ideally offered vaccination. It is advised that patients taking three or more immunosuppressant medications in combination should receive co-trimoxazole prophylaxis (Rahier et al., 2009). This is particularly relevant if they are taking a calcineurin inhibitor such as ciclosporin. Patients on immunosuppressant drugs who develop an opportunistic infection should be discussed with gastroenterology and microbiology teams. The immunosuppressant medication can usually be stopped temporarily and recommenced once the infection is treated.

Thiopurine medication is used as steroid-sparing and maintenance treatment in IBD and is usually well tolerated. There is an approximate 3% idiosyncratic risk of myelotoxicity which reverses upon drug cessation. Three-monthly full blood count monitoring is advised to check for neutropenia whilst receiving treatment. Patients taking long-term thiopurines have a fivefold increased risk of developing a lymphoproliferative disorder and an increased risk of non-melanoma skin cancer, although the absolute risk remains very small (Mowat et al., 2011).

Methotrexate is used in induction and maintenance treatment of CD. Co-prescription of folic acid is essential and blood monitoring should be performed monthly. It is renally excreted and is contraindicated in end-stage renal failure. The dose should be reduced by 50% if the estimated glomerular filtration rate (eGFR) < 50 mL/min.

Biologic anti-tumour necrosis factor (TNF) monoclonal antibody drugs are primarily used in the treatment of moderate to severe CD. Recent studies have shown that anti-TNF treatment is of benefit in the treatment of renal cell carcinoma (Harrison et al., 2007).

Nephrolithiasis

Nephrolithiasis is common in CD patients. With small bowel resection, there is a two- to threefold increase in oxalate stones and a 4–16% incidence of uric acid stones following ileostomy (Worcester, 2002; Ishii et al., 2009). In extensive small bowel disease or intestinal resection, fat malabsorption leads to luminal free fatty acids binding to calcium. Thus less calcium is available to bind and clear oxalate and resulting hyperoxaluria causes calcium oxalate stone formation. Uric acid stones are formed in hypermetabolic states and hypovolaemia (Feldman et al., 2011). Hypocitraturia and hypomagnaesuria have also been found to factors in stone formation in CD (Viana et al., 2007). Treatment should be directed towards treatment of fat malabsorption and rehydration. Low-oxalate diets may be trialled but are usually unpalatable (Hanson et al., 2005).

Hepatology and renal medicine

(See also Chapters 185, 186 on hepatitis B and C, and Chapter 169 on hepatorenal syndrome.)

Box 130.1 Interpretation of viral serology

- The presence of anti-HCV antibodies with undetectable HCV RNA confirms exposure, in absence of chronic activity.
- The presence of anti-HCV antibodies and HCV RNA confirms chronic active HCV.
- HCV subtype and genotype is only required after chronic activity is confirmed.

Hepatitis C virus: introduction

Hepatitis C virus (HCV) can cause a chronic systemic infection. Three per cent of the world population is chronically infected. The interpretation of viral serology tests is summarized in Box 130.1.

Hepatitis C virus: renal manifestations

Patients with chronic HCV are 40% more likely to develop end-stage renal disease (ESRD) (Tsui et al., 2007). Type II cryoglobulinaemia (TC) leading to membranoproliferative glomerulonephritis (MPGN), and isolated MPGN are the most common renal manifestations (Latt et al., 2012).

Approximately 10–15% of patients with chronic HCV will develop TC (Latt et al., 2012). Anti-HCV antibodies are almost always present, and HCV RNA is detected in 70–100% of cases (Latt et al., 2012). The renal manifestation ranges from asymptomatic proteinuria and/or haematuria to nephrotic/nephritic syndrome, causing typically a type I MPGN with immune complex deposition in the glomeruli (Ferri and Zignego, 2000). Ten per cent of cases can progress to ESRD (Tarantino et al., 1995).

Type III cryoglobulinaemia, membranous nephropathy, focal segmental glomerulosclerosis, post-infectious glomerulonephritis, thrombotic microangiopathies, immunoglobulin A nephropathy, and fibrillary or immunotactoid glomerulopathy are also associated with HCV infection (Latt et al., 2012). The first-line therapy for any HCV-related glomerulopathy should aim for eradication of HCV infection. Meta-analysis data confirms reduction in proteinuria after 6 months of therapy with interferon alpha (IFN- α) (Fabrizi et al., 2007). The presence of TC may be a positive response predictor to HCV-treatment (Vigani et al., 2011).

Symptomatic treatment (ACEIs, angiotensin receptor blockers, systemic vasodilators, diuretics, and lipid-lowering agents) have shown favourable outcomes for HCV-related CKD (Latt et al., 2012). Pathogenic therapies for TC including corticosteroids, cytotoxic agents, plasma exchange, and rituximab have also been used in severe HCV-related glomerulopathies (Latt et al., 2012).

Hepatitis C virus: dialysis patients

Ten to sixty-five per cent of haemodialysis (HD) patients are infected with chronic HCV, and geographical variation is considerable (Hayashi et al., 1991). The increased prevalence is secondary to increased exposure to contaminated medical equipment/blood products and because of long-term vascular access (Hayashi et al., 1991). The prevalence is declining because of routine blood screening for HCV, increased compliance with stringent infection control protocols, and with routine use of recombinant erythropoietin, but still remains higher than the prevalence reported in non-HD populations (Tang and Lai, 2005). Screening with HCV antibody is recommended for all patients prior to commencing dialysis, and upon transfer from other dialysis units. Re-testing is recommended for unexplained abnormal aminotransferases. If a new infection is suspected to be nosocomial, testing is recommended for all patients potentially exposed.

Spontaneous clearance of HCV RNA is documented annually in 1% of treatment-naïve dialysis patients (Gordon et al., 2008). The natural disease progression towards cirrhosis and hepatocellular carcinoma (HCC) is possibly less aggressive in HD patients compared to non-HD patients, but is still associated with increased all-cause mortality (Trevizoli et al., 2008).

Hepatitis C virus: renal transplantation

Outcomes after renal transplantation in HCV-seropositive recipients are inferior with respect to all-cause mortality and graft survival. One study reported 5-year survival at 77% in HCV-seropositive recipients compared to 90% in seronegative recipients, the increase in mortality secondary to cardiovascular disease, malignancy, and liver failure (Scott et al., 2010). Currently there are no safe licensed treatment options for HCV in renal transplant recipients. All current available regimens are IFN based, and have a significant risk of graft failure. Successful eradication in renal transplant recipients with current available regimens also remains unsatisfactory. Post-transplantation immunosuppression can also significantly accelerate the natural course of HCV in a minority with fatal outcome, leading to poorer outcome than remaining on dialysis (Zylberberg et al., 2002).

Current UK transplant guidelines and European best practice guidelines recommend that potential transplant recipients always have consideration of HCV treatment prior to transplantation, irrespective of liver fibrosis stage (British Transplantation Society, n.d.). Successful treatment pre transplantation improves long-term post-transplantation outcomes with better graft survival and reduced mortality. Post-transplantation rates of diabetes, progressive liver fibrosis, fibrosing cholestatic hepatitis, *de novo* glomerulonephritis, sepsis, and chronic allograft nephropathy are all significantly reduced (Vallet-Pichard et al., 2011). Regression of cirrhosis/fibrosis is also reported, and viral rebound after transplantation has not been reported (Serpaggi et al., 2006).

After successful eradication, transplant assessment should first exclude the presence of cirrhosis. In the absence of cirrhosis, the standard workup should continue, and patients while on the waiting list should continue to have the liver disease evaluated regularly (at least annually). HCC always needs exclusion and remains a contraindication for renal transplantation.

Of equal importance is that the survival of the majority of HCV-seropositive recipients is significantly improved when compared to HCV-seropositive patients remaining on dialysis (Kamar et al., 2006; Kalantar-Zadeh et al., 2007; Ingsathit et al., 2013). Therefore some centres will not preclude HCV seropositive patients from isolated renal transplantation as this still remains the optimal management strategy for their ESRD, accepting inferior survival compared to HCV-seronegative recipients, and accepting currently there are no safe treatment options for HCV post renal transplantation. The decision for isolated renal transplant will depend on local policy, and the risk of accelerating HCV after immunosuppression will be balanced against inferior outcome to remaining on dialysis.

HCV-seropositive potential recipients with mild liver damage confirmed histologically prior to transplantation have limited

progression of liver fibrosis in the first 5 years after isolated renal transplantation (Roth et al., 2011). Therefore such candidates could be considered for isolated renal transplantation. After renal transplantation, HCV-related liver fibrosis monitoring and HCC surveillance are required as immunosuppression may accelerate both. In view of constraints on available suitable organs, HCV-seropositive patients may be candidates to receive organs from HCV-seropositive donors, with superior outcomes compared to remaining on dialysis (Kasprzyk et al., 2007).

If cirrhosis is confirmed, the Model for End-Stage Liver Disease (MELD) score, and/or hepatic venous pressure gradient should be measured. The mortality associated with major non-hepatic abdominal surgery in cirrhosis can be predicted by the severity of liver disease reflected by the MELD score and co-morbid conditions as defined by the American Society of Anaesthesiologists (ASA) physical status class (Teh et al., 2007). ASA class status IV and V predict significant risk for early (within 7 days) postoperative mortality. MELD scores predict 30-day and 90-day mortality. Patients with a MELD score of 0–11, 12–25, and ≥ 26 have 5–10%, 25–54%, and 90% 90-day postoperative mortality for non-hepatic abdominal surgery respectively (Bhangui et al., 2012). Therefore higher MELD scores preclude isolated renal transplantation without further investigation. A patient on dialysis automatically receives a minimum MELD score of at least 20 which may over-score the significance of underling liver disease. In most instances, hepatic venous pressure gradient measurement will be required. If the gradient is > 10 mmHg, then simultaneous liver–kidney transplantation assessment should be considered, as the mortality from isolated renal transplant is significant secondary to fatal cirrhosis progression (Paramesh et al., 2012).

Hepatitis C virus: treatment in renal disease

In the absence of renal disease, pegylated interferon alpha (PEG-IFN-α) and ribavirin can achieve sustained virological response in 30–50% of patients with genotype 1 HCV, and in 65–90% of patients with genotypes 2 or 3 HCV (European Association for the Study of the Liver (EASL), 2011). Regimens including first-generation protease inhibitors (telaprevir/boceprevir) in patients with renal disease remain in trials or off-licence for selected individuals in experienced centres. Despite concerns of significant anaemia, successful treatment with triple therapy in HD patients who have failed standard treatment has been reported (Dumortier et al., 2013). The pharmacokinetics of calcineurin inhibitors and protease inhibitors are shared, and therefore there are significant concerns regarding drug accumulation and toxicity in transplant recipients on calcineurin inhibitors.

Two preparations of PEG-IFN-α are currently available, PEG-IFN-α2a which is primarily hepatically excreted, and PEG-IFN-α2b which is primarily renally excreted. In view of this, PEG-IFN-α2a remains the first-line agent in most centres, and INF-α is the agent recommended by the Kidney Disease Improved Global Outcome Foundation (Kidney Disease: Improving Global Outcomes (KDIGO), 2008). Dose adjustment as per glomerular filtration rate (GFR)/creatinine clearance is required.

Ribavirin is renally excreted, and increased accumulation leads to significant haemolysis. Therefore combination therapy in CKD stages 3, 4, or 5 is relatively contraindicated and not licensed, when creatinine clearance is < 50 mL/min (EASL, 2011). In the absence of ribavirin, long-term response rates are substantially lower in the general population (EASL, 2011). Experienced physicians may therefore adopt dual therapy with cautious use of ribavirin to increase success rates, with appropriate dose titration and haematopoietic support.

Ribavirin dosing of 200 mg per day to 200 mg every other day with haematopoietic support (increased erythropoietin doses) has been suggested by a few studies for advanced kidney disease, and has been routinely offered by experienced physicians (EASL, 2011). HD patients can be treated similarly with 200 mg of ribavirin after dialysis sessions (EASL, 2011). Experienced centres may also utilize low accelerated dosing regimens (LADR), starting with low doses of both drugs, and titrating up if tolerated. Viral kinetics are utilized with these regimens to both prolong treatment when kinetics are favourable, and discontinue when futile treatment is predicted. Successful treatment has been reported in 27.3–78.8% of dialysis patients (average ~ 40%), and most studies have used monotherapy with PEG-IFN-α or IFN-α (Vallet-Pichard et al., 2011). Treatment for acute hepatitis C in dialysis patients is better tolerated and successful in 50–90% of cases (Fabrizi et al., 2012).

For CKD stages 1 or 2, combined antiviral treatment using either PEG-INF-α and ribavirin is recommended by KDIGO recommendations (Kidney Disease: Improving Global Outcomes (KDIGO), 2008). Ribavirin is safe while creatinine clearance is > 50 mL/min. For CKD 3, 4, or 5, and HD patients, monotherapy with appropriate dose adjustment to PEG-IFN-α2a or IFN-α is recommended by KDIGO. HD patients need IFN dose adjusted for a GFR of < 10 mL/min.

Dialysis patients will experience increased significant adverse effects and therefore increased treatment drop-out rates compared to the general population. Mortality is reported with monotherapy and combined therapy, and while some centres will use combined therapy, the increased efficacy for this approach has not always been demonstrated in reported studies (Vallet-Pichard et al., 2011).

Renal transplant recipients have significant risk of acute or chronic cellular rejection (30–60%) with IFN treatment, resulting in graft loss and reduced patient survival (Vallet-Pichard et al., 2011). Successful treatment chances are reduced in most studies (< 20%), and treatment drop-out rates are also significant. Therefore treatment is contraindicated unless benefits definitely outweigh risks, and considered if development of fatal fibrosing cholestatic hepatitis or severe *de novo* glomerulonephritis (Vallet-Pichard et al., 2011). Only in this instance is the potential loss of graft function justified and most patients will need switching to HD (Vallet-Pichard et al., 2011). The specific treatment regimen will be in accordance with the centre experience, with either PEG-IFN-α2a or IFN- α, and with or without ribavirin.

Numerous IFN-free regimens are currently in trials. These regimens have shown significant promise in phase II/III clinical studies in the general population, and are likely to provide safer IFN-free and possibly ribavirin-free alternative regimens in the near future. Promising regimens include the combination of the potent NS5B polymerase inhibitor sofosbuvir with a NS5A inhibitor, either ledipasvir or daclatasvir. Success rates of > 93% have been shown irrespective of other treatment predictors such as HCV genotype, host genetics, and previous non-response to conventional treatment (Sulkowski et al., 2012; Gane et al., 2013). These regimens may offer the prospect of safe successful treatment in renal transplant recipients without the need for IFN, and are likely to increase treatment success rates in dialysis patients.

Table 130.4 Serological, virological, and biochemical profiles of hepatitis B virus

	HBsAg	Anti-HBs	Anti-HBc (total)	Anti-HBc IgM	HBeAg	Anti-HBe	HBV DNA (IU/mL)	ALT
Acute HBV	+	–	+	+	+	+/–	High	↑
Resolved infection	–	+	+	–	–	+/–	Absent	N
Resolved infection with low level viraemia (occult HBV)	-	–/+	+	–	–	+/–	< 200	N
Vaccination	–	+	–	–	–	–	Absent	N
Susceptibility	–	–	–	–	–	–	Absent	N
Chronic HBVeAg + Immune tolerance phase	+	–	+	–	+	–	> 20,000	N
Chronic HBVeAg + Immune reactive phase	+	–	+	–	+	–/+	Fluctuating	↑
Chronic HBVeAg – Immune control/inactive carrier phase	+	–	+	–	–	+	< 2000[a]	N
Chronic HBVeAg – Immune escape phase	+	–	+	–	–	+/–	> 2000[a]	↑
Reactivation of HBV	+	–	+	+/–	+	+/–	> 20,000	↑

+ = positive, – = negative, N = normal, ↑ = elevated. ALT = alanine aminotransferase;

[a] HBV DNA cut-off levels may change in the future.

Hepatitis B virus: introduction

Hepatitis B virus (HBV) is the most prevalent worldwide chronic infection, affecting 350–400 million individuals. Chronic infection is confirmed when HBV surface antigen (HBsAg) is positive for > 6 months. The natural history of chronic HBV (CHB) varies significantly between individuals from an inactive carrier state to progressive CHB, which can progress to cirrhosis and HCC. The serological, virological, and biochemical characteristics of the different phases of CHB are summarized in Table 130.4. Treatment is indicated when there is significant necroinflammation or significant fibrosis (both more likely to occur in the immune reactive and immune escape phases), or CHB-related complication (EASL, 2012).

Hepatitis B virus in renal disease: prevalence and vaccination

The current prevalence of CHB in dialysed patients is < 10% in industrialized countries and 2–20% in developing countries, with significant prevalence in South East Asia and sub-Saharan Africa (Fabrizi et al., 2008b). This has declined because of blood screening and hygiene/infection control measures, and routine vaccination has been shown to be the best preventative intervention (prevalence of ~ 45% before vaccination era) (Crosnier et al., 1981; Fabrizi et al., 2008a).

The primary aim in renal patients is to avoid CHB. All patients should be tested at diagnosis of renal disease, and susceptible individuals with negative HBsAg and negative HBV core antibodies (anti-HBc) should be vaccinated. Maximum efficacy of the vaccine is derived if vaccination occurs early in the course or renal disease and this should be the aim. Susceptible patients should always be vaccinated before HD and before transplantation. Dialysis patients demonstrate low vaccine immunogenicity at 70%, and renal transplant recipients even lower at 30%, compared to 90% in the general population (Crosnier et al., 1981). Booster vaccines may play a role in improving immunogenicity, and could be offered every 3–5 years if primary non-response or poor response to vaccination has been demonstrated (Vallet-Pichard et al., 2011).

Hepatitis B virus: renal manifestations

Membranous glomerulonephritis and MPGN are the most common renal manifestations, with renal biopsies demonstrating immune complex deposition and cytoplasmic inclusions in the glomerular basement membrane. In adults, there is slow progression of renal disease, usually presenting with nephrotic syndrome. Treatment of renal disease has been accomplished with long-term control of viral replication, and this can also be combined with immunosuppressant therapy (Zheng et al., 2012). Cryoglobulinaemia is much rarer in CHB compared to HCV.

Hepatitis B virus: treatment options

The nucleos(t)ide analogues entecavir or tenofovir are recommended as first-line treatment for treatment naive CHB (EASL, 2012). Both drugs are potent HBV inhibitors with a high barrier to resistance. Finite treatment with (PEG)IFN-α can also be considered as first-line treatment, but is contraindicated in cirrhosis, autoimmune disease, severe depression, and in psychosis (EASL, 2012). All three drugs can be used in patients with renal disease with relevant dose adjustment (Table 130.5), but there is no recommended dose of tenofovir if creatinine clearance is < 10 mL/min and the patient is not on HD. IFN should not be used in renal transplant recipients due to the significant rejection risk and the availability of alternative treatments.

Table 130.5 Dose adjustments required to first-line recommended treatments

	Pegylated interferon alpha 2a (Pegasys®)	Tenofovir disoproxil (Viread®)	Entecavir (Baraclude®)
Standard dose	180 mcg OW	245 mg OD	NN: 0.5 mg OD; LR: 1 mg OD
GFR 30–50 mL/min	180 mcg OW but monitor renal function and FBC closely. Adjust to 90–135 mcg OW if required	245 mg every 48 hours	NN: 0.5 mg every 48 hours; LR: 0.5 mg OD
GFR 10–30 mL/min	180 mcg OW but monitor renal function closely. Adjust to 90–135 mcg OW if required	245 mg every 72–96 hours	NN: 0.5 mg every 72 hours; LR: 0.5 mg every 48 hours
GFR < 10mL/min	135 mcg OW	No safe recommended dose	NN: 0.5 mg every 5–7 days; LR: 0.5 mg every 72 hours
Renal replacement therapy	Not dialysed as large molecule, thus may accumulate. Smaller doses of 90–135 mcg OW usually required	For HD 245 mg every 7 days after dialysis session	For HD; NN: 0.5 mg every 5–7 days; LR: 0.5 mg every 72 hours after dialysis session

FBC = full blood count; GFR = glomerular filtration rate; HD = haemodialysis; LR = lamivudine resistance; NN = nucleoside naïve; OD = once daily; OW = once weekly.

In the general population, individuals with risk factors for kidney disease are at highest susceptibility to tenofovir-induced renal disease. Most studies exclude these patients in their inclusion criteria, and this is potentially why reported studies may have under-scored the importance of tenofovir-induced renal disease. Therefore concerns regarding safety understandably exist in individuals with CKD. Some consider entecavir a safer agent in these patients.

Tenofovir exposure is associated with a small but significant decline in GFR, and this progression may be clinically silent (Rodriguez-Novoa et al., 2010). Toxicity is targeted mainly at the proximal tubule, developing in up to 15% with long-term use. Chronic reduction in GFR, severe cases of renal Fanconi syndrome, and acute kidney injury are rarer (Rodriguez-Novoa et al., 2010). Prompt discontinuation of tenofovir will lead to renal recovery in the majority of cases, highlighting the importance of aggressive renal function monitoring (with serum creatinine /urea and electrolytes, eGFR, urine protein/creatinine ratio, and phosphate levels) monthly for the first 12 months when tenofovir is commenced.

Treatment is started and continued in non-transplant candidates in accordance with EASL guidelines, when liver biopsy shows moderate to severe active necroinflammation and/or fibrosis using a standardized scoring system (≥ A2 for necroinflammation and/or ≥ F2 for fibrosis by METAVIR) (EASL, 2012). In regions where the newer nucleos(t)ide analogues are not available, lamivudine remains an alternative with appreciation that resistance to lamivudine develops in 70% after 5 years of use (EASL, 2012).

Hepatitis B virus: renal transplantation

UK transplant guidelines recommend potential recipients who are HBsAg positive require assessment by a hepatologist if circulating HBV DNA is present (British Transplantation Society, n.d.). Active viral replication and chronic active hepatitis confirmed by liver biopsy both have a poor prognosis if untreated before transplantation. In the absence of liver cirrhosis, long-term graft survival after isolated kidney transplantation is acceptable with appropriate pre-emptive treatment, with similar 5-year outcomes to HBsAg-negative recipients (Kalia et al., 2011). Recipients with CHB-related cirrhosis require additional workup like those with HCV-related cirrhosis and usually require consideration for simultaneous liver–kidney transplantation (discussed earlier).

All HBsAg-positive individuals for potential renal transplantation and immunosuppression should be treated as should all anti-HBc-positive/HBsAg-negative patients with detectable HBV DNA (occult CHB), irrespective of donor status and irrespective of liver biopsy findings (EASL, 2012; British Transplantation Society, n.d.). Treatment should be with entecavir or tenofovir, and should be pre-emptive. There is a risk of HBV viral reactivation resulting in severe fibrosing cholestatic hepatitis or fulminant hepatitis when immunosuppression is commenced and equally there is a risk of immune restoration leading to rapid clearance of infected hepatocytes with spontaneous arrest of viral multiplication, which may result in fulminant hepatitis when immunosuppression is withdrawn (Vallet-Pichard et al., 2011). Pre-emptive treatment is recommended to avoid both complications.

EASL guidelines recommend transplant recipients who are anti-HBc-positive/HBsAg-negative with undetectable HBV DNA should be followed carefully by means of 3-monthly alanine aminotransferase (ALT) and HBV DNA. Treatment should commence upon confirmation of HBV reactivation before ALT elevation (EASL, 2012). However, expert opinion is that HBV is still present in the liver and prior to immunosuppression is well controlled by the host's cellular immunity. In the first phase after transplantation when the cellular immune system is severely impaired, pre-emptive therapy is advisable to avoid the risk of viral reactivation and subsequent potentially disastrous consequences. Pre-emptive treatment is an acceptable strategy (with lamivudine or entecavir).

With constraints on organ availability, kidney transplantation matching donor and recipient HBV status is not always possible. To expand the organ pool available, donors with CHB/HBV exposure are not excluded. UK transplant guidelines recommend a potential recipient must be consented appropriately prior to receiving organs exposed to HBV, and the risks of recipient acquiring HBV discussed (British Transplantation Society, n.d.).

Transplantation from HBsAg-positive donors into recipients who are HBsAg positive is acceptable, in accordance with UK transplant guidelines when deemed necessary, and HBV treatment should be commenced pre-emptively. UK transplant guidelines do not contraindicate transplantation from HBsAg-positive donors to HBV-immune recipients when deemed necessary. CHB risk following this is preventable by pre-emptive treatment or by boosting protective anti-HBs titres (to > 10mIU/mL) (Tuncer et al., 2012; British Transplantation Society, n.d.).

The CHB risk following transplantation of kidneys from HBsAg-positive donors to HBV-susceptible recipients is high but

can be minimized by administering lifelong pre-emptive antiviral therapy (Akalin et al., 2005). Such a policy could be considered when renal transplant is deemed urgent, when, for example, vascular access for HD is not possible.

Kidneys from anti-HBc-positive/HBsAg-negative donors with undetectable HBV DNA are associated with a low rate of CHB in the recipient, with no excess risk of graft failure or short-term mortality (Ouseph et al., 2010; Mahboobi et al., 2012). Lifelong treatment with lamivudine or booster vaccination to ensure ongoing protective HBV immunity or HBV immunoglobulin administration at transplantation prevents CHB. Current UK transplant guidelines advise the recipient must be immunized to HBV in this situation, and further preventive therapy co-ordinated with a local hepatologist (British Transplantation Society, n.d.).

Hepatorenal syndrome: clinical features and classification

Hepatorenal syndrome (HRS) is a functional disorder with rapid deterioration in renal function in individuals with either cirrhosis or acute liver failure (Arroyo et al., 1996). The diagnosis requires a high index of clinical suspicion and confirmation after exclusion of other potential causes of renal injury. The most recent diagnostic criteria have been summarized in Box 130.2 (Arroyo et al., 1996; Salerno et al., 2007). Histologically, the kidneys are normal in HRS. The annual frequency in cirrhotic patients with ascites is 8%, however some reports suggest that incidence is as high as 40%. Thirty per cent of cirrhotic patients with spontaneous bacterial peritonitis or other infections, 25% of patients with severe alcoholic hepatitis, and 10% of patients requiring serial large volume paracentesis will develop HRS. It is classified traditionally into two types on the basis of clinical characteristics, and this has been summarized in Table 130.5 (Arroyo et al., 1996; Salerno et al., 2007). The prognosis remains poor, with an average median survival time of only 3 months with treatment and 1 month without treatment (Box 130.3) (Ginès et al., 1993; Alessandria et al., 2005).

Hepatorenal syndrome: treatments

See also Chapter 169.

Medical therapies for HRS focus on reversing the underlying splanchnic and systemic vasodilation with vasoconstrictors, and expansion of circulatory volume. Terlipressin (a selective vasopressin 1 receptor agonist) has been approved in Europe and in combination with albumin improves serum creatinine levels with a benefit in short-term survival (meta-analysis data suggest a survival benefit of 15.9%, and reversal of type 1 HRS occurs in 40–50%) (Fabrizi et al., 2006). Fifteen per cent will have recurrence on treatment withdrawal, and repeat treatment is appropriate. EASL always recommend therapeutic trial with terlipressin and albumin prior to liver transplantation assessment (EASL, 2010). Adjunctive renal replacement therapy is reserved for individuals who fail medical therapy, or patients who satisfy the standard criteria for emergency renal replacement therapy. The American Association for the Study of the Liver recommend medical therapy with octreotide and/or midodrine with albumin as first-line medical management as terlipressin is not available in the United States (EASL, 2010).

Medical therapy in isolation is appropriate in the context of an acute insult such as HRS precipitated by nephrotoxic drugs, GI bleeding, or spontaneous bacterial peritonitis until the acute insult has resolved. Otherwise medical management serves as a bridge to definitive treatment for the liver disease (liver transplantation assessment).

Liver transplantation remains the only current therapeutic modality which can potentially treat and reverse both the underlying liver dysfunction and HRS. Post liver transplantation, up to 35% of patients with HRS can require long-term renal replacement

Box 130.2 Diagnostic criteria for hepatorenal syndrome (as defined by the International Ascites Club Consensus)

Major criteria

- Cirrhosis and ascites
- Serum creatinine >133 μmol/L (> 1.5 mg/dL)
- Absence of shock and hypovolaemia as defined by no sustained improvement of renal function (creatinine decreasing to <133 μmol/L) following at least 2 days of diuretic withdrawal, and volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal renal disease as defined by proteinuria < 0.5 g/day, no microhaematuria (< 50 red cells/high powered field), and normal renal ultrasonography

Minor criteria

- Urine volume < 500 mL/24 hours, urine sodium < 10 mEq/L
- Urine osmolality greater than plasma osmolality
- Serum sodium < 130 mEq/L.

Box 130.3 Classification of hepatorenal syndrome

Type 1

- Rapidly progressive acute kidney injury, with doubling of initial serum creatinine to > 221 μmol/L (> 2.5 mg/dL) in < 2 weeks
- Often develops after a precipitating event (spontaneous bacterial peritonitis, haemorrhage, surgery, systemic infection, acute liver injury)
- Associated with impaired cardiac and liver function as well as encephalopathy

Type 2

- Moderate renal failure, not meeting type 1 criteria, which tends to fluctuate over time and may convert to type 1 HRS if there is a further insult such as the development of spontaneous bacterial peritonitis
- Serum creatinine level increases to > 133 μmol/L (> 1.5 mg/dL)
- Associated with refractory or diuretic resistant ascites
- Steady or slowly progressive course.

therapy, and 3-year survival rate is approximately 60–65% compared to 70–80% for patients transplanted without HRS (EASL, 2010). Vasopressin analogue treatment prior to liver transplantation may improve outcomes post transplantation, and therefore should always be offered prior to transplantation (EASL, 2010). EASL guidelines recommend combined liver and kidney transplantation assessment only be considered for individuals dependent on renal replacement therapy for > 12 weeks, as the majority of patients will have some recovery in renal function after liver transplantation (EASL, 2010).

References

Akalin, E., Ames, S., Sehgal, V., *et al.* (2005). Safety of using hepatitis B virus core antibody or surface antigen-positive donors in kidney or pancreas transplantation. *Clin Transplant*, 19(3), 364–6.

Alessandria, C., Ozdogan, O., Guevara, M., *et al.* (2005). MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. *Hepatology*, 41, 1282–9.

Alivanis, P., Aperis, G., Lambrianou, F., *et al.* (2010). Reversal of refractory sulfasalazine-related renal failure after treatment with corticosteroids. *Clin Ther*, 32(11), 1906–10.

Allison, M. C., Sandoe, J. A. T., Tighe, R., *et al.* (2009). Antibiotic prophylaxis in gastrointestinal endoscopy. *Gut*, 58, 869–80.

Arroyo, V., Ginès, P., Gerbes, A. L., *et al.* (1996). Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology*, 23, 164–76.

Bhangui, P., Laurent, A., Amathieu, R., *et al.* (2012). Assessment of risk for non-hepatic surgery in cirrhotic patients. *J Hepatol*, 57(4), 874–84.

Blaker, P. A. and Goldsmith, D. (2012). Detection of bowel cancer in kidney transplant recipients. *BMJ*, 345, e5081.

Connor, A., Tolan, D., Hughes, S., *et al.* (2012). Consensus guidelines for the safe prescription and administration of oral bowel-cleansing agents. *Gut*, 61(11), 1525–32.

Crosnier, J., Jungers, P., Courouce, A. M., *et al.* (1981). Randomised placebo-controlled trial of hepatitis B surface antigen vaccine in French haemodialysis units: I, Medical staff. *Lancet*, 1(8218), 455–9.

Dumortier, J., Guillaud, O., Gagnieu, M. C., *et al.* (2013). Anti-viral triple therapy with telaprevir in haemodialysed HCV patients: is it feasible? *J Clin Virol*, 56(2), 146–9.

European Association for the Study of the Liver (2010). EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol*, 53(3), 397–417.

European Association for the Study of the Liver (2011). EASL clinical practice guidelines: management of hepatitis C virus infection. *J Hepatol*, 55(2), 245–64.

European Association for the Study of the Liver (2012). EASL clinical practice guidelines. Management of chronic hepatitis B virus infection. *J Hepatol*, 57(1), 167–85.

Fabrizi, F., Bruchfeld, A., Mangano, S., *et al.* (2007). Interferon therapy for HCV-associated glomerulonephritis: meta-analysis of controlled trials. *Int J Artif Organs*, 30(3), 212–19.

Fabrizi, F., Dixit, V., and Martin, P. (2006). Metaanalysis: terlipressin therapy for hepatorenal syndrome. *Aliment Pharmacol Ther*, 24, 935–44.

Fabrizi, F., Dixit, V., Messa, P., *et al.* (2012). Interferon therapy of acute hepatitis C in dialysis patients: meta-analysis. *J Viral Hepat*, 19(11), 784–91.

Fabrizi, F., Marzano, A., Messa, P., *et al.* (2008a). Hepatitis B virus infection in the dialysis population: current perspectives. *Int J Artif Organs*, 31(5), 386–94.

Fabrizi, F., Messa, P., and Martin, P. (2008b). Hepatitis B virus infection and the dialysis patient. *Semin Dial*, 21(5), 440–6.

Feldman, M., Friedman, L. S., and Brandt, L. J. (eds.) (2011). *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management* (9th ed.). Philadelphia, PA: Elsevier Saunders.

Ferreira, L. E. and Baron, T. H. (2007). Post-sphincterotomy bleeding: who, what, when and how. *Am J Gastroenterol*, 102, 2850–8.

Ferri, C. and Zignego, A. L. (2000). Relation between infection and autoimmunity in mixed cryoglobulinemia. *Curr Opin Rheumatol*, 12(1), 53–60.

Gane, E., Hyland, R., Ding, X., et al. (2013). *ELECTRON: 100% Suppression of Viral Load through 4 Weeks' Post-treatment for Sofosbuvir + Ledipasvir (GS-5885) + Ribavirin for 12 Weeks in Treatment-naïve and -experienced Hepatitis C Virus GT 1 Patients*. Presented at the 20th Conference on Retroviruses and Opportunistic Infections. Atlanta, GA, USA, 3–6 March. Abstract 41LB.

Ginès, A., Escorsell, A., Ginès, P., *et al.* (1993). Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology*, 105, 229–36.

Goddard, A. F., James, M. W., McIntyre, A. S., *et al.* (2011). Guidelines for the management of iron deficiency anaemia. *Gut*, 60, 1309–16.

Gordon, C. E., Uhlig, K., Lau, J., *et al.* (2008). Interferon treatment in hemodialysis patients with chronic hepatitis C virus infection: a systematic review of the literature and meta-analysis of treatment efficacy and harms. *Am J Kidney Dis*, 51(2), 263–77.

Hanson, K. (2005). Urinary stones and Crohn's disease. *Urol Nurs*, 25(6), 466–8.

Harrison, M. L., Obermueller, E., Maisey, N. R., *et al.* (2007). Tumour necrosis factor alpha as a new target for renal cell carcinoma: two sequential phase II trials of infliximab at standard and high dose. *J Clin Oncol*, 25(29), 4542–9.

Hassan, C., Bretthauer, M., Kaminski, M. F., *et al.* (2013). Bowel preparation for colonoscopy: European society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy*, 45, 142–50.

Hayashi, J., Nakashima, K., Kajiyama, W., *et al.* (1991). Prevalence of antibody to hepatitis C virus in hemodialysis patients. *Am J Epidemiol*, 134(6), 651–7.

Hedges, S. J., Dehoney, S. B., Hooper, J. S., *et al.* (2007). Evidence-based treatment recommendations for uraemic bleeding. *Nat Clin Pract Nephrol*, 3(3), 138–53.

Ingsathit, A., Kamanamool, N., Thakkinstian, A., *et al.* Survival advantage of kidney transplantation over dialysis in patients with hepatitis C: a systematic review and meta-analysis. *Transplantation*, 95(7), 943–8.

Ishii, G., Nakajima, K., Tanaka, N., *et al.* (2009). Clinical evaluation of urolithiasis in Crohn's disease. *Int J Urol*, 16(5), 477–80.

Kalantar-Zadeh, K., Kilpatrick, R. D., McAllister, C. J., *et al.* (2007). Hepatitis C virus and death risk in hemodialysis patients. *J Am Soc Nephrol*, 18(5), 1584–93.

Kalia, H., Fabrizi, F., and Martin, P. (2011). Hepatitis B virus and renal transplantation. *Transplant Rev*, 25(3), 102–9.

Kamar, N., Ribes, D., Izopet, J., *et al.* (2006). Treatment of hepatitis C virus infection (HCV) after renal transplantation: implications for HCV-positive dialysis patients awaiting a kidney transplant. *Transplantation*, 82(7), 853–6.

Kasprzyk, T., Kwiatkowski, A., Wszola, M., *et al.* (2007). Long-term results of kidney transplantation from HCV-positive donors. *Transplant Proc*, 39(9), 2701–3.

Kidney Disease: Improving Global Outcomes (KDIGO) (2008). KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of Hepatitis C in chronic kidney disease. *Kidney Int*, 73 (Suppl 109), S1–99.

Kumar, P. and Clark, M. (eds.) (2002). *Clinical Medicine* (5th ed.). Edinburgh: W. B. Saunders.

Latt, N., Alachkar, N., and Gurakar, A. (2012). Hepatitis C virus and its renal manifestations: a review and update. *Gastroenterol Hepatol*, 8(7), 434–45.

Mahboobi, N., Tabatabaei, S. V., Blum, H. E., *et al.* (2012). Renal grafts from anti-hepatitis B core-positive donors: a quantitative review of the literature. *Transplant Infect Dis*, 14(5), 445–51.

Marinella, M. A. (2008). Refeeding syndrome in cancer patients. *Int J Clin Pract*, 62(3), 460–5.

Mowat, C., Cole, A., Windsor, A., *et al.* (2011). Guidelines for the management of inflammatory bowel disease in adults. *Gut*, 60(5), 571–607.

Muller, A. F., Stevens, P. E., McIntyre, A. S., *et al.* (2005). Experience of 5-aminosalicylate nephrotoxicity in the United Kingdom. *Aliment Pharmocol Ther*, 21, 1217–24.

Ouseph, R., Eng, M., Ravindra, K., *et al.* (2010). Review of the use of hepatitis B core antibody-positive kidney donors. *Transplant Rev*, 24, 167–71.

Pape, E., Bene, J., Buchdal, A. L., *et al.* (2013). Desmopressin-related myocardial infarction in a patient with Wegener's granulomatosis: a case report and review of the literature. *J Mal Vasc*, 38(1), 43–6.

Paramesh, A. S., Davis, J. Y., Mallikarjun, C., *et al.* (2012). Kidney transplantation alone in ESRD patients with hepatitis C cirrhosis. *Transplantation*, 94(3), 250–4.

Piraino, B., Bernardini, J., Brown, E., *et al.* (2011). ISPD position statement on reducing the risks of peritoneal dialysis-related infections. *Perit Dial Int*, 31, 614–30.

Rahier, J. F., Ben-Horin, S., Chowers, Y., *et al.* (2009). European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis*, 3(2), 47–91.

Ray, S., Delaney, M., and Muller, A. F. (2010). Proton pump inhibitors and acute interstital nephritis. *BMJ*, 341, c4412.

Rockall, T. A., Logan, R. F., Devlin, H. B., *et al.* (1996). Risk assessment after acute upper gastrointestinal haemorrhage. *Gut*, 38(3), 316–21.

Rodriguez-Novoa, S., Alvarez, E., Labarga, P., *et al.* (2010). Renal toxicity associated with tenofovir use. *Expert Opin Drug Saf*, 9(4), 545–59.

Roth, D., Gaynor, J. J., Reddy, K. R., *et al.* (2011). Effect of kidney transplantation on outcomes among patients with hepatitis C. *J Am Soc Nephrol*, 22(6), 1152–60.

Salerno, F., Gerbes, A., Ginès, P., *et al.* (2007). Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut*, 56, 1310–18.

Schwartz, D. A., Loftus, E. V., Tremaine, W. J., *et al.* (2002). The natural history of fistulizing Crohn's disease in Olstead County, Minnesota. *Gastroenterology*, 122, 875–80.

Scott, D. R., Wong, J. K., Spicer, T. S., *et al.* (2010). Adverse impact of hepatitis C virus infection on renal replacement therapy and renal transplant patients in Australia and New Zealand. *Transplantation*, 90(11), 1165–71.

Serpaggi, J., Carnot, F., Nalpas, B., *et al.* (2006). Direct and indirect evidence for the reversibility of cirrhosis. *Hum Pathol*, 37(12), 1519–26.

Stanley, A. J., Ashley, D., Dalton, H. R., *et al.* (2009). Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multicentre validation and prospective evaluation. *Lancet*, 373(9657), 42–7.

Sulkowski, M. F., Gardiner, D. F., Rodriguez-Torres, M., *et al.* (2012). *High Rate of Sustained Virologic Response with the All-Oral Combination of Daclatasvir (NS5A Inhibitor) Plus Sofosbuvir (Nucleotide NS5B Inhibitor), with or without Ribavirin, in Treatment-Naive Patients Chronically Infected with HCV Genotype 1, 2, or 3*. Presented at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases, Boston, MA, USA, 9–13 November. Abstract LB-2.

Tang, S. and Lai, K. N. (2005). Chronic viral hepatitis in hemodialysis patients. *Hemodial Int*, 9(2), 169–79.

Tarantino, A., Campise, M., Banfi, G., *et al.* (1995). Long-term predictors of survival in essential mixed cryoglobulinemic glomerulonephritis. *Kidney Int*, 47(2), 618–23.

Teh, S. H., Nagorney, D. M., Stevens, S. R., *et al.* (2007). Risk factors for mortality after surgery in patients with cirrhosis. *Gastroenterology*, 132(4), 1261–9.

Trevizoli, J. E., de Paula, M. R., Ribeiro Velasco, L. F., *et al.* (2008). Hepatitis C is less aggressive in hemodialysis patients than in nonuremic patients. *Clin J Am Soc Nephrol*, 3(5), 1385–90.

Tsui, J. I., Vittinghoff, E., Shlipak, M. G., *et al.* (2007). Association of hepatitis C seropositivity with increased risk for developing end-stage renal disease. *Arch Intern Med*, 167(12), 1271–6.

Tuncer, M., Tekin, S., Yucetin, L., *et al.* (2012). Hepatitis B surface antigen positivity is not a contraindication for living kidney donation. *Transplant Proc*, 44(6), 1628–9.

British Transplantation Society (n.d.). *UK Transplant Guidelines*. [Online] <http://www.bts.org.uk/MBR/Clinical/Guidelines>

Vallet-Pichard, A., Fontaine, H., Mallet, V., *et al.* (2011). Viral hepatitis in solid organ transplantation other than liver. *J Hepatol*, 55(2), 474–82.

Viana, M. L., Pontes, R. M., Garcia, W. E., *et al.* (2007). Crohn's disease and kidney stones: much more than coincidence? *Arq Gastroenterol*, 44(3), 210–14.

Vigani, A. G., Macedo de Oliveira, A., Tozzo, R., *et al.* (2011). The association of cryoglobulinaemia with sustained virological response in patients with chronic hepatitis C. *J Viral Hepat*, 18(4), e91–8.

Worcester, E. (2002). Stones from bowel disease. *Endocrinol Metab Clin North Am*, 4, 979–99.

Zallot, C., Billioud, V., Frimat, L., *et al.* (2012). 5-Aminosalicylates and renal function monitoring in inflammatory bowel disease: a nationwide survey. *J Crohns Colitis*, 7(7), 551–5.

Zheng, X. Y., Wei, R. B., Tang, L., *et al.* (2012). Meta-analysis of combined therapy for adult hepatitis B virus-associated glomerulonephritis. *World J Gastroenterol*, 18(8), 821–32.

Zylberberg, H., Nalpas, B., Carnot, F., *et al.* (2002). Severe evolution of chronic hepatitis C in renal transplantation: a case control study. *Nephrol Dial Transplant*, 17(1), 129–33.

CHAPTER 131

Cutaneous manifestations of end-stage renal disease

Timur A. Galperin, Kieron S. Leslie, and Antonia J. Cronin

Introduction

A broad range of skin diseases occur in patients with end-stage renal disease (ESRD). Some of these conditions are benign, and have little impact on patients' lives. Others, however, have a greater impact on quality of life, may be physically disabling, and even life-threatening. Mostly, they result from a combination of factors, such as electrolyte imbalance and co-morbid disease. Their early recognition and treatment is essential in order to reduce morbidity and mortality, and improve patient outcomes and quality of life.

In this chapter, we focus on two main categories of the cutaneous manifestations of ESRD: non-specific and specific. The non-specific manifestations include skin-colour changes, xerosis, half-and-half nails, and pruritus. The specific manifestations include acquired perforating dermatosis, bullous dermatoses, metastatic calcification, and nephrogenic systemic fibrosis (NSF). Pathophysiology, clinical presentation, diagnosis, and treatment options are discussed.

Non-specific manifestations

Skin-colour changes

These are a heterogeneous group of asymptomatic disorders commonly seen in ESRD patients. They do not have dermatological sequelae (Attia et al., 2010; Markova et al., 2012).

- Pallor occurs in approximately 40% of patients with ESRD. Its occurrence is secondary to the anaemia of chronic renal disease. Pallor frequently improves with erythropoietin therapy.
- Hyperpigmentation is seen in approximately 20% of patients with ESRD. It is secondary to elevated melanocyte-stimulating hormone. Sun protection and daily sunscreen use are beneficial in reducing pigment alteration over time.
- Yellowing of the skin occurs as a result of excess urochrome and carotenoid deposition. It has no known effective treatment.
- Ecchymosis is common. It occurs as a result of platelet dysfunction, which is associated with increased serum urea and creatinine levels. It may improve with treatment with dialysis.

Half-and-half nails

Half-and-half nails, or Lindsay's nails, occurs in about 20% of ESRD patients. The pathogenesis is unknown. Clinically, patients have asymptomatic nail changes. The proximal nail-plate turns white, and the distal nail-plate remains normal or becomes brown coloured. There is no effective treatment (Markova et al., 2012).

Xerosis

Xerosis occurs in approximately 50–85% of ESRD patients. Xerosis may be due to the dehydration of the stratum corneum, and reduced sebum and sweat production secondary to sebaceous and sweat gland atrophy. Xerosis presents with asymptomatic to pruritic, dry, scaly skin on the trunk and extremities, as seen in Fig. 131.1. Repeated scratching leads to lichenification (skin thickening) and prurigo nodularis (dome-shaped papules/nodules), as seen in Fig. 131.2. Xerotic skin is susceptible to cutaneous infection from abnormal barrier function. In order to reduce irritation, patients should limit hand-washing, showering, and bathing. Applying topical moisturizing emollients, avoiding contact with known skin irritants, and using non-irritating fabrics such as cotton should also be recommended (Markova et al., 2012).

Pruritus

Pruritus is one of the most common symptoms associated with ESRD and occurs in approximately 40–50% of ESRD patients. The exact pathophysiology of uraemic pruritus is unknown, but it is complex and likely multifactorial (Kuypers, 2009; Wang and Yosipovitch, 2010). The aetiological factors involved include the following:

- Neurocutaneous abnormalities:
  - peripheral neuropathy
  - increased substance P secretion in the epidermis
  - aberrant signalling of cutaneous C nerve fibres
  - increased serum β-endorphin (μ-receptor agonist)
- Electrolyte imbalance:
  - hypercalcaemia
  - hyperphosphataemia
  - hypervitaminosis A
  - hypermagnesaemia

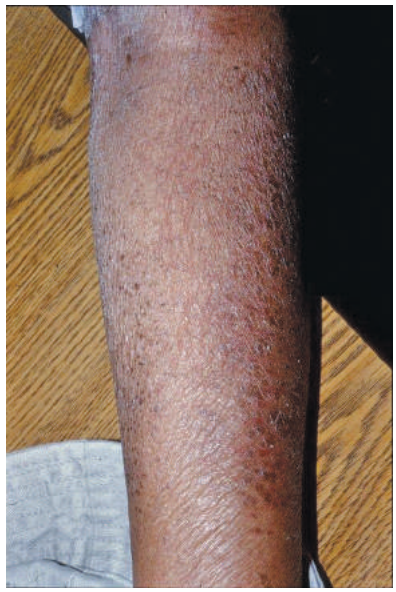
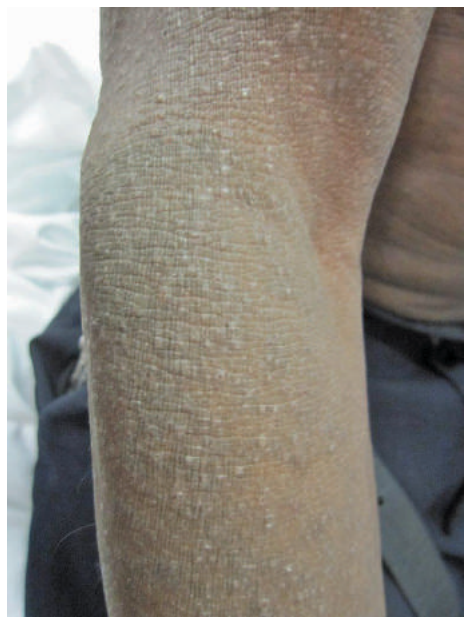


Fig. 131.1 Xerotic eczema.

(A)



(B)

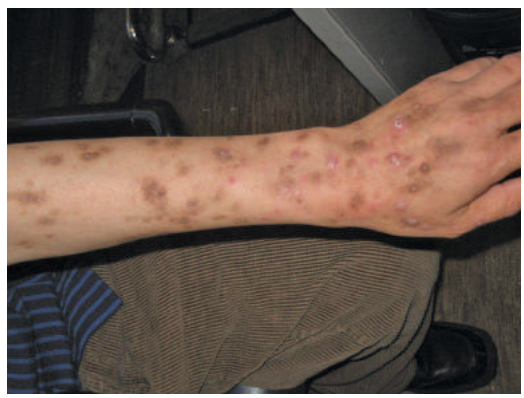


Fig. 131.2 (A) Lichenified papules. (B) Prurigo nodules.

- Secondary hyperparathyroidism
- Xerosis
- Elevated interleukin 2 (IL-2) and interleukin 6 (IL-6)
- Iron deficiency anaemia
- Increased serum C-reactive protein
- Increased number of dermal mast cells and histamine
- Increased gamma-aminobutyric acid (GABA).

Uraemic pruritus may be localized to one area, but more commonly it is generalized. The severity and clinical characteristics vary considerably among patients. Patients may present clinically with lichen simplex chronicus, excoriations, or prurigo nodularis from incessant scratching (Kuypers, 2009; Wang and Yosipovitch, 2010).

Before making the diagnosis of uraemic pruritus other causes of pruritus should be ruled out. Uraemic pruritus is notoriously difficult to treat. Table 131.1 presents a summary of effective treatments to ameliorate the severity of pruritus. No single agent is entirely effective. Topical therapy, to relieve the xerosis that many patients have, has been of modest value, and few systemic medications have had significant effectiveness. Treatment is best personalized, and generally requires a combination of topical and systemic treatment (Kuypers, 2009; Feramisco et al., 2010; Wang and Yosipovitch, 2010).

Specific manifestations

Acquired perforating dermatosis

Perforating disorders are a heterogenous group of dermatoses characterized by transepidermal elimination of dermal material. The acquired perforating dermatosis (APD) seen in ESRD patients is both clinically and histologically similar to the primary perforating disorders. APD usually develops once dialysis treatment has started. The prevalence of APD in dialysis patients is 2–11% (Markova et al., 2012). APD predominately affects African American patients. There is a strong association with chronic kidney disease (CKD) and diabetes mellitus (DM) (Kuypers, 2009).

Localized cutaneous irritation may lead to an inflammatory reaction to uraemic substances within the dermis, leading to the development of lesions. Patients present with firm, pruritic, dome-shaped papules/nodules with a central keratotic plug, distributed on the extensor portions of the extremities and trunk. The appearance of lesions in areas of traumatized skin (koebnerization), especially from scratching, is common (Kuypers, 2009; Karpouzis et al., 2010). Spontaneous resolution of lesions can occur.

APD is diagnosed clinically, and can be confirmed with a lesional biopsy. Individual case reports and small case series have provided evidence of effective treatment with topical and systemic therapies, phototherapy, and cryotherapy. A summary of these are set out in Table 131.2 (Kuypers, 2009; Karpouzis et al., 2010). There has not, as yet, been a randomized controlled trial to evaluate the efficacy of a single treatment.

Bullous diseases

Bullous diseases present with vesicles, or bullae on the skin and/or mucous membranes. In ESRD patients, porphyria cutanea tarda (PCT), or pseudoporphyria may be seen. Both are due to the

Table 131.1 Effective treatments to ameliorate the severity of pruritus in dialysis patients

Topical	Systemic	Other
1. Moisturizing emollients	1. Gabapentin 100–300 mg PO 3 times/week after dialysis	1. High-permeability dialysis
2. Capsaicin 0.03% ointment 4 times per day	2. Pregabalin 25–75 mg PO QD	2. Narrow-band UVB 3 times/week
3. Pramoxine 1% lotion BID	3. Nalfurafine 5 micrograms IV 3 times/week after dialysis or 2.5–5 micrograms PO nightly	
4. Sericin 8% cream BID	4. Cromolyn 135 mg PO TID	
5. Topical cromolyn 4% cream QD	5. Sertraline 50 mg PO QD	
6. Gamma-linolenic acid 2.2% cream TID	6. Thalidomide 100 mg PO nightly	
7. Glycerine 15% and paraffin 10% oil-water emulsion BID	7. Activated charcoal 6 g QD	

BID = twice daily; IV = intravenous; PO = per oral; QD = daily; TID = three times daily; UVB = ultraviolet-B.

build-up of photosensitive molecules in the skin which causes skin fragility and vesiculation upon sun exposure (Markova et al., 2012).

Porphyria cutanea tarda

PCT is classified as acquired/sporadic, where uroporphyrinogen-decarboxylase (URO-D) is defective/deficient only in the liver, or an autosomal dominant, familial type, where the enzyme is deficient in all tissues. Heavy alcohol use, hepatitis C virus infection, human immunodeficiency virus infection, iron supplementation, and oestrogen use in women, decrease URO-D activity. Iron induces 5-aminolevulinate synthase, a regulatory enzyme that suppresses URO-D activity, increasing the plasma porphyrins. Plasma porphyrins can form complexes with high-molecular-weight proteins, such as albumin, which are poorly dialysable. PCT occurs as a result of decreased URO-D activity and limited clearance of the plasma porphyrins in haemodialysis (HD) patients. Peritoneal dialysis (PD) is more effective at clearing large molecules, compared to HD, and is the most probable reason that PCT is uncommon in patients on PD (Balwani and Desnick, 2012; Markova et al., 2012).

Patients have skin photosensitivity and fragility, and manifest clinically with tense vesicles/bullae distributed on the extensor forearms, and dorsum of the hands. Lesions heal leaving behind erosions, crusts, atrophic scarring, and milial cysts as seen in Fig. 131.3. Sclerodermatous plaques, hypertrichosis, and hyperpigmentation in sun-exposed areas, especially on the face, are also commonly seen (Fig. 131.4). Increased serum levels of iron and ferritin, increased excretion of uroporphyrin-I > uroporphyrin-III in the urine, increased levels of isocoproporphyrin-III in the faeces, and increased levels of plasma uroporphyrin are typical. In ESRD patients with true PCT, the total plasma porphyrin levels range from 39.8 to 291.0 g/dL (Balwani and Desnick, 2012; Markova et al., 2012).

Treatment includes avoiding triggers like alcohol, hepatotoxic medications, and sun exposure. Daily use of sunscreen/sunblock is an important preventative measure. Effective symptomatic management involves decreasing hepatic iron stores. Erythropoiesis-stimulating agents (ESAs) in combination with small-volume phlebotomy (50–100 mL) once or twice weekly can induce remission within several months. Patients unable to tolerate phlebotomy can use desferrioxamine as an alternative with each dialysis session. High-flux membrane HD is better at removing plasma porphyrins, and can be used as an effective adjunct (Balwani and Desnick, 2012; Markova et al., 2012).

Pseudoporphyria

Pseudoporphyria is clinically and histologically identical to PCT without the serum and urine porphyrin abnormalities. The pathophysiology of pseudoporphyria in ESRD patients is unknown. Patients develop vesicles/bullae, skin fragility, and scarring on sun-exposed surfaces, but not the sclerodermoid changes, hypertrichosis, or hyperpigmentation as seen in PCT. Treatment involves sun avoidance and sun protection as in PCT, and avoiding medications that induce pseudoporphyria, such as diuretics, antibiotics, and antifungals. *N*-acetylcysteine, which increases antioxidant activity and reduces the number of free radicals, is an effective treatment for pseudoporphyria (Markova et al., 2012).

Metastatic calcification

Metastatic calcification is the deposition of calcium into cutaneous and/or subcutaneous tissues, which occurs as a result of elevated serum levels of calcium. It can also affect the blood vessels and

Table 131.2 Effective treatments for acquired perforating dermatosis

Topical therapy	Systemic therapy	Other therapies
1. Superpotent topical steroid: clobetasol or betamethasone alone or in combination with a keratolytic agent 2. Keratolytic agent: salicylic acid, urea, or ammonium lactate alone or in combination with a topical steroid 3. Retinoid	1. Antihistamines 2. Allopurinol 100 mg 3. Acitretin 4. Doxycycline 100 mg or minocycline 100–200 mg	1. Narrow-band ultraviolet B 2. Cryotherapy with liquid nitrogen

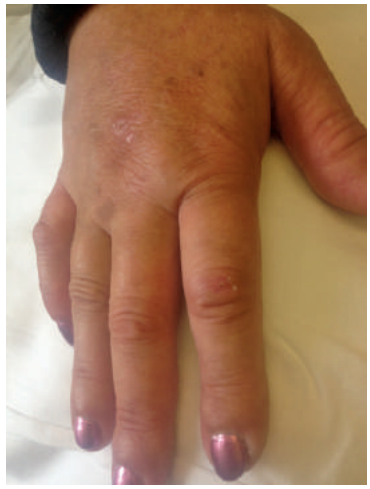


Fig. 131.3 Porphyria cutanea tarda. Healing crusted papules.

viscera (Markova et al., 2012). In ESRD, metastatic calcification is characterized by abnormal calcium and/or phosphate metabolism and presents as either calcinosis cutis, or calcific uraemic arteriolopathy (CUA).

Calcinosis cutis

Calcinosis cutis, also known as benign nodular calcification, refers to the deposition of calcium within the cutaneous and subcutaneous tissues without tissue necrosis. Hyperphosphataemia, as a result of reduced renal clearance and insufficient removal with dialysis, is typical. Secondary hyperparathyroidism, with increased levels of intact parathyroid hormone (iPTH), mobilizes the release of calcium and phosphate from the bone into the serum which in turn increases serum calcium and phosphate levels. When serum calcium and phosphate levels reach a solubility threshold, calcinosis cutis can occur (Reiter et al., 2011; Markova et al., 2012).

Patients present with firm, white papules/plaques and nodules, with occasional exudation of white material. Lesions are distributed on the fingertips and peri-articularly. Fingertip lesions are usually painful. Peri-articular lesions are generally asymptomatic. The number and size of the lesions correlates with the serum phosphate level. Dietary phosphate restriction and phosphate binders can lower the serum phosphate levels. If necessary, parathyroidectomy in patients with elevated iPTH levels can be beneficial (Reiter et al., 2011; Markova et al., 2012). Lesions improve when the hyperphosphataemia improves.

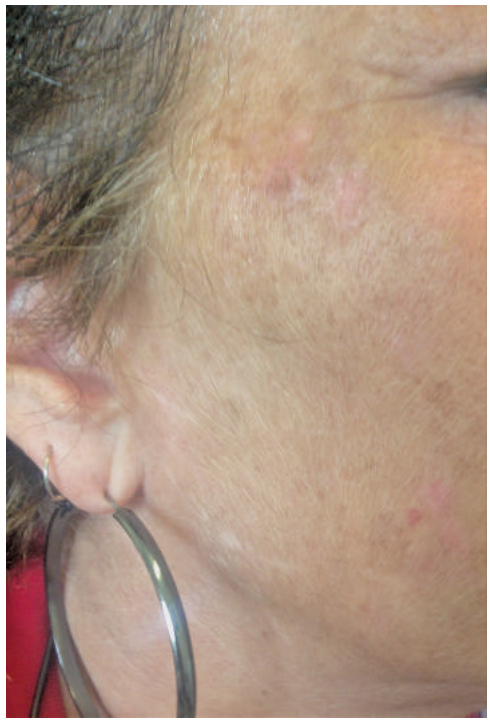


Fig. 131.4 Porphyria cutanea tarda. Hypertrichosis, hyperpigmented patches, and pink sclerodermatous plaques on the cheek.

Calcific uraemic arteriolopathy

CUA, also known as calciphylaxis, is characterized by thrombosis of calcified small and medium-sized arteries and arterioles, along with fibrosis of the dermis and subcutaneous fat. CUA is a rare but potentially life-threatening complication of ESRD. It has an estimated incidence of 1%, and prevalence of 1–4% in ESRD patients. Patients typically present in their 50s. CUA has a mortality rate of 60–80%. Death usually occurs following sepsis and organ failure (Reiter et al., 2011; Markova et al., 2012).

The exact aetiology of CUA is unclear, but it is multifactorial. Metabolic factors, systemic inflammation, oxidative stress, endothelial injury, along with certain triggers have been implicated. A number of risk factors including local trauma, female gender, Caucasian ethnicity, hypoalbuminaemia, therapy with calcium salts, vitamin D supplements, treatment with ESAs, warfarin, and iron supplements, have been implicated as triggering CUA. A summary of these and other independent risk factors are set out in Table 131.3.

CKD/ESRD, dialysis treatment, and commonly occurring co-morbid conditions, such as hypertension, hypercholesterolaemia, and DM, increase oxidative stress (Sowers and Hayden, 2010). Vascular calcification is stimulated by increased reactive oxygen species (ROS) from oxidative stress. Increased ROS also cause systemic inflammation, as evidenced by increased levels of tumour necrosis factor alpha, and IL-1 and -6 (Sowers and Hayden, 2010). Glutathione, and other natural antioxidants, are decreased with chronicity of ESRD and other comorbid disorders. Endothelial injury and subsequent luminal narrowing are triggered by vascular calcification. Luminal narrowing, combined with the naturally low-flow rate of the cutaneous blood vessels, causes reduced blood flow, and can lead to blood stasis. Blood stasis contributes to a procoagulant environment in the narrowed vessels, increasing the risk of thrombosis. Thrombosis can lead to local ischaemia and necrosis (Daudén and Oñate, 2008; Weenig, 2008; Sowers and Hayden, 2010).

Patients initially present with discomfort or localized pain overlying areas of erythema, or violaceous, reticulated discolouration of the skin, resembling levido reticularis. Progression of lesions can take several days to weeks. Lesions develop into painful plaques (Fig. 131.5), or sometimes nodules, bordered by a net-like violaceous discolouration. Lesions are distributed bilaterally and symmetrically, and are generally located on the lower legs, which can be related to reduced circulation, and the abdomen and buttocks, both

Table 131.3 Risk factors and triggering factors in calcific uraemic arteriolopathy

Demographic risk factors	Medications and supplements	Metabolic abnormalities
Female gender	Calcium salts	Albumin < 3.5 g/dL
Caucasian ethnicity	Vitamin D	Phosphate > 5.0 mg/dL
Obesity (BMI > 30 kg/m2)	Erythropoietin-stimulating agents	Calcium > 10.0 mg/dL
	Warfarin	iPTH > 300 ng/L
	Iron	Calcium × phosphate product > 70 mg^2/dL^2
	Systemic corticosteroids	Alkaline phosphatase > 300 IU/L
		Aluminium >25 ng/mL

Factors increasing systemic inflammation and oxidative stress:

- Local trauma
- ESRD and associated dialysis therapy
- Hypertension, hypercholesterolaemia, obesity, and diabetes
- 4. Liver disease

iPTH = intact parathyroid hormone.

of which contain a large percentage of adipose tissue (Daudén and Oñate, 2008; Reiter et al., 2011). Haemorrhagic vesicles/bullae may precede the development of necrosis. Patients frequently develop tender, asymmetrical, non-healing ulcers. Lesion distribution is not a clear prognostic factor as previously thought (Daudén and Oñate, 2008; Reiter et al., 2011). Systemic symptoms from vascular and extravascular calcification can also occur. Cardiac valvular or electrical conduction dysfunction, myocardial, pulmonary, cerebrovascular, and bowel infarction, myositis, and muscle weakness have also been reported (Daudén and Oñate, 2008).

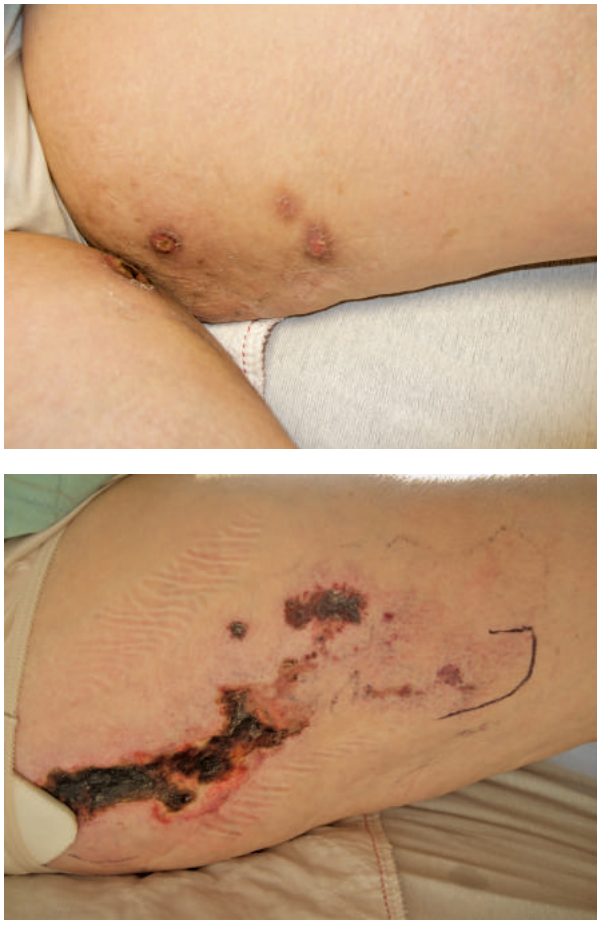


Fig. 131.5 Calcific uraemic arteriolopathy. (A) Eroded plaques on inner thighs. (B) Ulcerated plaques with a violaceous rim and central necrosis.

At presentation, patients may have metabolic abnormalities, such as an elevated calcium-phosphate product, and elevated serum iPTH levels. However, most recent data indicates that electrolyte and iPTH levels are often within the normal range at presentation (Hayashi et al., 2012). Elevated C-reactive protein and erythrocyte sedimentation rate, hyperglycaemia, and hypercholesterolaemia may also be seen (Hayashi et al., 2012). Metabolic abnormalities alone are not predictive of disease, but should be noted, as they are thought to increase a person's risk for vascular calcification.

Radiographic imaging may be helpful in reaching the diagnosis. On plain radiography small vascular calcifications can be identified, and a 'net-like pattern' of soft-tissue calcification has also been described; however, this observation has not been validated. Computed tomography can identify calcification of the internal organs, and calcified arterioles of the soft tissues. Mammography is the best modality currently available to identify soft-tissue arteriolar calcifications, although it is limited by affected tissue thickness. Bone scans can identify increased tracer uptake in affected regions of the sub-cutis (Shmidt et al., 2012). Lesion biopsy with dermatopathological examination remains the gold standard diagnostic method.

Early recognition, diagnosis, and treatment of CUA are imperative in order to stop disease progression, and improve patient outcomes. There is, however, a lack of data from controlled clinical trials to guide treatment, which is often difficult and supportive. Even with early intervention and management, it is generally acknowledged that pain relief can take weeks, and lesion healing can take several months. Management options are presented in Table 131.4 (Ross, 2011; Vedvyas et al., 2012).

Management includes adjusting and maintaining the serum calcium and phosphate levels at target according to national guidelines (Vedvyas et al., 2012), whenever possible.

Sodium thiosulphate (STS) is a dialysable calcium chelator that improves antioxidant glutathione production, increases endothelial

Table 131.4 Therapeutic modalities for calcific uraemic arteriolopathy

Correction of electrolyte imbalance	Treatments to promote wound healing
Lower calcium concentration in the dialysate to 1.0–1.5 mEq/L	Sodium thiosulphate
Increase dialysis to 4–6 times per week	Enhance nutritional status
Bisphosphonates (intravenous and oral)[a]	Albumin replacement, if required
Parathyroidectomy in patients with iPTH levels > 300 ng/L[b]	Wound care, with surgical debridement[c]
Cinacalcet	Antibiotics for infected lesions
	Skin grafting, and biologic dressings
	Hyperbaric oxygen therapy

[a] Controversial in those with a glomerular filtration rate < 30 mL/min, due to a possible risk of adynamic bone disease, and direct nephrotoxicity.

[b] Medical management is the 'gold standard' for normal to slightly elevated iPTH. Parathyroidectomy should only be considered if medical management fails.

[c] Controversial; there is a potential to induce new lesions, or lead to the progression of current lesions if the disease course is still active.

iPTH, intact parathyroid hormone.

nitric oxide production, and can lessen systemic inflammation. STS can relieve pain within days, and improve wound healing in around 8 weeks (Vedvyas et al., 2012). Cinacalcet, a calcimimetic agent, is effective in patients with both normal and elevated iPTH levels. Cinacalcet is considered to be an effective medical alternative to parathyroidectomy in this setting (Vedvyas et al., 2012). Tissue plasminogen activator (tPA) does not have a survival benefit when utilized as an adjunct treatment, but does have variable effectiveness for wound healing, albeit with several significant risks (el-Azhary et al., 2013). The utility of tPA as an adjunct therapy needs to be further evaluated. Hyperbaric oxygen therapy (HBO) improves tissue oxygenation, which promotes wound healing. Several studies have reported that HBO prevented calciphylaxis progression. HBO has few sideeffects, but its use is limited by machine costs and limited access (Ross, 2011; Vedvyas et al., 2012).

The treatment of CUA is challenging. Controlling and minimizing the deleterious effects of associated co-morbid conditions, and triggering factors is important (Ross, 2011). Identifying and treating the various aetiologies of vascular calcification and hypercoagulability with an individualized approach also appears to be important. A multi-intervention, standardized approach to treatment has been effective in a single case series (Baldwin et al., 2011). Further investigation to evaluate the effectiveness and utility of a multi-intervention, standardized protocol for CUA is required.

Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis (NSF) is a rare, scleroderma-like disorder caused by exposure to gadolinium-based contrast agents (GBCAs) used in diagnostic imaging. NSF can occur infrequently in normouraemic patients, but is most commonly seen in patients with renal insufficiency and a glomerular filtration rate (GFR) < 30 mL/min. Individuals with the highest risk of acquiring NSF are those with a GFR of < 15 mL/min, dialysis patients with severe acute kidney injury (AKI), and those with ESRD on. It can also occur in renal transplant patients with abnormal graft function.

Improved awareness and screening of patients prior to GBCA-enhanced magnetic resonance imaging/angiography has reduced the incidence of NSF. NSF affects all ethnic groups, and affects males and females equally, with the majority of cases occurring in middle-aged adults. The average age at onset is 51 years. The risk factors and disease triggers are set out in Table 131.5 (Elmholdt et al., 2011; Zou et al., 2011).

The pathogenesis of NSF is associated with Gd exposure, GFR, type and frequency of dialysis, and the occurrence of a concomitant pro-inflammatory triggering event, such as vascular injury or infection. Gd is eliminated almost exclusively by the kidneys. It has a half-life of 1–2 hours in patients with normal renal function, but this is significantly elevated, to 9 hours or greater, in patients with renal insufficiency. Insoluble Gd–phosphate complexes can deposit into the tissues, where Gd is phagocytized by macrophages. Macrophages and free Gd increase the production of transforming growth factor beta-1, and pro-fibrotic cytokines (IL-4, -6, -13, and interferon-gamma), which recruit circulating fibrocytes (CFs) into the area. Pro-inflammatory states, such as vascular injury, which induce the release of inflammatory cytokines, may also stimulate production of CFs (Bernstein et al., 2012; Igreja et al., 2012).

CFs are bone marrow-derived, fibroblast-like, collagen-producing spindle cells that circulate within the blood and enter areas of injury and inflammation. Participate in wound healing, pathologic fibrosis, and cytokine/chemokine production. CFs are associated with fibrotic disorders, like keloid production, and scleroderma. The pathogenic role of CFs in NSF is supported by the rapidity of disease progression, symmetry of lesions, and the propagation of CD34+ dermal, spindled fibroblasts which are typically seen on biopsy specimens (Bernstein et al., 2012; Igreja et al., 2012).

Table 131.5 Risk factors and triggering factors in nephrogenic systemic fibrosis

Risk factors	Triggering factors[a]
Peritoneal dialysis[b]	Vascular injury
Elevated serum phosphate level	Infection
High-dose (>0.2 mmol/kg) of GBCA	High-dose erythropoietin therapy
Multiple cumulative doses of GBCA (with an overall GBCA volume >0.2 mmol/kg)	
Use of linear or non-ionic GBCA chelating agents[c]	
Iron[d]	

[a] Pro-inflammatory states; may stimulate production of bone-marrow derived circulating fibrocytes.

[b] Less effective at removing gadolinium than haemodialysis.

[c] Have less *in vitro* stability and affinity for gadolinium than the ionic and macrocyclic GBCAs.

[d] Can induce transmetallation of gadolinium.

GBCA = gadolinium-based contrast agents.

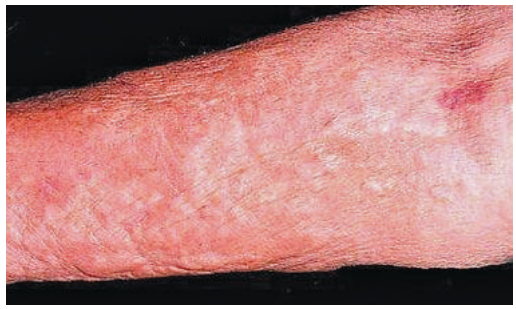


Fig. 131.6 Nephrogenic systemic fibrosis. Skin fibrosis with indurated yellowish-orange papules.

Patients present within several weeks to months following GBCA exposure with painful erythema and oedema that evolves rapidly into an erythematous firmness of the skin with indurated papules, and plaques, which may have a cobblestone appearance (Fig. 131.6). Lesions are generally symmetric, and distributed on the lower legs. There is a cephalad progression to the thighs, hands, arms, and less often to the trunk. Brawny hyperpigmentation of the skin, cutaneous fibrosis, and swelling, commonly occur, especially on the hands. Pain, burning, and pruritus may be felt in fibrotic areas. Flexion contractures result from progressive fibrosis, causing restricted joint mobility. Systemic fibrosis, affecting the skeletal muscle, liver, intestines, lungs, heart, or kidneys is not uncommon. Rarely patients can present with rapidly progressive fibrosis and fulminant disease, sometimes within weeks of disease onset (Zou et al., 2011; Bernstein et al., 2012; Igreja et al., 2012).

A clinical diagnosis may be challenging, since the initial presentation is frequently subtle, and often mimics scleroderma. Other fibrosing disorders in the differential diagnosis include eosinophilic fasciitis, and scleromyxoedema. Clinicians should suspect NSF in ESRD patients recently exposed to Gd. Laboratory studies can help exclude the fibrosing disorders. An example is autoantibody testing, such as anti-topoisomerase I (Scl-70), which is typically absent in NSF, but is more commonly present in scleroderma. The clinical and laboratory data, in conjunction with a deep skin biopsy, will help confirm the diagnosis (Bernstein et al., 2012; Igreja et al., 2012).

As a preventative measure, it is recommended that clinicians utilize macrocyclic and ionic GBCAs in ESRD patients, or those with AKI, avoid using high doses of GBCA, and dialyse patients as soon as practically feasible after GBCA exposure (Zou et al., 2011).

Spontaneous resolution of NSF has been reported in cases of rapidly improved AKI, and in several renal transplant cases. Improved renal function has been shown to slow NSF progression, and can improve the symptoms of disease. Renal transplant for patients with NSF does not guarantee improvement of disease manifestations. However, several case reports suggest that successful transplantation may produce skin softening, and increased joint mobility (Zou et al., 2011; Bernstein et al., 2012; Igreja et al., 2012). Oral corticosteroids, ultraviolet-A phototherapy, plasmapheresis, sirolimus, methotrexate, and pentoxifylline have shown minimal benefit. Several case reports of extracorporeal photopheresis and a few cases of high-dose intravenous immunoglobulin demonstrated clinical improvement. Physical therapy is an effective adjunct, decreasing the degree of joint contractures and restoring joint mobility (Bernstein et al., 2012; Igreja et al., 2012).

Imatinib mesylate (Gleevec®), a platelet-derived growth factor-receptor inhibitor, blocks signal transduction involved in fibrosis. Imatinib slowed NSF progression, improved disease symptoms, improved joint mobility, and caused skin softening in several cases (Igreja et al., 2012). Alefacept inhibits CD4+/CD8+ T-lymphocyte activation, and induces apoptosis of memory-effector T lymphocytes. Alefacept is effective in treating graft-versus-host disease, which can have a scleroderma-like appearance, and alleviated the skin manifestations of NSF in a single case series (Robinson et al., 2011). Sodium thiosulphate improved the skin symptoms and joint mobility in a single case series (Bernstein et al., 2012). Further investigation is needed to identify optimal treatment.

Further Reading

Galperin, T. A., Cronin, A. J., and Leslie, K. S. (2014). Cutaneous manifestations of ESRD. *Clin J Am Soc Nephrol*, 9(1), 201–18.

References

Attia, E. A. S., Hassan, S. I., and Youssef, N. M. (2010). Cutaneous disorders in uremic patients on hemodialysis: an Egyptian case-controlled study. *Int J Dermatol*, 49, 1024–30.

Baldwin, C., Farah, M., Leung, M., *et al.* (2011). Multi-intervention management of calciphylaxis: a report of 7 cases. *Am J Kidney Dis*, 58, 988–91.

Balwani, M. and Desnick, R. J. (2012). The porphyrias: advances in diagnosis and treatment. *Blood*, 120, 4496–504.

Bernstein, E. J., Schmidt-Lauber, C., and Kay, J. (2012). Nephrogenic systemic fibrosis: a systemic fibrosing disease resulting from gadolinium exposure. *Best Pract Res Clin Rheumatol*, 26, 489–503.

Daudén, E. and Oñate, M. -J. (2008). Calciphylaxis. *Dermatol Clin*, 26, 557–68, ix.

El-Azhary, R. A., Arthur, A. K., Davis, M. D. P., *et al.* (2013). Retrospective analysis of tissue plasminogen activator as an adjuvant treatment for calciphylaxis. *JAMA Dermatol*, 149, 63–7.

Elmholdt, T. R., Pedersen, M., Jørgensen, B., *et al.* (2011). Nephrogenic systemic fibrosis is found only among gadolinium-exposed patients with renal insufficiency: a case-control study from Denmark. *Br J Dermatol*, 165, 828–36.

Feramisco, J. D., Berger, T. G., and Steinhoff, M. (2010). Innovative management of pruritus. *Dermatol Clin*, 28, 467–78.

Hayashi, M., Takamatsu, I., Kanno, Y., *et al.* (2012). A case-control study of calciphylaxis in Japanese end-stage renal disease patients. *Nephrol Dial Transplant*, 27, 1580–4.

Igreja, A. C. de S. M., Mesquita, K. de C., Cowper, S. E., *et al.* (2012). Nephrogenic systemic fibrosis: concepts and perspectives. *An Bras Dermatol*, 87, 597–607.

Karpouzis, A., Giatromanolaki, A., Sivridis, E., *et al.* (2010). Acquired reactive perforating collagenosis: current status. *J Dermatol*, 37, 585–92.

Kuypers, D. R. J. (2009). Skin problems in chronic kidney disease. *Nat Clin Pract Nephrol*, 5, 157–70.

Markova, A., Lester, J., Wang, J., *et al.* (2012). Diagnosis of common dermopathies in dialysis patients: a review and update. *Semin Dial*, 25, 408–18.

Reiter, N., El-Shabrawi, L., Leinweber, B., *et al.* (2011). Calcinosis cutis: part I. Diagnostic pathway. *J Am Acad Dermatol*, 65, 1–12.

Robinson, M. R., Routhouska, S. B., Paspulati, R. M., *et al.* (2011). Alefacept therapy for nephrogenic systemic fibrosis: a case series. *J Drugs Dermatol*, 10, 922–4.

Ross, E. A. (2011). Evolution of treatment strategies for calciphylaxis. *Am J Nephrol*, 34, 460–7.

Shmidt, E., Murthy, N. S., Knudsen, J. M., *et al.* (2012). Net-like pattern of calcification on plain soft-tissue radiographs in patients with calciphylaxis. *J Am Acad Dermatol*, 67, 1296–301.

Sowers, K. M. and Hayden, M. R. (2010). Calcific uremic arteriolopathy: pathophysiology, reactive oxygen species and therapeutic approaches. *Oxid Med Cell Longev*, 3, 109–21.

Vedvyas, C., Winterfield, L. S., and Vleugels, R. A. (2012). Calciphylaxis: a systematic review of existing and emerging therapies. *J Am Acad Dermatol*, 67, e253–60.

Wang, H. and Yosipovitch, G. (2010). New insights into the pathophysiology and treatment of chronic itch in patients with end-stage renal disease, chronic liver disease, and lymphoma. *Int J Dermatol*, 49, 1–11.

Weenig, R. H. (2008). Pathogenesis of calciphylaxis: Hans Selye to nuclear factor kappa-B. *J Am Acad Dermatol*, 58, 458–71.

Zou, Z., Zhang, H. L., Roditi, G. H., *et al*. (2011). Nephrogenic systemic fibrosis: review of 370 biopsy-confirmed cases. *JACC Cardiovasc Imaging*, 4, 1206–16.

CHAPTER 132

The patient with reduced renal function: endocrinology

Tomas Thor Agustsson and Paul Carroll

Effects of reduced renal function on hormonal concentration and function

Over a century ago, Starling coined the term 'hormone' for the first time when describing the role of secretin in the control of pancreatic secretion (Bayliss and Starling, 1902). Although advances in biochemistry, physiology, cell biology, molecular biology, and genetics have since then explained many of the mechanisms of endocrine disease and hormone function, the essential subject of endocrinology remains the same—the signalling, by secreted substances, which control and coordinate the function of multiple organs and processes. These processes affect both the precise short-term control of whole-body homeostasis and longer-term adaptation and developmental changes.

Effects on hormonal concentration

Most endocrine systems are tightly regulated in a cascade-like manner involving multiple-level feedback loops to attain circulating hormone levels that are most conducive to eliciting the appropriate target tissue response (Fig. 132.1). Thus circulating hormone concentrations are a function of the efficacy of these control mechanisms, glandular secretion patterns, and clearance rates. Reduced renal function and uraemia can interfere with all of these factors and cause significant derangements, which are often challenging to detect and interpret.

Effects on hormonal secretion

Reduced renal function alters metabolic and biochemical states resulting in appropriate responses to secretory stimuli with consequent changes in hormonal concentration. A good example is secondary hyperparathyroidism related to hypocalcaemia in renal failure.

The kidney itself is an important endocrine organ and is responsible for the secretion of erythropoietin (involved in the regulation of red cell production) and 1,25-dihydroxy vitamin D_3 ((1,25 $(OH)_2D_3$) involved in calcium and bone metabolism. Reduced secretion of these hormones follows reduced functional renal mass in progressive renal failure.

The most common effect of reduced renal function on other endocrine organs is one of reduced secretion. This effect can be caused by direct toxic effects on the endocrine gland, reduced stimulation from the superior part of the hormonal axis, or hyporesponsiveness of the gland. Hypersecretion is less common but has been described. Hyperprolactinaemia in renal failure is, for example, partly caused by increased production (as well as reduced renal clearance), most likely related to changes in hypothalamic function and reduced dopamine production.

Effects on hormone clearance and metabolism

The kidney plays a key role in the catabolism of many polypeptide hormones, which therefore accumulate in renal failure.

At least one- to two-thirds of the metabolic clearance of various polypeptide hormones is handled by the kidney. In early renal impairment, hormone clearance declines in parallel with renal blood flow, but as renal failure progresses, peritubular uptake decreases causing a disproportionate increase in serum concentrations.

Extrarenal catabolism and elimination of hormones can also be affected, especially in prolonged uraemia. There is some older experimental evidence to suggest that breakdown of insulin in skeletal muscle is reduced (Rabkin et al., 1979), and hepatic catabolism of biologically active parathyroid hormone (PTH) is impaired (Hruska et al., 1981).

Effects on hormonal action

Various factors affected by renal function other than the circulating concentration can influence the function and effect of hormones.

Impaired activation of precursors

Many biologically active hormones are products of prohormones. These are sometimes elevated in renal failure indicating less effective conversion or activation. Pro-insulin is, for example, not converted peripherally to insulin and C-peptide in end-stage renal failure (Zilker et al., 1988). The effects of impaired renal function to reduce the peripheral conversion of thyroxine (T_4) to the more biologically active triiodothyronine (T_3) are also well described (Lim et al., 1977).

Multimolecular forms of variable bioactivity

Abnormalities in the metabolism of carbohydrates, lipids, and proteins are well documented in chronic renal failure. In 1983, Kishore et al. described the abnormal glycosylation and sialylation of serum proteins in chronic renal failure (Kishore et al., 1983). Such abnormalities can lead to changes in the relative concentration of different bioactive forms of a hormone, and change their excretion rate, thereby shifting the balance towards a less or even a more active form (Schaefer et al., 1991).

Hormone binding to plasma proteins

In plasma, most hormones are to varying degrees bound to proteins. These binding proteins can change the action of the hormone

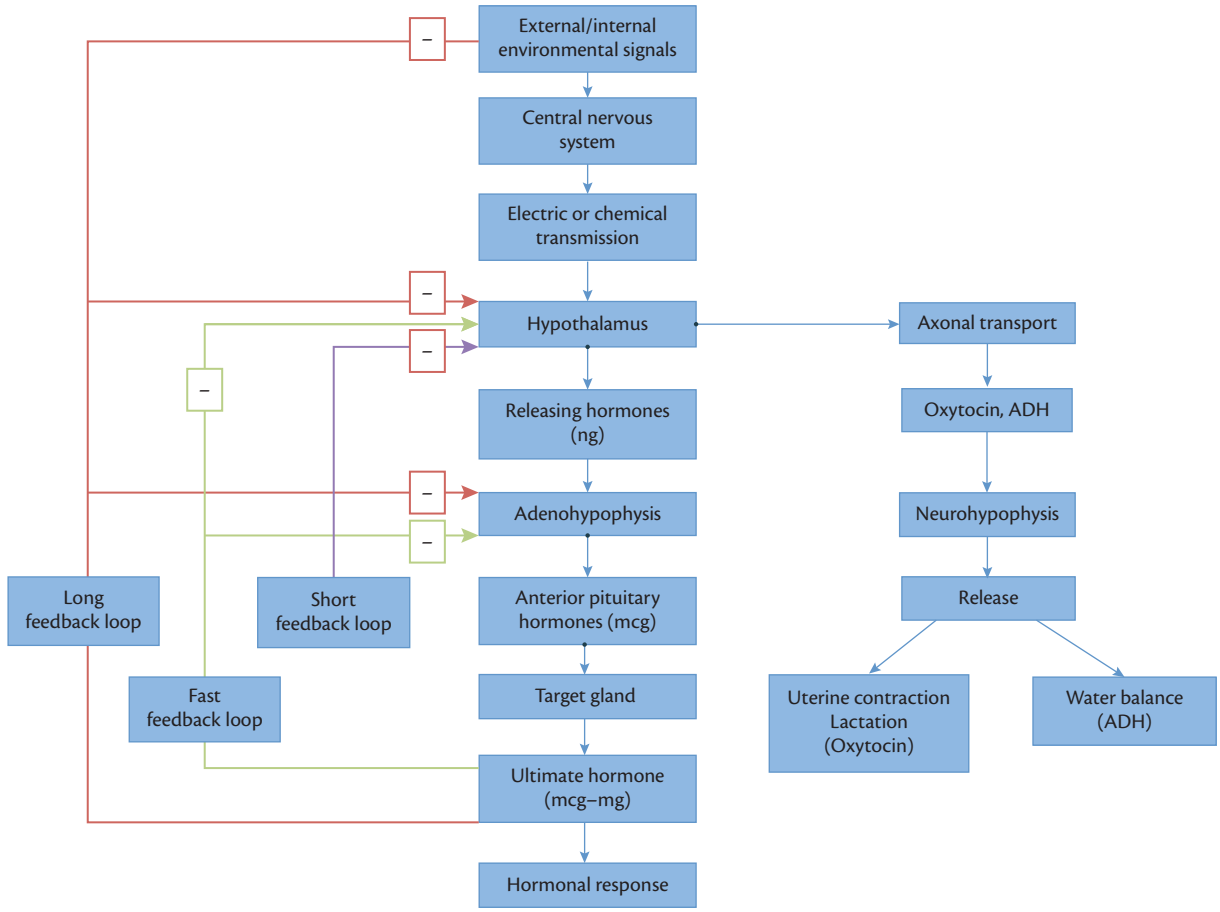


Fig. 132.1 Peripheral feedback mechanism and the million-fold amplifying cascade of hormonal signals. Environmental signals are transmitted to the central nervous system, which innervates the hypothalamus, which responds by secreting nanogram amounts of a specific hormone. Releasing hormones are transported down a closed portal system pass the blood–brain barrier at either end through fenestrations, and bind to specific anterior pituitary cell membrane receptors to elicit secretion of micrograms of specific anterior pituitary hormones. These enter the venous circulation through fenestrated local capillaries, bind to specific target gland receptors, trigger release of micrograms to milligrams of daily hormone amounts, and elicit responses by binding to receptors in distal target tissues. Peripheral hormone receptors enable widespread cell signalling by a single initiating environmental signal, thus facilitating intimate homeostatic association with the external environment. Arrows with a dot at the start indicate a secretory process.
Reproduced from Norman and Litwack (1997).

by competing at the receptor site or by affecting circulating concentrations of bioactive free hormone. The concentration of a number of insulin-like growth factor 1 (IGF-1) binding proteins with such inhibitory effect are for example raised in renal failure affecting its function (Lee et al., 1989; Blum et al., 1991; Tönshoff et al., 1996; Ulinski et al., 2000).

Changes in target tissue sensitivity

Target organ responsiveness to hormonal action can be affected by impaired renal function. The result is most often a reduced response, which can be caused by a number of factors:

1. Accumulation of competing or inhibiting molecules or toxins at the receptor level
2. The presence of molecules inhibiting or affecting active hormone concentrations, for example, the above mentioned IGF-1 binding proteins (Blum et al., 1991)
3. Structural changes in the hormone itself or its receptors, for example, by changes in glycosylation and sialylation (Kishore et al., 1993)
4. Changes in intracellular or post-receptor events. This is an increasingly recognized mechanism for increased hormone resistance in uraemia. Perhaps the best described example is the effect on the JAK2 and STAT signal transducing proteins in response to growth hormone (Fig. 132.2) (Schaefer et al., 2001; Rabkin et al., 2005).

Hypothalamic function and appetite control in reduced renal function

The hypothalamus plays a central role in the endocrine system. With its interplay with the pituitary, it organizes the appropriate hormonal responses to stimuli from higher centres, which arise from changes in the external environment. These range from alteration in the supply of nutrients and ambient temperature to challenges that result in physical or psychological stress. Secretion of most of the hormones from the anterior pituitary is stimulated by peptide-releasing hormones, which are secreted from the hypothalamus directly into the adenohypophyseal portal circulation.

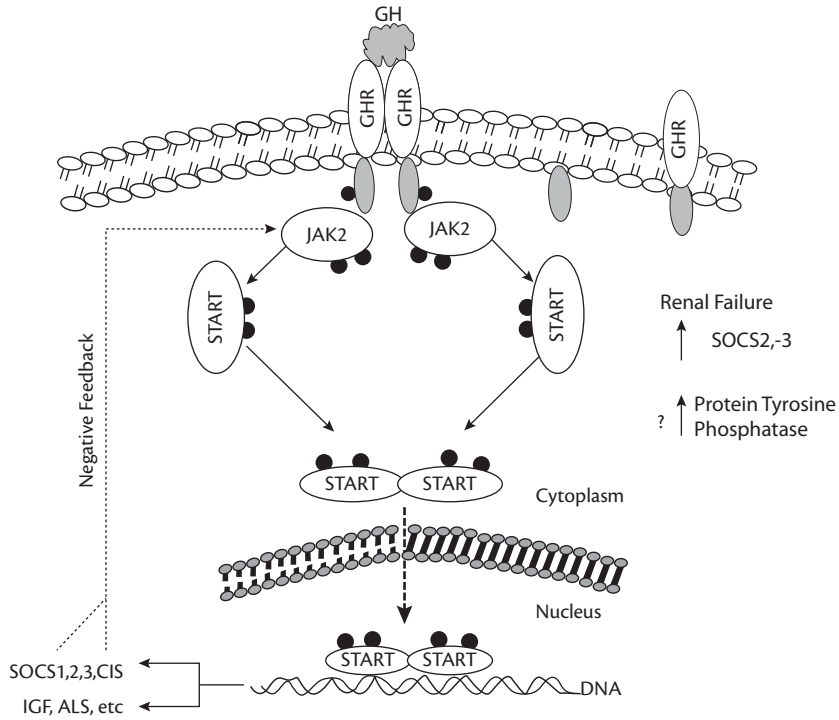


Fig. 132.2 Growth hormone-mediated JAK2/STAT signal transduction and changes in uraemia. GH activates several signalling pathways via JAK2, including the JAK/STAT pathways. Binding of GH to its receptor (GHR) activates JAK2, which then self-phosphorylates. This is followed by phosphorylation of the GHR and, subsequently, STAT 1a, STAT 3, STAT 5a, and STAT 5b, members of a larger family of cytoplasmic transcription factors. These phosphorylated STATs form dimers that enter the nucleus, where they bind to specific DNA sequences and activate their target genes, IGF-1 and some suppressors of cytokine signalling (SOCS). Deletion of STAT5 expression leads to retarded body growth, and STAT5b is required for GH-mediated IGF-1 gene expression. In renal failure phosphorylation of JAK2 and the downstream signalling molecules STAT5, STAT3, and STAT1 is impaired, as are the nuclear levels of phosphorylated STAT proteins. This important cause of uraemic GH resistance may result, in part, from upregulation of SOCS2 and SOCS3 expression with suppressed GH signalling and also from increased protein tyrosine phosphatase activity, with enhanced dephosphorylation and deactivation of the signalling proteins.
Adapted from Rabkin et al. (2005).

The hypothalamus is also under negative feedback control by hormones secreted by the target organ (Fig. 132.1).

Oxytocin and antidiuretic hormone (ADH) are synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and secreted from the posterior pituitary after being transported to the terminal of the nerve fibres. Oxytocin is produced in response to suckling of the nipple and stretching of the cervix, while ADH is produced in response to changes in water balance (Fig 132.1). These effects are covered in other chapters (see Chapter 22).

The effects of reduced renal function on the production of different pituitary hormones will be discussed in respective chapters but several studies have shown direct effects on the hypothalamus.

Considering the negative impact of anorexia and malnutrition on morbidity and mortality in chronic renal failure (Qureshi et al., 1998; Kopple, 1999; Kopple et al., 2000; Pupim et al., 2002) there has been considerable interest in the role of appetite hormones and hypothalamic control in this state.

Leptin is a small peptide hormone that is mainly, but not exclusively, produced in adipose tissue. The circulating leptin concentration therefore directly reflects the amount of body fat. Leptin has a pivotal role in regulating food intake and energy expenditure, by binding to its receptors in the hypothalamus and through the release of other neurotransmitters. Moreover, leptin exerts several other important metabolic effects on peripheral tissue, including modification of insulin action, induction of angiogenesis, and modulation of the immune system. Leptin levels have been found to be elevated in chronic renal impairment and may contribute to loss of appetite and cachexia (Heimbürger et al., 1997; Sharma et al., 1997; Landt et al., 1998). The exact role of leptin in renal anorexia and cachexia remains to be characterized further.

Ghrelin is another hormone secreted from the stomach and pancreas (Kojima et al., 1991) involved in appetite regulation. It can act as a signal for meal initiation and plays a role in the regulation of gastrointestinal motility via a hypothalamic circuit. Studies have shown that impaired expression of ghrelin and its hypothalamic receptors in renal failure, may play a role in uraemic anorexia (Fu et al., 2012, 2013). Recent studies have also indicated that links between low ghrelin concentrations and increased cardiovascular risk and inflammation in protein-energy wasted haemodialysis patients (Chou et al., 2010; Carrero et al., 2011a).

Changes to hypothalamic function and appetite control in reduced renal function are multifactorial and remain to be fully explained. In addition to the above described hormonal interplay, they are affected by inflammation, cytokine release, and input from higher centres. Implications for new treatment modalities are being explored.

Pituitary function in reduced renal function

The anterior pituitary gland secretes a number of hormones involved in bodily homeostasis, metabolism, and development. These include:

- prolactin
- growth hormone (GH)
- thyroid stimulating hormone (TSH)
- adrenocorticotrophic hormone (ACTH)
- the gonadotrophins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Once secreted into the circulation they interact with their target tissues, which are stimulated to secrete further hormones that feed back to inhibit release of the pituitary hormones (Fig 132.1). Where the target tissue does not produce a circulating hormone, such as in the case of prolactin, pituitary secretion is controlled by inhibitors. Prolactin is under inhibitory control of dopamine, but more complex releasing and inhibiting hormones control GH release.

Prolactin

Monomeric human prolactin consists of 199 amino acids. The most obvious and perhaps main action of prolactin is to stimulate lactation in the postpartum period. It also interferes with the hypothalamo–pituitary–gonadal axis causing reduction in the secretion of gonadotrophins. Hyperprolactinaemia can therefore cause gynaecomastia in men and galactorrhoea in both men and women, and sexual dysfunction and infertility. At least 300 other less well characterized potential functions of prolactin have been described.

A large proportion of dialysis patients have hyperprolactinaemia related to their renal failure (Bommer et al., 1979; Lim et al., 1979; Muir et al., 1983). Its prevalence varies from 16–20% in patients with moderate renal insufficiency to 35–80% in end-stage renal disease (ESRD) or dialysed patients (Lim et al., 1979; Cowden et al., 1981; Díez et al., 1995). Three molecular forms of prolactin with molecular weights of 23 (monomeric), 50–60, and > 100 kDa (macroprolactin) have been defined. All forms have been shown to increase in renal failure (Sari et al., 2012).

Hyperprolactinaemia is usually of modest magnitude and is due to a combination of reduced clearance and increased secretion (Sievertsen et al., 1980). In mild to moderate CKD, prolactin levels are usually < 100 ng/mL. In dialysis patients, serum prolactin levels > 100 ng/mL are found in 14% of cases, sometimes reaching 300–400 ng/mL (Iglesias et al., 2012). A primary mechanism seems to be inadequate dopaminergic inhibition leading to increased prolactin secretion (Lim et al., 1979). Hyperprolactinaemia in uraemic patients can be suppressed by chronic dopaminergic stimulation (Bommer et al., 1979; Muir et al., 1983). Prolactin response to well-known stimuli such as thyrotrophin-releasing hormone (TRH), chlorpromazine, metoclopramide, and arginine or to insulin-induced hypoglycaemia is, on the other hand, blunted (Ramirez et al., 1977; Schmitz and Møller, 1983; Rodger et al., 1986). There is therefore increased tonic background secretion with blunted response to more short-term stimuli. In renal failure the normal diurnal rhythm with sleep-induced nocturnal secretory bursts is also not found, although some episodic secretion occurs during the daytime (Biasioli et al., 1988).

Hyperprolactinaemia negatively affects gonadal function. Prolactin inhibits gonadotropin-releasing hormone (GnRH) pulsatile secretion at the hypothalamus (Milenković et al., 1994) and suppresses both the normal pulsatile secretion of LH and FSH and their pituitary responsiveness to GnRH by a direct action at the anterior pituitary (Cheung, 1983). In addition, hyperprolactinaemia inhibits the positive feedback effect of oestrogen on gonadotropin secretion (McNeilly, 1980). Although the relationship between hyperprolactinaemia and signs and symptoms of hypogonadism and infertility in both sexes with normal renal function is well described (Franks et al., 1978; Spark et al., 1982) these mechanisms may not be as simple in renal failure and the pathogenesis of these features are more multifactorial. The GnRH release in uraemic patients with hyperprolactinaemia is, for example, blunted, but the reduced peripheral clearance of LH prevents the association of hyperprolactinaemia with low LH levels.

Hyperprolactinaemia does not seem to be affected by dialysis, but studies have shown that hyperprolactinaemia induced by uraemia is corrected following successful transplantation and the hypothalamo–pituitary–gonadal axis is restored (Lim et al., 1979; Peces et al., 1981; Rodríguez-Puyol et al., 1986; Grzeszczak et al., 1990; Saha et al., 2002).

Growth hormone

GH is a 191-amino acid, single-chain polypeptide hormone, which is synthesized, stored, and secreted by somatotropic cells of the anterior pituitary and plays a key role in normal growth and development in childhood. GH continues to be secreted in adulthood after growth cessation, implying important metabolic functions in adult life. Over the last decades our understanding of its importance throughout the entire lifespan has increased significantly. GH has an important function in carbohydrate metabolism where chronic GH exposure exerts potent anti-insulin effects at hepatic and peripheral sites, resulting in decreased glucose utilization, increased lipolysis, and tissue refractoriness of the acute insulin-like effects of GH. It is an anabolic hormone and causes urinary nitrogen retention, decreased plasma urea levels, and increased muscle mass. GH increases fat mobilization, decreases fat deposition, and activates hormone-sensitive lipase, resulting in increased lipolysis.

IGF-1, a critical growth factor induced by GH, is likely responsible for many of the growth-promoting activities of GH (Le Roith et al., 2001) and it also directly regulates GH receptor function (Leung et al., 1997). IGF-1 also has important paracrine activity in extrahepatic tissues which appear critical for normal growth (Yakar et al., 1999).

Growth hormone secretion, concentrations, and clearance in impaired renal function

Fasting GH concentrations are elevated in children and adults with impaired renal function. This increase is in proportion to the extent of renal failure (Davidson et al., 1976; Ramirez et al., 1978). Basal GH concentrations and glucose or tolbutamide stimulated responses do not seem related to the nutritional state in uraemic patients (Allegra et al., 1988). Changes in GH concentrations and dynamics in renal failure are due to complex changes in both GH secretion and impaired clearance.

The kidney plays a key role in GH catabolism (Johnson and Maack, 1977). The clearance rate of GH is reduced by approximately 50% in end-stage renal failure (Haffner et al., 1994). The increased

half-life of circulating GH both increases its basal concentration, and affects secretory and feedback mechanisms.

Most studies have shown increased secretion rates for GH in both children and adults with renal failure. Tönshoff et al. found a high-normal calculated GH secretion rate and an amplified number of GH secretory bursts in prepubertal children with ESRD, and postulated a relationship with attenuated pituitary feedback of bioactive IGF-1 (Tönshoff et al., 1995b). Veldhuis et al. identified elevated GH secretion rates in adults on haemodialysis (Veldhuis et al., 1994). GH secretion in pubertal patients with advanced renal impairment has, on the other hand, been found to be reduced (Schaefer et al., 1994). This may be because of altered somatotroph sensitivity of sex hormones, which are important for increased GH secretion during this stage.

Some work has been done to identify the underlying mechanisms for these alterations in secretion rates, focusing mainly on hypothalamo–pituitary control. At least in children with renal failure, the GH response to intravenous GH-releasing hormone is augmented and prolonged (Bessarione et al., 1987). In normal renal function TRH does not affect GH secretion to any significant extent. Studies have shown a marked increase in GH secretion in response to exogenous TRH (Ramirez et al., 1978; Weissel et al., 1979; Giordano et al., 1984). GH response to common dynamic stimulation tests is also altered in uraemia. Induced hypoglycaemia causes a sustained exaggerated GH rise, which is more pronounced in patients on haemodialysis than continuous ambulatory peritoneal dialysis (CAPD) (Ramirez et al., 1978; Marumo et al., 1979; Rodger et al., 1986). Acute hyperglycaemia, which normally causes GH suppression, is related to a paradoxical GH increase in uraemia (Ramirez et al., 1978; Alvestrand et al., 1989). Interpretations of these results is challenging as the concentration of releasing factors and provocative agents is also affected by changes in renal function.

Two high- and low-affinity circulating growth hormone binding proteins (GHBPs) are a 20-kDa low-affinity binding protein and a 60-kDa high-affinity binding protein, the latter of which corresponds to the extracellular domain of the hepatic GH receptor and binds half of circulating GH (Herington et al., 1986; Leung et al., 1987). Concentrations of these high-affinity binding proteins have been found to be low in patients with chronic renal impairment (Baumann et al., 1989; Postel-Vinay et al., 1991). Concentrations of the high-affinity binding protein have been associated with GH receptor expression (Leung et al., 1987), and low concentrations are usually found in relative GH resistance. Elevated circulating GH and low concentrations of competing binding proteins may result in increased free GH at the receptor site, but studies showing impaired intracellular signalling in response to GH indicate impaired intracellular signal transduction (Schaefer et al., 2001).

IGF-1 and other growth factors in impaired renal function

Plasma concentrations and bioactivity of IGF-1 and other growth factors, which mediate the effects of GH, are also affected by changes in renal function. Serum IGF-1 and IGF-2 levels in children with preterminal chronic renal failure are in the normal range, whereas in ESRD mean age-related serum IGF-1 levels are slightly, but significantly decreased and IGF-2 levels slightly but significantly elevated (Tönshoff et al., 1995a, 1996). As for GH, measured immunoreactive IGF is therefore near-normal in renal impairment, but studies have indicated that bioactivity is significantly reduced and meaningful interpretation of measured values can be challenging. Levels of free IGF-1 are reduced by 50% in relation to the degree of renal dysfunction (Frystyk et al., 1999). The same researchers have also shown the hepatic sensitivity to GH to be reduced by 50% in end-stage renal failure (Frystyk et al., 2012).

This discrepancy between low growth factor activity by bioassay and normal or even elevated IGF and GH by radioimmunoassay or radioreceptor assay suggest either the presence of a circulating inhibitor, changes in protein binding in plasma, altered receptor function, or impaired function of intracellular signal transduction pathways.

Six insulin-like growth factor-binding proteins have been identified in humans (IGFBP1–6). Of these IGFBP3 seems to be the most abundant, constituting > 95% of all circulating IGFBPs. In children with chronic renal failure the serum concentrations of IGFBP1, IGFBP2, IGFBP4, and IGFBP6 are increased (Lee et al., 1989; Blum et al., 1991; Tönshoff et al., 1995a; Powell et al., 1997a, 1999). Intact IGFBP3 (38 and 41 kDa) is, on the other hand, reduced in uraemia. The apparent increase in IGFBP3 on radioimmunoassay is due to increased low-molecular-weight IGFBP3 (14–19 kDa) with altered function (Liu et al., 1990; Lee et al., 1994). IGFBP1, IGFBP2, and IGFBP6 inhibit IGF-1 bioactivity *in vitro*, while the relationship to IGFBP3 is more complex (Kiepe et al., 2002). These inhibitory effects can be reduced by removing unsaturated IGFBP from serum (Blum et al., 1991). Some work has been done to determine what effects changes in IGFBP concentrations have on growth in children with renal failure. Serum levels of IGFBP1, IGFBP2, and IGFBP4 correlate significantly and inversely with standardized height in children with renal failure, indicating a role in growth failure in this setting (Tönshoff et al., 1995a; Powell et al., 1997a; Ulinski et al., 2000). The relationship with IGFBP3 is more complex. Normally there is a positive correlation between IGFBP3 levels and height in children. In chronic renal failure there is neither a positive nor a clear negative correlation. Studies have shown the effects on IGF-1 bioactivity in renal failure to depend on the temporal relationship to IGF-1 exposure, which may explain this. GH therapy in children with chronic renal failure is known to elevate intact IGFBP3 where it is related to improved growth (Powell et al., 1997b).

These various effects of chronic renal failure on GH production and function are summarized in Fig. 132.3.

Growth hormone therapy in impaired renal function

As detailed above, average circulating GH concentrations are high in chronic renal failure but biological activity of growth factors, such as IGF-1, is low due to a number of factors. Delayed growth and reduced final height are well-known complications of renal failure in children. Therapy with pharmacological doses of recombinant GH has had significant interest in the last few decades. Early studies confirmed marked stimulation of growth with such treatment (Tönshoff et al., 1990). In addition to improved height, treatment with GH has shown improved concomitantly bone modelling/remodelling, which appears beneficial for bone matrix mineralization in this setting (Nawrot-Wawrzyniak et al., 2013).

As mentioned previously, impaired growth in children with renal failure is multifactorial, and care must be taken to address all possible contributing factors. Failure to achieve adequate height despite optimal medical therapy is now considered an indication for GH therapy (Mahan and Warady, 2006). Studies have confirmed the efficacy of such treatment, both in children on dialysis and kidney transplant recipients, with regards to height and other parameters

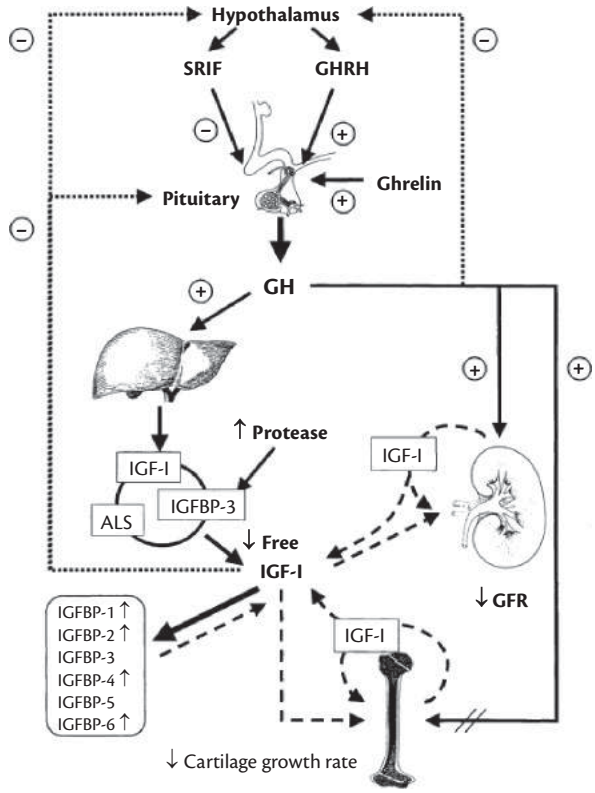


Fig. 132.3 Deranged growth hormone/IGF-1 axis in CKD. The GH/IGF-I axis in chronic renal failure (CRF) is changed markedly, compared with the normal axis shown here. In CRF the total concentrations of the hormones in the GH/IGF-I axis are not reduced, but there is reduced effectiveness of endogenous GH and IGF-I, which probably plays a major role in reducing linear bone growth. The reduced effectiveness of endogenous IGF-I likely is due to decreased levels of free, bioactive IGF-I as levels of circulating inhibitory IGF-binding proteins (*IGFBPs*) are increased. In addition, less IGF-I is circulating in the complex with acid labile subunit (ALS) and IGFBP-3 as a result of increased proteolysis of IGFBP-3. Together, these lead to decreased IGF-I receptor activation and a decreased feedback to the hypothalamus and pituitary. Low free IGF-I and high IGFBP-1 and IGFBP-2 levels probably contribute to reduced renal function and lead to reduced stature. The direct effects of GH on bone, which are poorly understood, also are blunted. Reproduced from Roelfsema and Clark (2001).

such as body weight, muscle mass, and psychological health without any concerns about safety (Hokken-Koelega et al., 1991; Fine et al., 1994, 1996; Postlethwaite et al., 1998; Haffner Schaefer, 2001; Vimalachandra et al., 2001; Nissel et al., 2008; Seikaly et al., 2009; Müller-Wiefel et al., 2010; Santos et al., 2010; Van den Heijkant et al., 2011). More recent reviews have shown an increased incidence of intracranial hypertension amongst children treated with GH who have renal impairment, which underlines the importance of careful monitoring during treatment (Noto et al., 2011).

Studies in adults with ESRD indicate that GH may stimulate anabolism and improve indicators of body composition known to be associated with increased survival. These include decreased net urea production and/or serum urea, and sometimes phosphate and potassium (Ziegler et al., 1991; Ikizler et al., 1994; Iglesias et al., 1998; Kopple et al., 2005). Metabolic studies have also indicated increased protein synthesis and more positive protein or nitrogen balance (Garibotto et al., 1997; Kopple et al., 2005; Pupim et al., 2005). Mild hyperglycaemia occurred in some short-term studies (Iglesias et al., 1998; Ikizler et al., 1994). Most longer-term studies showed some increase in muscle mass, decrease in fat mass, and new bone formation (Jensen et al., 1999; Johannsson et al., 1999; Hansen et al., 2000; Kotzmann et al., 2001). GH was also found to increase serum erythropoietin, leptin, IGF-1, and IGFBP3, increase target organ sensitivity to PTH and bone mineral density in GH-deficient patients, and reduce serum PTH levels (Ziegler et al., 1991; Sohmiya et al., 1998; Iglesias et al., 2002; Kopple et al., 2005; White et al., 2005, 2007; Joseph et al., 2008). The role of GH therapy in chronic renal failure may therefore be expanding, but larger controlled trials are needed to substantiate this, particularly in adults. In the United Kingdom and other countries GH is licensed for use in pre-pubertal children provided nutrition and steroid use, along with stabilization of other medical issues has been achieved. The goals of therapy are to maintain muscle mass, well-being and maximize linear growth.

GH therapy has been shown to increase renal plasma flow and glomerular filtration rate (GFR) in healthy individuals (Christiansen et al., 1981). This observation and postulated effects of renal hyperfiltration (Brenner et al., 1982) on the progression of renal failure led to concerns about long-term safety of GH therapy in children with chronic renal failure. There is both experimental evidence and evidence from clinical studies in men that in chronic renal failure GH therapy does not increase GFR (Haffner et al., 1989) with no confirmed effects on progression rates of renal failure (Seikaly et al., 2009).

Thyroid function in impaired renal function

The importance and complexity of the interactions between thyroid hormones and renal function have been recognized for decades (Feinstein et al., 1982; Kaptein et al., 1982, 1984). During growth, thyroid hormones are important for normal renal development (Bräunlich, 1984; Katyare et al., 2007; Gattineni et al., 2008). Thyroid hormones also have a role in maintaining normal renal function with their effects on water and electrolyte handling. The kidney, on the other hand, plays an important role in the metabolism of thyroid hormones. In renal failure there are significant changes in synthesis, secretion, metabolism, and elimination of thyroid hormones. The clinical characteristics and management of people with advanced kidney disease and thyroid dysfunction also warrant specific attention. It has also become increasingly important to recognize that modern treatments used for kidney disease can affect thyroid function, antithyroid drugs can affect renal function, and drugs used for other conditions can affect both organs.

Uraemia affects both the function and size of the thyroid. Uraemic patients have a higher prevalence of goitre, especially women, and an overall increase in thyroid volume (Ramirez et al., 1976; Lim et al., 1977; Hegedüs et al., 1985; Kaptein, 1996; Kutlay et al., 2005). Thyroid nodules and thyroid cancer also appears to be more common in people with chronic renal failure (Miki et al., 1992, 1993).

Functional thyroid disease is also observed more commonly in people with chronic renal failure. Both hypothyroidism and hyperthyroidism are associated with changes in renal perfusion and function, and water and electrolyte homeostasis (Table 132.1). Chronic renal failure is associated with a higher prevalence of both overt and subclinical hypothyroidism, but not hyperthyroidism (Kaptein et al., 1988; Kaptein, 1996; Kutlay et al., 2005; Lo et al., 2005). The prevalence of hypothyroidism in ESRD has been found

Table 132.1 Effects of thyroid dysfunction on the kidney

Hypothyroidism	Thyrotoxicosis
Increased serum creatinine	Decreased serum creatinine
Decreased glomerular filtration	Increased glomerular filtration
Decreased renal plasma flow	Increased renal plasma flow
Decreased sodium reabsorption	Increased tubular reabsorption
Decreased renal ability to dilute urine	Resistance to recombinant human erythropoietin action?
Hyponatraemia	

Adapted from Iglesias and Díez (2009).

to lie between 0% and 9.5%. Kaptein et al. described a 2.5-fold increase in primary hypothyroidism in dialysis patients compared with people with other chronic conditions (Kaptein et al., 1988). Hypothyroidism in uraemia is more common in women and is associated with an increased frequency of high antithyroid antibody titres (Kaptein, 1996). Lo et al. (2005) also showed the frequency of primary hypothyroidism, mainly in the subclinical form, increases as the GFR decreases. Such results may be difficult to interpret because the prevalence of other autoimmune conditions are higher in this patient group, which in itself infers a higher risk for thyroid disease.

The clinical assessment of thyroid status may be very challenging in the context of chronic renal failure. Many of the signs and symptoms, such as lethargy, pallor, and hypothermia, may be indistinguishable. Biochemical assessment and careful interpretation is therefore necessary.

Thyroid function is affected in several different ways in chronic renal failure (Fig. 132.4). In the following sections we will discuss effects on the hypothalamo–pituitary–thyroid axis and peripheral thyroid hormone metabolism separately.

The hypothalamo–pituitary–thyroid axis in impaired renal function

Renal failure affects secretory activity and responsiveness to stimulation and feedback inhibition in the hypothalamo–pituitary–thyroid axis at multiple levels. The result can be regarded as resetting of the central thyrostat towards lower circulating thyroid hormone concentrations.

In chronic renal failure, circulating TSH concentrations are usually normal or elevated, and several studies have confirmed a blunted response to its releasing hormone, TRH (Ramirez et al., 1976; Weetman et al., 1981; Kaptein, 1996; Singh et al., 2006; Witzke et al., 2007). Normal TSH in the face of the elevated free thyroid hormones, usually observed in renal failure, also indicates an intrapituitary and/or intrathyroidal disturbance in thyroid hormone secretory control. Studies in rodents have suggested impaired sensitivity of thyrotroph cells to negative feedback by thyroid hormones. The duration and temporal pattern of the TSH response is also altered because of the prolonged half-life of both TSH and TRH with impaired clearance (Davis et al., 1982; Duntas et al., 1992). Previous studies have suggested that although the basal production of thyroid hormones is low, the gland's responsiveness to exogenous TSH is preserved in renal failure (Silverberg et al., 1973).

The normal circadian rhythm of TSH secretion is disrupted in chronic renal failure, which also suggests a hypothalamic defect. The physiological nocturnal TSH surge is often blunted in these patients (Wheatley et al., 1989; Bartalena et al., 1990) and the usual pattern of pulsatile TSH secretion is altered towards low-amplitude, high-frequency pulses (Wheatley et al., 1989). TSH glycosylation is also altered, which may affect its bioactivity including during feedback inhibition (Kaptein, 1996).

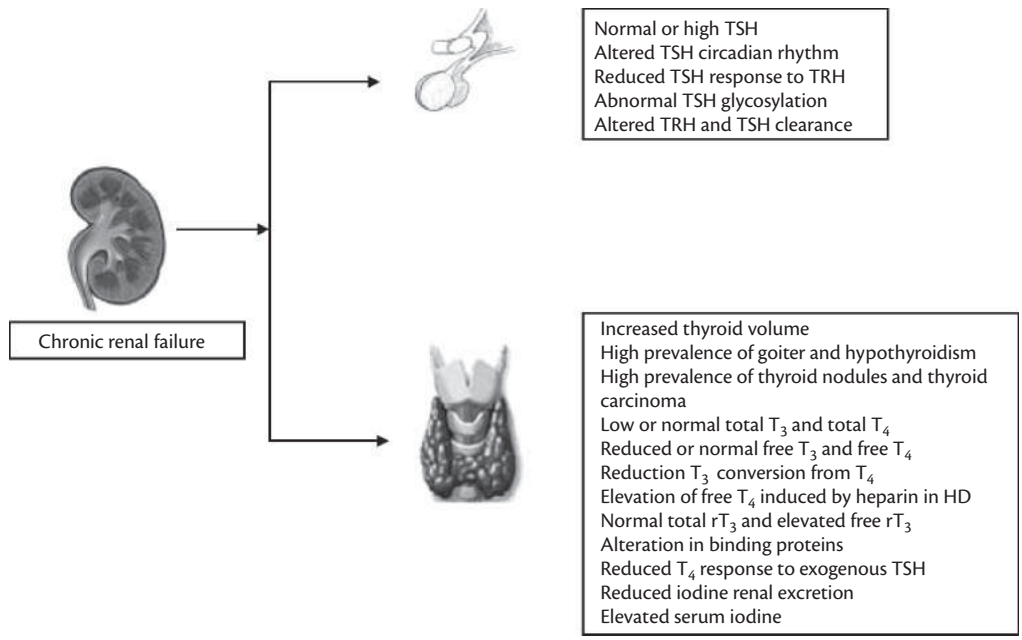


Fig. 132.4 Effects of chronic renal failure on hypothalamo–pituitary–thyroid axis.
Adapted from Iglesias and Díez (2009).

Thyroid hormone concentration and metabolism in impaired renal function

The kidneys contribute to the clearance of inorganic iodine, mainly through glomerular filtration (Koutras et al., 1972). As renal function deteriorates, serum iodine concentrations rise, but are not directly correlated to the degree of renal failure (Ramirez et al., 1976). A link between these high iodine concentrations in chronic renal failure and the development of goitre and hypothyroidism has been postulated (Sato et al., 1992; Kaptein, 1996), and high iodine exposure has been linked to the development of hypothyroidism in these patients (Brough and Jones, 2006). Some authors have even suggested treating hypothyroidism in dialysis patients primarily with iodine restriction before considering T_4 replacement (Sanai et al., 2008).

Free and total T_3 and T_4 concentrations are usually normal or low in patients with chronic renal failure (Ramirez et al., 1976; Lim et al., 1977; Hegedüs et al., 1985; Kaptein et al., 1988; Kaptein, 1996; Singh et al., 2006). The most frequently observed change is relative or absolute reduction in T_3 concentrations, which has been linked to decreased peripheral synthesis of T_3 from T_4 (Lim et al., 1977; Kaptein et al., 1988; Kaptein, 1996; Lo et al., 2005; Singh et al., 2006; Lim, 2001; Witzke et al., 2007). Several factors, including malnutrition and intercurrrent processes, may play a role in reduced T_3 production in uraemic patients. Both fasting and chronic disease are known to alter iodothyronine deiodination and reduce peripheral production of T_3. Binding proteins are reduced because of chronic protein malnutrition causing reduced total thyroid hormone concentrations. Inflammatory cytokines, such as tumour necrosis factor alpha and interleukin 1 have been shown to inhibit the expression of type 1 5′-deiodinase, the enzyme responsible for T_3 conversion from T_4 in peripheral tissue. This may explain how chronic inflammation and vascular damage associated with uraemia lead to reduced T_3 production (Zoccali et al., 2005, 2006; Tauchmanovà et al., 2006; Carrero et al., 2007; Enia et al., 2007). Chronic metabolic acidosis may also contribute to this effect (Wiederkehr et al., 2004).

Table 132.2 Changes in thyroid hormone concentrations in ESRD, primary hypothyroidism, and other chronic non-thyroidal illness ('sick euthyroid syndrome')

	ESRD	Primary hypothyroidism	'Sick euthyroid'
Total T_3	↓	↓	↓
Total T_4	↓	↓	↓
Reverse T_3	=	↓	↑
Reverse T_3	↓	↓	↓
Free T_4	↓	↓	↓
TBG	CAPD: ↓ HD: =	=	=
TSH	=	↑	=
TRH test	= or ↓	↑	=

CAPD: continuous ambulatory peritoneal dialysis; HD: haemodialysis; TBG: thyroid binding globulin; TRH: thyrotrophin-releasing hormone; TSH: thyroid stimulating hormone.

Reverse T_3 (rT_3) is an inactive metabolite of thyroid hormone which is typically raised in patients with non-thyroidal disease. This rise in total rT_3 is absent in chronic renal failure (Kaptein et al., 1983; Adler and Wartofsky, 2007). As for other thyroid hormones, rT_3 clearance is reduced in renal failure, but there is redistribution from the vascular to the extravascular space and an increase in rT_3 cellular uptake. Measured free rT_3 is usually high due to a reduction in its renal clearance (Kaptein et al., 1983; Kaptein, 1996).

The majority of thyroid hormones are bound to proteins in plasma with only a very small fraction circulating free. Only free T_4 (fT_4) and free T_3 (fT_3) are biologically active. The binding proteins include thyroid hormone binding globulin, albumin, and pre-albumin. Changes in the concentrations of these binding proteins can affect the measured values of thyroid hormones and the bioactive fraction. Measurement of free thyroid hormone by radioimmunoassay is now readily available. Thyroid hormone-binding globulin concentrations are usually normal in haemodialysis patients (Pagliacci et al., 1987) and low or normal in patients on CAPD (Pagliacci et al., 1987). In nephrotic syndrome there is significant loss of thyroxine binding proteins. Measured total thyroid hormones are therefore reduced, but free hormones are usually within the normal reference range (Feinstein et al., 1982). Patients with such protein loss who receive thyroxine replacement therapy may require significantly larger doses to compensate for this loss while maintaining euthyroidism.

The characteristic changes of the thyroidal axis in uraemia, primary hypothyroidism, and other states of chronic illness are compared in Table 132.1. Chronic non-thyroidal diseases are characterized by a low T_3 syndrome (Table 132.2). In this so-called sick euthyroid syndrome increased rT_3 results from impaired peripheral conversion of T_4 to T_3. In chronic renal failure, T_3 is low as in the low T_3 syndrome, but rT_3 is normal or even low as explained above.

Thyroid hormone activity, morbidity, and mortality in impaired renal function

As discussed earlier, the clinical assessment of thyroid status in chronic renal failure can be challenging, but patients often appear euthyroid. Normal or near-normal TSH production also suggests euthyroidism at the pituitary level.

There has been some debate about the role of thyroid hormones and the potential effects of thyroid replacement therapy on nitrogen balance and cachexia in chronic renal failure. Serum T_3 is inversely related to serum protein concentrations. Maintaining a lower T_3 may therefore be of benefit by reducing protein breakdown (Verger et al., 1987). Earlier studies also showed T_3 supplementation to result in negative nitrogen balance in uraemic patients (Lim, 2001). These observations led to the believe that the low circulating thyroid hormones in chronic renal failure represented adaptation to this abnormal metabolic milieu to protect from unwanted protein loss and thyroid hormone supplementation would be of little use and even harmful.

More recent work has changed this view by showing a relationship between plasma levels of T_3, and various markers of nutrition, inflammation, and endothelial activation in chronic renal failure (Carrero et al., 2007). These studies have shown a relationship between low T_3 values and raised inflammatory markers (e.g. high-sensitivity C-reactive protein, interleukin 6, vascular adhesion molecule 1), and poor cardiac function. This means that low T_3 is in fact associated with a survival disadvantage. Similar relationships

with T_4 are less well described. The same study showed a correlation between total T_3 and increased all-cause and cardiac mortality in euthyroid patients with chronic renal failure. T_3 has been found to be a survival marker for patients with chronic renal failure both on dialysis (Zoccali et al., 2006; Zoccali and Mallamaci, 2012) and peritoneal dialysis (Enia et al., 2007). Low levels of T_3 before renal transplantation are also linked to decreased survival of the graft (Rotondi et al., 2008). Some authors therefore suggest measuring T_3 in these populations to assess the relationship between thyroid dysfunction and risk of mortality.

Clinical management of thyroid dysfunction in impaired renal function

The prevalence of hypothyroidism is increased in chronic renal failure and there are potential implications for excessive morbidity and mortality. The clinical diagnosis can be challenging. All patients with ESRD should therefore be screened for thyroid disease. Hypothyroidism should only be diagnosed if fT_4 and fT_3 are low and TSH is clearly elevated. If diagnosed, replacement therapy with regular monitoring is indicated.

Iodine clearance is reduced in chronic renal failure. Patients who receive large iodine loads related to repeated investigations involving contrast medium are therefore at increased risk of developing iodine related hyperthyroidism. Primary hyperthyroidism is very rare in patients with ESRD with only a few cases described in the literature (Soffer et al., 1980; Foley and Hamner, 1985; McKillop et al., 1985; Alarcon et al., 1992; Nibhanupudy et al., 1993). Treatment of thyrotoxicosis in these circumstances is challenging. Renal clearance of antithyroid drugs is reduced, radioiodine may also accumulate, and due to the expanded iodine pool in ESRD large doses must be used to affect thyroid function. A preferred method might therefore be thyroid surgery after a short period of antithyroid drug therapy.

Drugs in thyroid and renal disease

A number of drugs used in kidney disease can cause thyroid dysfunction and drugs used in thyroid disease can affect renal function (Tables 132.3 and 132.4). Hypothyroidism caused by antithyroid drug therapy (carbimazole, neo-mercazole, propylthiouracil) can contribute to renal failure. These drugs have also been shown to cause different immunological reactions leading to different types of glomerulonephritis causing renal failure (Wang et al., 2003; Calañas-Continente et al., 2005; Yu et al., 2007).

The development of autoimmune thyroid disease following use of immunomodulatory drugs in renal disease has become more common and better described with increased use of such agents (Table 132.3). Autoimmune thyroid disease can develop after use of alemtuzumab in transplant patients (Kirk et al., 2006). Treatment with interferon-α and lenalidomide in metastatic renal cell carcinoma has been linked to hyperthyroidism due to thyroiditis (Kirk et al., 2006; Umemoto et al., 2007). The use of sunitinib in the therapy for patients with metastatic renal cell cancer is also linked to the development of thyroid dysfunction, mainly hypothyroidism (Feldman et al., 2007; Rini et al., 2007), but thyrotoxicosis has also been described. The reason here is most likely transient destructive thyroiditis with subsequent hypothyroidism (Grossmann et al., 2008). This course is unpredictable though. Careful monitoring of thyroid function is indicated in these patients and thyroid hormone supplementation should be started only if true hypothyroidism is confirmed. Over the last decade there has been an expansion in the development of such immunomodulatory drugs which will inherently carry risks for the development of thyroid dysfunction. Careful monitoring and caution is therefore suggested.

Several drugs used in routine therapy of chronic renal failure can affect thyroid hormone measurements and kinetics. Heparin competes with T_4 at intra- and extravascular binding sites which leads to elevated measured total T_4 and fT_4. Heparin used during dialysis raises T_4 significantly for the following 24 hours (Van Leusen et al., 1982). Blood samples to assess thyroid function should therefore be drawn at the beginning of a dialysis session. Frusemide, especially in high doses, also has a similar effect (Liewendahl et al., 1987).

Adrenal function in impaired renal function

Glucocorticoid secretion and metabolism are altered in renal failure. Patients with kidney disease are often treated with exogenous steroids which also affect investigative results and complicate their interpretation. The signs and symptoms of both glucocorticoid excess and deficiency are also difficult to distinguish from those of uraemia. Glucocorticoid excess, or Cushing syndrome, can present with lethargy, proximal muscle weakness and atrophy, glucose intolerance, osteopenia, and hypertension, and can easily be missed in the context of chronic renal failure (Sharp et al., 1986). Adrenal insufficiency also shares many signs and symptoms with renal failure such as lethargy, hypotension, and hyperkalaemia. The accurate diagnosis of adrenal dysfunction therefore relies heavily on interpretation of both basal and stimulated cortisol status. This requires understanding of the changes in dynamics associated with renal failure.

Hypothalamo–pituitary–adrenal axis in impaired renal function

In a similar way to other endocrine systems described above, the hypothalamo–pituitary–adrenal axis is affected at multiple levels in uraemia, affecting both secretion and feedback control. Basal ACTH is within the appropriate reference range (Ramirez et al.,

Table 132.3 Drugs that can cause thyroid dysfunction and/or renal disease

Drug	Indication	Thyroid dysfunction	Renal disease
Antithyroid drugs	Hyperthyroidism	Hypothyroidism	Glomerulonephritis
Lithium	Bipolar disorder	Hypothyroidism	Nephrogenic diabetes insipidus
Amiodarone	Arrhythmias	Hypo/hyperthyroidism	Acute kidney injury
Rifampicin	Tuberculosis	Hyperthyroidism	Tubulointerstitial nephritis

Adapted from Iglesias and Díez (2009).

Table 132.4 Drugs used in kidney disease that can affect thyroid function

Drug	Indication	Thyroid pathology
Alemtuzumab	Renal transplant	Autoimmune thyroiditis
Lenalidomide	Metastatic renal cell carcinoma	Hyperthyroidism
Sunitinib	Metastatic renal cell carcinoma	Hypo/hyperthyroidism

Adapted from Iglesias and Díez (2009).

1988; Siamopoulos et al., 1988) or increased in uraemia (McDonald et al., 1979; Luger et al., 1987). Elevated ACTH in the context of normal or elevated cortisol has raised speculations around altered ACTH bioactivity in uraemia. Despite this, cortisol production in response to exogenous synthetic ACTH has been found to be normal in chronic renal failure (Zager et al., 1985; Oguz et al., 2003). Further research in this area is needed.

Cortisol concentration and metabolism in impaired renal function

Most studies have shown basal cortisol concentrations within the normal reference range in chronic renal failure, although results have been somewhat discrepant (Wallace et al., 1980; Nolan et al., 1981; Oguz et al., 2003). Cortisol is conjugated to water-soluble metabolites by the liver which are then excreted by the kidneys but accumulate in renal failure. This complexity may explain why experimental results have varied. Some studies have indicated that although basal morning cortisol is within the normal range, both integrated 24-hour total and free cortisol are significantly raised in uraemia (Wallace et al., 1980). Most circulating cortisol is bound to proteins, including corticosteroid binding globulin and albumin. Studies indicate that protein binding is not altered in renal failure (McDonald et al., 1979; Wallace et al., 1980), but availability of binding proteins may be altered with protein loss. The diurnal rhythm and pulsatile mode of cortisol secretion normally observed is retained in renal failure. This may not be obvious from measured values in plasma as half-life is prolonged (Cooke et al., 1979; Wallace et al., 1980; Ramirez et al., 1982).

The enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) converts cortisol to cortisone in the distal convoluted tubule and cortical collecting duct (Edwards et al., 1988). It is also expressed in the human glomerulus (Kataoka et al., 2002). In normal human subjects, renal 11β-HSD2 acts as a tissue-specific protector of the non-specific type 1 mineralocorticoid receptor in aldosterone-selective tissues by shuttling cortisol to the inactive steroid cortisone, permitting selective occupancy of these receptors by aldosterone (Edwards et al., 1988). A number of studies have indicated impaired renal 11β-HSD2 activity in chronic renal failure. The aberrant metabolism of cortisol with increased mineralocorticoid receptor activity could contribute to some of the consequences of renal disease (hypertension and sodium retention) or may modify others (hyperkalaemia and decreased GFR) (Whitworth et al., 1989; Homma et al., 2001; Mangos et al., 2003). These results have been confirmed in later studies and extended in the haemodialysis population. Two parameters considered to reflect 11β-HSD2 activity (cortisol/cortisone ratio and the ratio of their metabolites) were found to be significantly higher in dialysis patient compared with healthy controls (N'Gankam et al., 2002).

Pituitary–adrenal function tests

An overview of the most commonly used tests to assess disorders of glucocorticoid metabolism is given in Table 132.5 with a short description of each test in the following sections.

Baseline cortisol profile

A normal morning total cortisol can vary between around 180–620 nmol/L and falls by around 50% by 6 p.m. Pituitary hypersecretion predominantly leads to increased evening levels, hypopituitarism to decreased morning levels. Patients with Cushing syndrome often lose the normal diurnal variation in secretion. Other conditions such as obesity, depression, psychosis, and alcoholism can cause similar disruptions complicating interpretation. There is assay cross-reactivity with some synthetic steroids including prednisolone which must be kept in mind.

Dexamethasone suppression test

Today the dexamethasone suppression test is mainly used to exclude the diagnosis of Cushing syndrome. Variations of the test

Table 132.5 Clinical synopsis of function tests to assess disorders of glucocorticoid metabolism (details in Forest, 1996)

Parameters		Normal range	Cushing's		Addison's		uraemia	Post-transplant
			Central	Peripheral	Primary	Secondary		
Serum cortisol profile		9 a.m.: 180–620 nmol/L 6 p.m.: 140–270 nmol/L	Evening cortisol ↑	Loss of diurnal rhythmicity	Morning cortisol ↓	Morning cortisol ↓	=/↑	↓
Dexamethasone suppression test	Cortisol decrease	< 50 nmol/L	↓	↓	Not useful	Not useful	= $T_{1/2}$ ↑	Not useful
Basal ACTH		2.2–17.6 pmol/L	↑	↓	↑	↓	=/↑	↓
ACTH stimulation test	Cortisol increase	To above 550 nmol/L or by >150 nmol/L	Not useful	Not useful	↓↓	=/↓	=	=/↓
CRF test	ACTH increase	2–3fold basal	=	↓↓	=/↑	=/↓	=	↓
	Cortisol increase	>50% basal	=	↓↓	↓		↓	↓

can help to distinguish between central and peripheral hypercortisolism. Basal cortisol levels are measured and then a dose large enough to suppress cortisol production in healthy individuals is given. A post-suppression value of < 50 nmol/L is appropriate and excludes the diagnosis of Cushing syndrome.

In chronic renal failure, ACTH secretion is not suppressible by standard oral doses of dexamethasone (McDonald et al., 1979; Rosman et al., 1982). Oral absorption of dexamethasone is reduced in uraemia, and suppression is eventually seen with larger doses (166,175). The half-life of cortisol is also increased in renal failure giving a delayed measured response (Workman et al., 1986). A 2-day dexamethasone suppression test is therefore suggested to exclude Cushing syndrome in chronic renal failure.

ACTH stimulation test

The ACTH stimulation test (Synacthen test) is used to exclude or diagnose adrenocortical insufficiency. After baseline cortisol and ACTH measurements, 250 micrograms of synthetic ACTH are given and the biochemical response measured an hour later. A cortisol rise to above approximately 550 nmol/L or by at least 150 nmol/L is considered appropriate and excludes adrenocortical insufficiency. Most studies have shown stimulated cortisol responses within the normal range in chronic renal failure (Zager et al., 1985). There is an increased tendency towards insufficient response in patients on haemodialysis (Williams et al., 1973), especially in the period after commencing dialysis (Rodger et al., 1986). The use of salivary cortisol, as a measure of free cortisol, has increased in the last few years. Arregger et al. recently showed ACTH-stimulated salivary cortisol to be an accurate biomarker for the diagnosis of adrenocortical insufficiency in ESRD (Arregger et al., 2008).

CRH test

The CRH test assesses anterior pituitary function. Under normal conditions ACTH should increase two- to threefold and cortisol should rise by at least 50% after CRH administration. CRH pharmacokinetics are not altered in ESRD. ACTH release from the pituitary occurs earlier, the overall response is blunted in uraemia (Luger et al., 1987; Siamopoulos et al., 1988).

Gonadal function in impaired renal function

Gonadal dysfunction is a frequent finding in both men and women with chronic kidney disease (CKD). The development of hypogonadism, associated symptoms, and sexual dysfunction in chronic renal failure is multifactorial. Different and varied factors have been implicated such as chronic malnutrition and cachexia (Warren, 1983; Cavalli et al., 2010), chronic inflammation (Kalyani et al., 2007), increased oxidative stress (Vaziri, 2004), hypertension, atherosclerosis, and vascular disease (Isidori and Lenzi, 2005; Jackson et al., 2010; Santoro et al., 2010), drugs (Isidori and Lenzi, 2005), and other endocrine disorders such as diabetes (Grossmann et al., 2010) and hyperprolactinaemia (Corona et al., 2007). Psychological factors such as depression and stress are also well-known risk factors which are very relevant in this context.

The hypothalamo–pituitary–gonadal axis in impaired renal function

Under normal conditions, GnRH is produced in the hypothalamus to stimulate gonadotropin release in a pulsatile manner. Peaks at around 90-minute intervals are necessary for normal gonadotropin secretion. In chronic renal failure both the amplitude and pulsatility is impaired resulting in loss of normal pulsatile production of LH (Wheatley et al., 1987; Veldhuis et al., 1993). Basal GnRH levels are increased in ESRD, but improve after initiation of dialysis (Matsubara et al., 1983). The pituitary response to GnRH has also been found to be altered in CKD. Some authors have described a normal or impaired response (Lim and Fang, 1975; Ramirez et al., 1992; Díez et al., 1997), and others delayed and sustained (Distiller et al., 1975; Schalch et al., 1975; Holdsworth et al., 1977; Handelsman, 1985). Gonadotropin concentrations, both LH and FSH, are increased in renal failure. The reason may be altered, and overall increased secretion, in combination with reduced renal clearance (Handelsman, 1985; Iglesias et al., 2012).

The initiation of haemodialysis or peritoneal dialysis rarely improves function of the hypothalamo–pituitary–gonadal axis, it may even deteriorate (Handelsman, 1985; Albaaj et al., 2006; Karagiannis and Harsoulis, 2005; Zhang et al., 2008). Successful renal transplantation, on the other hand, is an effective way to improve gonadal dysfunction, although full improvement may be delayed by > 2 years (Stanley et al., 1991; De Celis et al., 1999; Palmer, 1999; Albaaj et al., 2006; Anantharaman and Schmidt, 2007; Zhang et al., 2008).

Hyperprolactinaemia is another hormone derangement associated with renal insufficiency, which affects the hypothalamo–pituitary–gonadal axis negatively (Box 132.1). This is described in a separate section.

FSH concentrations in uraemic men are in the upper normal range or elevated (Lim et al., 1980; Rodger et al., 1985; Rudolf et al., 1988). FSH secretion is regulated by a negative feedback via the testicular peptide inhibin. FSH regulates spermatogenesis. In men on dialysis, inhibin levels have not been found to correlate with either LH or FSH but are persistently raised (Sasagawa et al., 1998). This may be related to decreased metabolic clearance of inhibin or testicular dysfunction due to chronic renal failure. FSH secretion is also suppressed by oestrogen or oestradiol, which may explain the normal or only mildly elevated FSH levels in uraemic men despite deceased spermatogenesis (Rodger et al., 1985).

Testicular function in impaired renal function

Reduced testicular function and hypogonadism are common in chronic renal disease. Recent studies also suggest that testosterone deficiency can have important implications with regards to progression of kidney disease, libido, erectile dysfunction,

Box 132.1 Known changes in the hypothalamic–pituitary–gonadal axis in renal failure

- Impaired hypothalamic cyclic release and pulse amplitude of GnRH
- Loss of normal pulsatile LH release by the pituitary
- Elevated serum concentrations of LH and FSH
- Altered gonadotropin response to GnRH
- Hyperprolactinaemia
- Decreased gonadal function (low testosterone/anovulation).

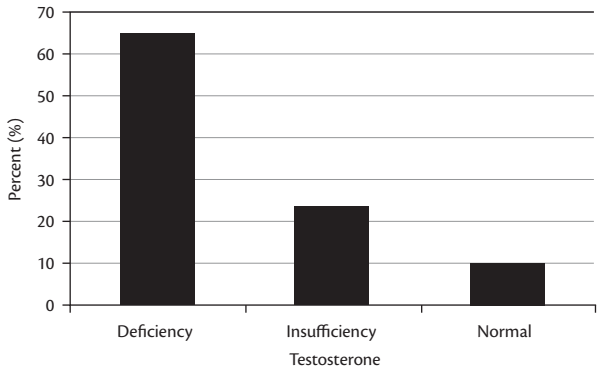


Fig. 132.5 Testosterone deficiency and insufficiency in chronic renal failure. Prevalence of normal testosterone levels (> 14 nmol/L), insufficiency (10–14 nmol/L), and deficiency (< 10 nmol/L) in the study population. Reproduced from Gungor et al. (2010).

reduction in muscle mass and strength, development of anaemia, progression of atherosclerotic disease, and even mortality in chronic renal failure. The importance of identifying this common problem and treating it if indicated is therefore becoming better recognized.

Gonadotropins are often raised in chronic renal failure, but circulating testosterone is often low. The resulting primary hypogonadism is a well-known hormonal derangement in chronic renal failure, and has even been termed uraemic hypogonadism (Handelsman, 1985; Foulks and Cushner, 1986; Andrade et al., 2001; Holley, 2004). To diagnose hypogonadism in men at least two morning blood samples confirming abnormally low testosterone concentration in addition to symptoms related to hypogonadism are recommended (Bhasin et al., 2010). Most male uraemic patients have low serum testosterone levels, although there is a wide overlap with age-corrected normal concentrations (Ramirez et al., 1987). Gungor et al. recently found the prevalence of testosterone insufficiency (24%) and deficiency (66%) to be markedly raised in CKD compared with the normal population (Gungor et al., 2010) (Fig. 132.5).

Testicular hormone secretion has been shown to be affected directly in renal failure. Plasma testosterone and 5α-dihydrotestosterone (DHT) concentrations are significantly reduced in ESRD. The DHT to testosterone ratio is also reduced suggesting impaired 5α-reductase activity. Sex hormone binding globulin (SHBG) or its binding capacity is within normal reference ranges (De Vries et al., 1984; Ramirez et al., 1987). The most important defect is with impaired testicular secretion rather than increased clearance (Handelsman, 1985). This may partly be related to Leydig cell resistance to LH, but studies have shown a subnormal response to acute administration of LH analogues (Stewart-Bentley et al., 1974; Ramirez et al., 1987). Normal circadian rhythm of plasma testosterone, with a peak at 4–8 a.m. and a nadir at 8–12 p.m., is maintained in uraemic patients (Zadeh et al., 1975).

Clinical implications of uraemic hypogonadism

In addition to affecting libido and sexual function, which is discussed in Chapter 133, hypogonadism may have important implications for a number of other features of CKD.

The progression rate of many renal disease is affected by sex (Silbiger and Neugarten, 2008; Carrero, 2010). Some research into the cause of faster progression of ESRD in men points towards a proinflammatory, proapoptotic, and profibrotic effect of both endogenous and exogenous testosterone during acute and chronic kidney injury (Gafter et al., 1990; Sakemi et al., 1997; Reckelhoff et al., 2000; Elliot et al., 2007; Metcalfe et al., 2008; Verzola et al., 2009). At present it is difficult to extrapolate these findings into clinical observations and the exact role and importance of hypogonadism in progression rates of ESRD in unknown.

Muscle mass, performance, and general physical function are impaired in ESRD, where the causes are multifactorial (Carrero et al., 2008). Hypogonadism causes sarcopenia and many of the same effects on muscle function as ESRD (Handelsman, 1985; Handelsman and Dong, 1993; Handelsman and Liu, 1998). An association between testosterone levels and muscle mass and strength has been shown in dialysis patients (Carrero et al., 2009). Interventional studies have shown somewhat discordant results. Transdermal testosterone was not shown to have any significant effect on muscle in a recent study (Johansen et al., 2006). The more anabolic agent nandrolone has on the other hand been shown improve muscle function in dialysis patients (Johansen et al., 1999, 2006).

Anaemia is a common complication of ESRD. Erythropoietin (EPO) deficiency is considered the main contributing factor, but other factors such as testosterone deficiency may also play a role. Testosterone is known to affect erythropoiesis positively and to increase the sensitivity of progenitor cells to circulating EPO (Shahidi, 1973; Ballal et al., 1991; Teruel et al., 1995). Recent work by Carrero et al. indicated that hypogonadism may be an additional independent cause of anaemia and reduced EPO responsiveness in men with CKD (Carrero et al., 2012).

Several studies have described a correlation between testosterone deficiency and atherosclerotic complications, cardiovascular disease, and mortality. These have indicated that endogenous testosterone concentrations are inversely related to all-cause and cardiovascular mortality (Khaw et al., 2007; Nettleship et al., 2009; Traish et al., 2009; Malkin et al., 2010). It may then follow that the increased risk of cardiovascular disease in ESRD is somehow linked to the increased prevalence of hypogonadism in this population. Several studies have explored this and confirmed correlations between low testosterone levels and many risk factors and markers of cardiovascular disease (Karakitsos et al., 2006; Yilmaz et al., 2011). Further studies have also shown a link between hypogonadism and all-cause and cardiovascular mortality in CKD, ESRD, and in patients on haemodialysis (Carrero et al., 2011b; Haring et al., 2011; Kyriazis et al., 2011; Yilmaz et al., 2011). In most of these studies inflammatory markers also showed a strong negative correlation to low testosterone indicating a high inflammatory, catabolic state.

Ovarian function in impaired renal function

The effects of uraemia has on the hypothalamo–pituitary–gonadal axis in women are in most ways similar to those in men. The cyclical nature of ovarian function and ovulation adds a few complexities which warrant discussion. Like in men physiological pulsatile release of GnRH is followed by pulsatile release of gonadotropins. In normal women, short-term peaks of these hormones occur about every 90 minutes during the follicular phase of the menstrual cycle. This pulsatile hormone release is modified by a positive and negative feedback mechanism via oestradiol

and progesterone. Oestrogen lowers the amplitude of LH pulses whereas progesterone increases the amplitude and lowers the frequency of these pulses (Djahanbakhch et al., 1984; Soules et al., 1984). This spontaneous pulsatile LH secretion is disturbed in uraemic women (Swamy et al., 1979). Some date indicate that it is absent in female dialysis patients (Swamy et al., 1979). The diurnal pulsatile secretion of LH and a high preovulatory peak of GnRH and, consequently, LH required for ovulation, are not found in most patients. Exogenous oestrogen does not induce the LH surge (Lim et al., 1980), suggesting an impaired positive feedback mechanism.

FSH is usually within the normal range found during the follicular and luteal phase in normal women; GnRH induces only a moderate increase in FSH. The decreased ratio of FSH to LH argues against primary ovarian failure and suggests a hypothalamic–hypophyseal dysregulation.

Normal oestradiol (E2) concentrations have been reported in pre-menopausal uraemic women. E2 levels are lower in uraemic women with hyperprolactinaemia (Gómez et al., 1980). The typical cyclic variations of E2 are not found in female dialysis patients. Luteinization of follicles (Morley et al., 1979) is absent or very rare, as indicated by indirect measures of progestional status (vaginal cytology, basal body temperature, luteal endometrial biopsies). As a consequence, the increase in progesterone which normally occurs in the second half of the menstrual cycle is absent. Non-luteal progesterone levels are normal or low, and testosterone also tends to be low (Hubinont et al., 1988).

References

Adler, S. M. and Wartofsky, L. (2007). The nonthyroidal illness syndrome. *Endocrinol Metab Clin North Am*, 36(3), 657–72.

Alarcon, R. D., Groover, A. M., and Jenkins-Ross, C. S. (1992). Organic anxiety disorder secondary to hyperthyroidism in a hemodialysis patient. A rare occurrence. *Psychosomatics*, 33(4), 457–60.

Albaaj, F., Sivalingham, M., Haynes, P., *et al.* (2006). Prevalence of hypogonadism in male patients with renal failure. *Postgrad Med J*, 82(972), 693–6.

Allegra, V., Amendolagine, F., Mengozzi, G., *et al.* (1988). Growth hormone secretion abnormalities in uremic patients: which is the role of impaired glucose hypothalamic sensitivity? *Nephron*, 48(1), 76–7.

Alvestrand, A., Mujagic, M., Wajngot, A., *et al.* (1989). Glucose intolerance in uremic patients: the relative contributions of impaired beta-cell function and insulin resistance. *Clin Nephrol*, 31(4), 175–83.

Anantharaman, P. and Schmidt, R. J. (2007). Sexual function in chronic kidney disease. *Adv Chronic Kidney Dis*, 14(2), 119–25.

Andrade, V. A., Gross, J. L., and Maia, A. L. (2001). The effect of methimazole pretreatment on the efficacy of radioactive iodine therapy in Graves' hyperthyroidism: one-year follow-up of a prospective, randomized study. *J Clin Endocrinol Metab*, 86(8), 3488–93.

Arregger, A. L., Cardoso, E. M. L., Tumilasci, O., *et al.* (2008). Diagnostic value of salivary cortisol in end stage renal disease. *Steroids*, 73(1), 77–82.

Ballal, S. H., Domoto, D. T., Polack, D. C., *et al.* (1991). Androgens potentiate the effects of erythropoietin in the treatment of anemia of end-stage renal disease. *Am J Kidney Dis*, 17(1), 29–33.

Bartalena, L., Pacchiarotti, A., Palla, R., *et al.* (1990). Lack of nocturnal serum thyrotropin (TSH) surge in patients with chronic renal failure undergoing regular maintenance hemofiltration: a case of central hypothyroidism. *Clin Nephrol*, 34(1), 30–4.

Baumann, G., Shaw, M. A., and Amburn, K. (1989). Regulation of plasma growth hormone-binding proteins in health and disease. *Metab Clin Exp*, 38(7), 683–9.

Bayliss, W. M. and Starling, E. H. (1902). The mechanism of pancreatic secretion. *J Physiol (Lond)*, 28(5), 325–53.

Bessarione, D., Perfumo, F., Giusti, M., *et al.* (1987). Growth hormone response to growth hormone-releasing hormone in normal and uraemic children. Comparison with hypoglycaemia following insulin administration. *Acta Endocrinol*, 114(1), 5–11.

Bhasin, S., Cunningham, G. R., Hayes, F. J., *et al.* (2010). Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*, 95(6), 2536–59.

Biasioli, S., Mazzali, A., Foroni, R., *et al.* (1988). Chronobiological variations of prolactin (PRL) in chronic renal failure (CRF). *Clin Nephrol*, 30(2), 86–92.

Blum, W. F., Ranke, M. B., Kietzmann, K., *et al.* (1991). Growth hormone resistance and inhibition of somatomedin activity by excess of insulin-like growth factor binding protein in uraemia. *Pediatr Nephrol*, 5(4), 539–44.

Bommer, J., Ritz, E., del Pozo, E., *et al.* (1979). Improved sexual function in male haemodialysis patients on bromocriptine. *Lancet*, 2(8141), 496–7.

Bräunlich, H. (1984). Thyroid hormones influencing renal electrolyte excretion in saline loaded rats of different ages. *Physiol Bohemoslov*, 33(4), 303–8.

Brenner, B. M., Meyer, T. W., and Hostetter, T. H. (1982). Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med*, 307(11), 652–9.

Brockenbrough, A. T., Dittrich, M. O., Page, S. T., *et al.* (2006). Transdermal androgen therapy to augment EPO in the treatment of anemia of chronic renal disease. *Am J Kidney Dis*, 47(2), 251–62.

Brough, R. and Jones, C. (2006). Iatrogenic iodine as a cause of hypothyroidism in infants with end-stage renal failure. *Pediatr Nephrol*, 21(3), 400–2.

Calañas-Continente, A., Espinosa, M., Manzano-García, G., *et al.* (2005). Necrotizing glomerulonephritis and pulmonary hemorrhage associated with carbimazole therapy. *Thyroid*, 15(3), 286–8.

Carrero, J. J. (2010). Gender differences in chronic kidney disease: underpinnings and therapeutic implications. *Kidney Blood Press Res*, 33(5), 383–92.

Carrero, J. J., Bárány, P., Yilmaz, M. I., *et al.* (2012). Testosterone deficiency is a cause of anaemia and reduced responsiveness to erythropoiesis-stimulating agents in men with chronic kidney disease. *Nephrol Dial Transplant*, 27(2), 709–15.

Carrero, J. J., Chmielewski, M., Axelsson, J., *et al.* (2008). Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. *Clin Nutr*, 27(4), 557–64.

Carrero, J. J., Nakashima, A., Qureshi, A. R., *et al.* (2011a). Protein-energy wasting modifies the association of ghrelin with inflammation, leptin, and mortality in hemodialysis patients. *Kidney Int*, 79(7), 749–56.

Carrero, J. J., Qureshi, A. R., Axelsson, J., *et al.* (2007). Clinical and biochemical implications of low thyroid hormone levels (total and free forms) in euthyroid patients with chronic kidney disease. *J Intern Med*, 262(6), 690–701.

Carrero, J. J., Qureshi, A. R., Nakashima, A., *et al.* (2011b). Prevalence and clinical implications of testosterone deficiency in men with end-stage renal disease. *Nephrol Dial Transplant*, 26(1), 184–90.

Carrero, J. J., Qureshi, A. R., Parini, P., *et al.* (2009). Low serum testosterone increases mortality risk among male dialysis patients. *J Am Soc Nephrol*, 20(3), 613–20.

Cavalli, A., Del Vecchio, L., and Locatelli, F. (2010). Geriatric nephrology. *J Nephrol*, 23 Suppl 15, S11–15.

Cheung, C. Y. (1983). Prolactin suppresses luteinizing hormone secretion and pituitary responsiveness to luteinizing hormone-releasing hormone by a direct action at the anterior pituitary. *Endocrinology*, 113(2), 632–8.

Chou, C. -C., Bai, C. -H., Tsai, S. -C., *et al.* (2010). Low serum acylated ghrelin levels are associated with the development of cardiovascular disease in hemodialysis patients. *Intern Med*, 49(19), 2057–64.

Christiansen, J. S., Gammelgaard, J., Orskov, H., *et al.* (1981). Kidney function and size in normal subjects before and during growth hormone administration for one week. *Eur J Clin Invest*, 11(6), 487–90.

Cooke, C. R., Whelton, P. K., Moore, M. A., *et al.* (1979). Dissociation of the diurnal variation of aldosterone and cortisol in anephric subjects. *Kidney Int*, 15(6), 669–75.

Corona, G., Mannucci, E., Fisher, A. D., *et al.* (2007). Effect of hyperprolactinemia in male patients consulting for sexual dysfunction. *J Sex Med*, 4(5), 1485–93.

Cowden, E. A., Ratcliffe, W. A., Ratcliffe, J. G., *et al.* (1981). Hypothalamic-pituitary function in uraemia. *Acta Endocrinol*, 98(4), 488–95.

Davidson, M. B., Fisher, M. B., Dabir-Vaziri, N., *et al.* (1976). Effect of protein intake and dialysis on the abnormal growth hormone, glucose, and insulin homeostasis in uremia. *Metab Clin Exp*, 25(4), 455–64.

Davis, F. B., Spector, D. A., Davis, P. J., *et al.* (1982). Comparison of pituitary-thyroid function in patients with endstage renal disease and in age- and sex-matched controls. *Kidney Int*, 21(2), 362–4.

De Celis, R. and Pedrón-Nuevo, N. (1999). Male fertility of kidney transplant patients with one to ten years of evolution using a conventional immunosuppressive regimen. *Arch Androl*, 42(1), 9–20.

De Vries, C. P., Gooren, L. J., and Oe, P. L. (1984). Haemodialysis and testicular function. *Int J Androl*, 7(2), 97–103.

Díez, J. J., Iglesias, P., Bajo, M. A., *et al.* (1997). Effects of erythropoietin on gonadotropin responses to gonadotropin-releasing hormone in uremic patients. *Nephron*, 77(2), 169–75.

Díez, J. J., Iglesias, P., and Selgas, R. (1995). Pituitary dysfunctions in uremic patients undergoing peritoneal dialysis: a cross sectional descriptive study. *Adv Perit Dial*, 11, 218–24.

Distiller, L. A., Morley, J. E., Sagel, J., *et al.* (1975). Pituitary-gonadal function in chronic renal failure: the effect of luteinizing hormone—releasing hormone and the influence of dialysis. *Metab Clin Exp*, 24(6), 711–20.

Djahanbakhch, O., Warner, P., McNeilly, A. S., *et al.* (1984). Pulsatile release of LH and oestradiol during the periovulatory period in women. *Clin Endocrinol (Oxf)*, 20(5), 579–89.

Duntas, L., Wolf, C. F., Keck, F. S., *et al.* (1992). Thyrotropin-releasing hormone: pharmacokinetic and pharmacodynamic properties in chronic renal failure. *Clin Nephrol*, 38(4), 214–8.

Edwards, C. R., Stewart, P. M., Burt, D., *et al.* (1988). Localisation of 11 beta-hydroxysteroid dehydrogenase—tissue specific protector of the mineralocorticoid receptor. *Lancet*, 2(8618), 986–9.

Elliot, S. J., Berho, M., Korach, K., *et al.* (2007). Gender-specific effects of endogenous testosterone: female alpha-estrogen receptor-deficient C57Bl/6J mice develop glomerulosclerosis. *Kidney Int*, 72(4), 464–72.

Enia, G., Panuccio, V., Cutrupi, S., *et al.* (2007). Subclinical hypothyroidism is linked to micro-inflammation and predicts death in continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant*, 22(2), 538–44.

Feinstein, E. I., Kaptein, E. M., Nicoloff, J. T., *et al.* (1982). Thyroid function in patients with nephrotic syndrome and normal renal function. *Am J Nephrol*, 2(2), 70–6.

Feldman, D. R., Martorella, A. J., Robbins, R. J., *et al.* (2007). Re: Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst*, 99(12), 974–5.

Fine, R. N., Kohaut, E., Brown, D., *et al.* (1996). Long-term treatment of growth retarded children with chronic renal insufficiency, with recombinant human growth hormone. *Kidney Int*, 49(3), 781–5.

Fine, R. N., Yadin, O., Moulton, L., *et al.* (1994). Five years experience with recombinant human growth hormone treatment of children with chronic renal failure. *J Pediatr Endocrinol*, 7(1), 1–12.

Foley, R. J. and Hamner, R. W. (1985). Hyperthyroidism in end-stage renal disease. *Am J Nephrol*, 5(4), 292–5.

Forest, M.G. (1996). Adrenal function tests. In M. B. Ranke (ed.) *Diagnostics of Endocrine Function in Children and Adolescents*, pp. 370–413. Heidelberg: J. Ambrosius Barth Verlag.

Foulks, C. J. and Cushner, H. M. (1986). Sexual dysfunction in the male dialysis patient: pathogenesis, evaluation, and therapy. *Am J Kidney Dis*, 8(4), 211–22.

Franks, S., Jacobs, H. S., Martin, N., *et al.* (1978). Hyperprolactinaemia and impotence. *Clin Endocrinol (Oxf)*, 8(4), 277–87.

Frystyk, J., Djurhuus, C. B., Johansen, T., *et al.* (2012). Measurement of free GH and bioactive IGF-I in non-diabetic haemodialysis patients treated with GH for 7 days. *Nephrol Dial Transplant*, 27(11), 4211–18.

Frystyk, J., Ivarsen, P., Skjaerbaek, C., *et al.* (1999). Serum-free insulin-like growth factor I correlates with clearance in patients with chronic renal failure. *Kidney Int*, 56(6), 2076–84.

Fu, R. -G., Ge, H., Yao, G. -L., *et al.* (2013). Uremic anorexia and gastrointestinal motility dysfunction correlate with the changes of ghrelin system in hypothalamus. *Nephrology (Carlton)*, 18(2), 111–6.

Fu, R. -G., Wang, L., Yao, G. -L., *et al.* (2012). Chronic renal failure impacts the expression of ghrelin and its receptor in hypothalamus and hippocampus. *Ren Fail*, 34(8), 1027–32.

Gafter, U., Ben-Bassat, M., and Levi, J. (1990). Castration inhibits glomerular hypertrophy and proteinuria in uninephrectomized male rats. *Eur J Clin Invest*, 20(4), 360–5.

Garibotto, G., Barreca, A., Russo, R., *et al.* (1997). Effects of recombinant human growth hormone on muscle protein turnover in malnourished hemodialysis patients. *J Clin Invest*, 99(1), 97–105.

Gattineni, J., Sas, D., Dagan, A., *et al.* (2008). Effect of thyroid hormone on the postnatal renal expression of NHE8. *Am J Physiol Renal Physiol*, 294(1), F198–204.

Giordano, C., De Santo, N. G., Carella, C., *et al.* (1984). Thyroid status and nephron loss—a study in patients with chronic renal failure, end stage renal disease and/or on hemodialysis. *Int J Artif Organs*, 7(3), 119–22.

Gómez, F., de la Cueva, R., Wauters, J. P., *et al.* (1980). Endocrine abnormalities in patients undergoing long-term hemodialysis. The role of prolactin. *Am J Med*, 68(4), 522–30.

Grossmann, M., Gianatti, E. J., and Zajac, J. D. (2010). Testosterone and type 2 diabetes. *Curr Opin Endocrinol Diabetes Obes*, 17(3), 247–56.

Grossmann, M., Premaratne, E., Desai, J., *et al.* (2008). Thyrotoxicosis during sunitinib treatment for renal cell carcinoma. *Clin Endocrinol (Oxf)*, 69(4), 669–72.

Grzeszczak, W., Kokot, F., Wiecek, A., *et al.* (1990). Prolactin secretion in kidney transplant patients. *Int Urol Nephrol*, 22(6), 567–71.

Gungor, O., Kircelli, F., Carrero, J. J., *et al.* (2010). Endogenous testosterone and mortality in male hemodialysis patients: is it the result of aging? *Clin J Am Soc Nephrol*, 5(11), 2018–23.

Haffner, D. and Schaefer, F. (2001). Does recombinant growth hormone improve adult height in children with chronic renal failure? *Semin Nephrol*, 21(5), 490–7.

Haffner, D., Schaefer, F., Girard, J., *et al.* (1994). Metabolic clearance of recombinant human growth hormone in health and chronic renal failure. *J Clin Invest*, 93(3), 1163–71.

Haffner, D., Zacharewicz, S., Mehls, O., *et al.* (1989). The acute effect of growth hormone on GFR is obliterated in chronic renal failure. *Clin Nephrol*, 32(6), 266–9.

Handelsman, D. J. and Dong, Q. (1993). Hypothalamo-pituitary gonadal axis in chronic renal failure. *Endocrinol Metab Clin North Am*, 22(1), 145–61.

Handelsman, D. J. and Liu, P. Y. (1998). Androgen therapy in chronic renal failure. *Baillieres Clin Endocrinol Metab*, 12(3), 485–500.

Handelsman, D. J. (1985). Hypothalamic-pituitary gonadal dysfunction in renal failure, dialysis and renal transplantation. *Endocr Rev*, 6(2), 151–82.

Hansen, T. B., Gram, J., Jensen, P. B., *et al.* (2000). Influence of growth hormone on whole body and regional soft tissue composition in adult patients on hemodialysis. A double-blind, randomized, placebo-controlled study. *Clin Nephrol*, 53(2), 99–107.

Haring, R., Nauck, M., Völzke, H., *et al.* (2011). Low serum testosterone is associated with increased mortality in men with stage 3 or greater nephropathy. *Am J Nephrol*, 33(3), 209–17.

Hegedüs, L., Andersen, J. R., Poulsen, L. R., *et al.* (1985). Thyroid gland volume and serum concentrations of thyroid hormones in chronic renal failure. *Nephron*, 40(2), 171–4.

Heimbürger, O., Lönnqvist, F., Danielsson, A., *et al.* (1997). Serum immunoreactive leptin concentration and its relation to the body fat content in chronic renal failure. *J Am Soc Nephrol*, 8(9), 1423–30.

Herington, A. C., Ymer, S. I., and Stevenson, J. L. (1986). Affinity purification and structural characterization of a specific binding protein for human growth hormone in human serum. *Biochem Biophys Res Commun*, 139(1), 150–5.

Hokken-Koelega, A. C., Stijnen, T., de Muinck Keizer-Schrama, S. M., *et al.* (1991). Placebo-controlled, double-blind, cross-over trial of growth hormone treatment in prepubertal children with chronic renal failure. *Lancet*, 338(8767), 585–90.

Holdsworth, S., Atkins, R. C., and de Kretser, D. M. (1977). The pituitary-testicular axis in men with chronic renal failure. *N Engl J Med*, 296(22), 1245–9.

Holley, J. L. (2004). The hypothalamic-pituitary axis in men and women with chronic kidney disease. *Adv Chronic Kidney Dis*, 11(4), 337–41.

Homma, M., Tanaka, A., Hino, K., *et al.* (2001). Assessing systemic 11beta-hydroxysteroid dehydrogenase with serum cortisone/cortisol ratios in healthy subjects and patients with diabetes mellitus and chronic renal failure. *Metab Clin Exp*, 50(7), 801–4.

Hruska, K. A., Korkor, A., Martin, K., *et al.* (1981). Peripheral metabolism of intact parathyroid hormone. Role of liver and kidney and the effect of chronic renal failure. *J Clin Invest*, 67(3), 885–92.

Hubinont, C. J., Goldman, M., Vanherweghem, J. L., *et al.* (1988). Effects of chronic renal failure and hemodialysis on hormonal evaluation of pregnancy. *Am J Nephrol*, 8(1), 57–61.

Iglesias, P., Carrero, J. J., and Díez, J. J. (2012). Gonadal dysfunction in men with chronic kidney disease: clinical features, prognostic implications and therapeutic options. *J Nephrol*, 25(1), 31–42.

Iglesias, P. and Díez, J. J. (2009). Thyroid dysfunction and kidney disease. *Eur J Endocrinol*, 160(4), 503–15.

Iglesias, P., Díez, J. J., Fernández-Reyes, M. J., *et al.* (1998). Recombinant human growth hormone therapy in malnourished dialysis patients: a randomized controlled study. *Am J Kidney Dis*, 32(3), 454–63.

Iglesias, P., Díez, J. J., Fernández-Reyes, M. J., *et al.* (2002). Effects of short-term recombinant human growth hormone therapy on plasma leptin concentrations in dialysis patients. *Nephrol Dial Transplant*, 17(2), 260–4.

Ikizler, T. A., Wingard, R. L., Breyer, J. A., *et al.* (1994). Short-term effects of recombinant human growth hormone in CAPD patients. *Kidney Int*, 46(4), 1178–83.

Isidori, A. M. and Lenzi, A. (2005). Risk factors for androgen decline in older males: lifestyle, chronic diseases and drugs. *J Endocrinol Invest*, 28(3 Suppl), 14–22.

Jackson, G., Montorsi, P., Adams, M. A., *et al.* (2010). Cardiovascular aspects of sexual medicine. *J Sex Med*, 7(4 Pt 2), 1608–26.

Jensen, P. B., Hansen, T. B., Frystyk, J., *et al.* (1999). Growth hormone, insulin-like growth factors and their binding proteins in adult hemodialysis patients treated with recombinant human growth hormone. *Clin Nephrol*, 52(2), 103–9.

Johannsson, G., Bengtsson, B. A., and Ahlmén, J. (1999). Double-blind, placebo-controlled study of growth hormone treatment in elderly patients undergoing chronic hemodialysis: anabolic effect and functional improvement. *Am J Kidney Dis*, 33(4), 709–17.

Johansen, K. L., Mulligan, K., and Schambelan, M. (1999). Anabolic effects of nandrolone decanoate in patients receiving dialysis: a randomized controlled trial. *JAMA*, 281(14), 1275–81.

Johansen, K. L., Painter, P. L., Sakkas, G. K., *et al.* (2006). Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: a randomized, controlled trial. *J Am Soc Nephrol*, 17(8), 2307–14.

Johnson, V. and Maack, T. (1977). Renal extraction, filtration, absorption, and catabolism of growth hormone. *Am J Physiol*, 233(3), F185–196.

Joseph, F., Ahmad, A. M., Ul-Haq, M., *et al.* (2008). Effects of growth hormone administration on bone mineral metabolism, PTH sensitivity and PTH secretory rhythm in postmenopausal women with established osteoporosis. *J Bone Miner Res*, 23(5), 721–9.

Kalyani, R. R., Gavini, S., and Dobs, A. S. (2007). Male hypogonadism in systemic disease. *Endocrinol Metab Clin North Am*, 36(2), 333–48.

Kaptein, E. M., Feinstein, E. I., and Massry, S. G. (1982). Thyroid hormone metabolism in renal diseases. *Contrib Nephrol*, 33, 122–35.

Kaptein, E. M., Feinstein, E. I., Nicoloff, J. T., *et al.* (1983). Serum reverse triiodothyronine and thyroxine kinetics in patients with chronic renal failure. *J Clin Endocrinol Metab*, 57(1), 181–9.

Kaptein, E. M. (1996). Thyroid hormone metabolism and thyroid diseases in chronic renal failure. *Endocr Rev*, 17(1), 45–63.

Kaptein, E. M., Quion-Verde, H., Chooljian, C. J., *et al.* (1988). The thyroid in end-stage renal disease. *Medicine (Baltimore)*, 67(3), 187–97.

Kaptein, E. M., Quion-Verde, H., and Massry, S. G. (1984). Hemodynamic effects of thyroid hormone. *Contrib Nephrol*, 41, 151–9.

Karagiannis, A. and Harsoulis, F. (2005). Gonadal dysfunction in systemic diseases. *Eur J Endocrinol*, 152(4), 501–13.

Karakitsos, D., Patrianakos, A. P., De Groot, E., *et al.* (2006). Androgen deficiency and endothelial dysfunction in men with end-stage kidney disease receiving maintenance hemodialysis. *Am J Nephrol*, 26(6), 536–43.

Kataoka, S., Kudo, A., Hirano, H., *et al.* (2002). 11beta-hydroxysteroid dehydrogenase type 2 is expressed in the human kidney glomerulus. *J Clin Endocrinol Metab*, 87(2), 877–82.

Katyare, S. S., Modi, H. R., Patel, S. P., *et al.* (2007). Thyroid hormone-induced alterations in membrane structure-function relationships: studies on kinetic properties of rat kidney microsomal Na(+),K (+)-ATPase and lipid/phospholipid profiles. *J Membr Biol*, 219(1–3), 71–81.

Khaw, K. -T., Dowsett, M., Folkerd, E., *et al.* (2007). Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation*, 116(23), 2694–701.

Kiepe, D., Ulinski, T., Powell, D. R., *et al.* (2002). Differential effects of insulin-like growth factor binding proteins-1, -2, -3, and -6 on cultured growth plate chondrocytes. *Kidney Int*, 62(5), 1591–600.

Kirk, A. D., Hale, D. A., Swanson, S. J., *et al.* (2006). Autoimmune thyroid disease after renal transplantation using depletional induction with alemtuzumab. *Am J Transplant*, 6(5 Pt 1), 1084–5.

Kishore, B. K., Gejyo, F., and Arakawa, M. (1983). Altered glycosylation and sialylation of serum proteins and lipid bound sialic acids in chronic renal failure. *Postgrad Med J*, 59(695), 551–5.

Kojima, M., Hosoda, H., Date, Y., *et al.* (1999). Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature*, 402(6762), 656–60.

Kopple, J. D. (1999). Therapeutic approaches to malnutrition in chronic dialysis patients: the different modalities of nutritional support. *Am J Kidney Dis*, 33(1), 180–5.

Kopple, J. D., Brunori, G., Leiserowitz, M., *et al.* (2005). Growth hormone induces anabolism in malnourished maintenance haemodialysis patients. *Nephrol Dial Transplant*, 20(5), 952–8.

Kopple, J. D., Greene, T., Chumlea, W. C., *et al.* (2000). Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. *Kidney Int*, 57(4), 1688–703.

Kotzmann, H., Yilmaz, N., Lercher, P., *et al.* (2001). Differential effects of growth hormone therapy in malnourished hemodialysis patients. *Kidney Int*, 60(4), 1578–85.

Koutras, D. A., Marketos, S. G., Rigopoulos, G. A., *et al.* (1972). Iodine metabolism in chronic renal insufficiency. *Nephron*, 9(1), 55–65.

Kutlay, S., Atli, T., Koseogullari, O., *et al.* (2005). Thyroid disorders in hemodialysis patients in an iodine-deficient community. *Artif Organs*, 29(4), 329–32.

Kyriazis, J., Tzanakis, I., Stylianou, K., *et al.* (2011). Low serum testosterone, arterial stiffness and mortality in male haemodialysis patients. *Nephrol Dial Transplant*, 26(9), 2971–7.

Landt, M., Brennan, D. C., Parvin, C. A., *et al.* (1998). Hyperleptinaemia of end-stage renal disease is corrected by renal transplantation. *Nephrol Dial Transplant*, 13(9), 2271–5.

Le Roith, D., Scavo, L., and Butler, A. (2001). What is the role of circulating IGF-I? *Trends Endocrinol Metab*, 12(2), 48–52.
Lee, K. O., Oh, Y., Giudice, L. C., *et al.* (1994). Identification of insulin-like growth factor-binding protein-3 (IGFBP-3) fragments and IGFBP-5 proteolytic activity in human seminal plasma: a comparison of normal and vasectomized patients. *J Clin Endocrinol Metab*, 79(5), 1367–72.
Lee, P. D., Hintz, R. L., Sperry, J. B., *et al.* (1989). IGF binding proteins in growth-retarded children with chronic renal failure. *Pediatr Res*, 26(4), 308–15.
Leung, D. W., Spencer, S. A., Cachianes, G., *et al.* (1987). Growth hormone receptor and serum binding protein: purification, cloning and expression. *Nature*, 330(6148), 537–43.
Leung, K. C., Waters, M. J., Markus, I., *et al.* (1997). Insulin and insulin-like growth factor-I acutely inhibit surface translocation of growth hormone receptors in osteoblasts: a novel mechanism of growth hormone receptor regulation. *Proc Natl Acad Sci U S A*, 94(21), 11381–6.
Liewendahl, K., Tikanoja, S., Mähönen, H., *et al.* (1987). Concentrations of iodothyronines in serum of patients with chronic renal failure and other nonthyroidal illnesses: role of free fatty acids. *Clin Chem*, 33(8), 1382–6.
Lim, V. S. (2001). Thyroid function in patients with chronic renal failure. *Am J Kidney Dis*, 38(4 Suppl 1), S80–4.
Lim, V. S. and Fang, V. S. (1975). Gonadal dysfunction in uremic men. A study of the hypothalamo-pituitary-testicular axis before and after renal transplantation. *Am J Med*, 58(5), 655–62.
Lim, V. S., Fang, V. S., Katz, A. I., *et al.* (1977). Thyroid dysfunction in chronic renal failure. A study of the pituitary-thyroid axis and peripheral turnover kinetics of thyroxine and triiodothyronine. *J Clin Invest*, 60(3), 522–34.
Lim, V. S., Henriquez, C., Sievertsen, G., *et al.* (1980). Ovarian function in chronic renal failure: evidence suggesting hypothalamic anovulation. *Ann Intern Med*, 93(1), 21–7.
Lim, V. S., Kathpalia, S. C., and Frohman, L. A. (1979). Hyperprolactinemia and impaired pituitary response to suppression and stimulation in chronic renal failure: reversal after transplantation. *J Clin Endocrinol Metab*, 48(1), 101–7.
Liu, F., Powell, D. R., and Hintz, R. L. (1990). Characterization of insulin-like growth factor-binding proteins in human serum from patients with chronic renal failure. *J Clin Endocrinol Metab*, 70(3), 620–8.
Lo, J. C., Chertow, G. M., Go, A. S., *et al.* (2005). Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. *Kidney Int*, 67(3), 1047–52.
Luger, A., Deuster, P. A., Kyle, S. B., *et al.* (1987). Acute hypothalamic-pituitary-adrenal responses to the stress of treadmill exercise. Physiologic adaptations to physical training. *N Engl J Med*, 316(21), 1309–15.
Mahan, J. D. and Warady, B. A. (2006). Assessment and treatment of short stature in pediatric patients with chronic kidney disease: a consensus statement. *Pediatr Nephrol*, 21(7), 917–30.
Malkin, C. J., Channer, K. S., and Jones, T. H. (2010). Testosterone and heart failure. *Curr Opin Endocrinol Diabetes Obes*, 17(3), 262–8.
Mangos, G. J., Whitworth, J. A., Williamson, P. M., *et al.* (2003). Glucocorticoids and the kidney. *Nephrology*, 8(6), 267–73.
Marumo, F., Sakai, T., and Sato, S. (1979). Response of insulin, glucagon and growth hormone to arginine infusion in patients with chronic renal failure. *Nephron*, 24(2), 81–4.
Matsubara, M., Nakagawa, K., Nonomura, K., *et al.* (1983). Plasma LRH levels in chronic renal failure before and during haemodialysis. *Acta Endocrinol*, 103(2), 145–50.
McDonald, W. J., Golper, T. A., Mass, R. D., *et al.* (1979). Adrenocorticotropin-cortisol axis abnormalities in hemodialysis patients. *J Clin Endocrinol Metab*, 48(1), 92–5.
McKillop, J. H., Leung, A. C., and Wilson, R. (1985). Successful management of Graves' disease in a patient undergoing regular dialysis therapy. *Arch Intern Med*, 145(2), 337–9.
McNeilly, A. S. (1980). Prolactin and the control of gonadotrophin secretion in the female. *J Reprod Fertil*, 58(2), 537–49.
Metcalfe, P. D., Leslie, J. A., Campbell, M. T., *et al.* (2008). Testosterone exacerbates obstructive renal injury by stimulating TNF-alpha production and increasing proapoptotic and profibrotic signaling. *Am J Physiol Endocrinol Metab*, 294(2), E435–443.
Miki, H., Oshimo, K., Inoue, H., *et al.* (1992). Thyroid carcinoma in patients with secondary hyperparathyroidism. *J Surg Oncol*, 49(3), 168–71.
Miki, H., Oshimo, K., Inoue, H., *et al.* (1993). Thyroid nodules in female uremic patients on maintenance hemodialysis. *J Surg Oncol*, 54(4), 216–18.
Milenković, L., D'Angelo, G., Kelly, P. A., *et al.* (1994). Inhibition of gonadotropin hormone-releasing hormone release by prolactin from GT1 neuronal cell lines through prolactin receptors. *Proc Natl Acad Sci U S A*, 91(4), 1244–7.
Morley, J. E., Distiller, L. A., Epstein, S., *et al.* (1979). Menstrual disturbances in chronic renal failure. *Horm Metab Res*, 11(1), 68–72.
Muir, J. W., Besser, G. M., Edwards, C. R., *et al.* (1983). Bromocriptine improves reduced libido and potency in men receiving maintenance hemodialysis. *Clin Nephrol*, 20(6), 308–14.
Müller-Wiefel, D., Frisch, H., Tulassay, T., *et al.* (2010). Treatment of growth failure with growth hormone in children with chronic kidney disease: an open-label long-term study. *Clin Nephrol*, 74(2), 97–105.
N'Gankam, V., Uehlinger, D., Dick, B., *et al.* (2002). Increased cortisol metabolites and reduced activity of 11beta-hydroxysteroid dehydrogenase in patients on hemodialysis. *Kidney Int*, 61(5), 1859–66.
Nawrot-Wawrzyniak, K., Misof, B. M., Roschger, P., *et al.* (2013). Changes in bone matrix mineralization after growth hormone treatment in children and adolescents with chronic kidney failure treated by dialysis: a paired biopsy study. *Am J Kidney Dis*, 61(5), 767–77.
Nettleship, J. E., Jones, R. D., Channer, K. S., *et al.* (2009). Testosterone and coronary artery disease. *Front Horm Res*, 37, 91–107.
Nibhanupudy, J. R., Hamilton, W., Sridhar, R., *et al.* (1993). Iodine-131 treatment of hyperthyroidism in a patient on dialysis for chronic renal failure. *Am J Nephrol*, 13(3), 214–17.
Nissel, R., Lindberg, A., Mehls, O., *et al.* (2008). Factors predicting the near-final height in growth hormone-treated children and adolescents with chronic kidney disease. *J Clin Endocrinol Metab*, 93(4), 1359–65.
Nolan, G. E., Smith, J. B., Chavre, V. J., *et al.* (1981). Spurious overestimation of plasma cortisol in patients with chronic renal failure. *J Clin Endocrinol Metab*, 52(6), 1242–5.
Norman, A. W. and Litwack G. (1997). *Hormones* (2nd ed.). New York: Academic Press.
Noto, R., Maneatis, T., Frane, J., *et al.* (2011). Intracranial hypertension in pediatric patients treated with recombinant human growth hormone: data from 25 years of the Genentech National Cooperative Growth Study. *J Pediatr Endocrinol Metab*, 24(9–10), 627–31.
Oguz, Y., Oktenli, C., Ozata, M., *et al.* (2003). The midnight-to-morning urinary cortisol increment method is not reliable for the assessment of hypothalamic-pituitary-adrenal insufficiency in patients with end-stage kidney disease. *J Endocrinol Invest*, 26(7), 609–15.
Pagliacci, M. C., Pelicci, G., Grignani, F., *et al.* (1987). Thyroid function tests in patients undergoing maintenance dialysis: characterization of the 'low-T4 syndrome' in subjects on regular hemodialysis and continuous ambulatory peritoneal dialysis. *Nephron*, 46(3), 225–30.
Palmer, B. F. (1999). Sexual dysfunction in uremia. *J Am Soc Nephrol*, 10(6), 1381–8.
Peces, R., Horcajada, C., López-Novoa, J. M., *et al.* (1981). Hyperprolactinemia in chronic renal failure: impaired responsiveness to stimulation and suppression. Normalization after transplantation. *Nephron*, 28(1), 11–16.
Postel-Vinay, M. C., Tar, A., Crosnier, H., *et al.* (1991). Plasma growth hormone-binding activity is low in uraemic children. *Pediatr Nephrol*, 5(4), 545–7.
Postlethwaite, R. J., Eminson, D. M., Reynolds, J. M., *et al.* (1998). Growth in renal failure: a longitudinal study of emotional and behavioural changes during trials of growth hormone treatment. *Arch Dis Child*, 78(3), 222–9.

Powell, D. R., Durham, S. K., Brewer, E. D., *et al.* (1999). Effects of chronic renal failure and growth hormone on serum levels of insulin-like growth factor-binding protein-4 (IGFBP-4) and IGFBP-5 in children: a report of the Southwest Pediatric Nephrology Study Group. *J Clin Endocrinol Metab*, 84(2), 596–601.

Powell, D. R., Liu, F., Baker, B. K., *et al.* (1997a). Insulin-like growth factor-binding protein-6 levels are elevated in serum of children with chronic renal failure: a report of the Southwest Pediatric Nephrology Study Group. *J Clin Endocrinol Metab*, 82(9), 2978–84.

Powell, D. R., Liu, F., Baker, B. K., *et al.* (1997b). Modulation of growth factors by growth hormone in children with chronic renal failure. The Southwest Pediatric Nephrology Study Group. *Kidney Int*, 51(6), 1970–9.

Pupim, L. B., Flakoll, P. J., Brouillette, J. R., *et al.* (2002). Intradialytic parenteral nutrition improves protein and energy homeostasis in chronic hemodialysis patients. *J Clin Invest*, 110(4), 483–92.

Pupim, L. B., Flakoll, P. J., Yu, C., *et al.* (2005). Recombinant human growth hormone improves muscle amino acid uptake and whole-body protein metabolism in chronic hemodialysis patients. *Am J Clin Nutr*, 82(6), 1235–43.

Qureshi, A. R., Alvestrand, A., Danielsson, A., *et al.* (1998). Factors predicting malnutrition in hemodialysis patients: a cross-sectional study. *Kidney Int*, 53(3), 773–82.

Rabkin, R., Sun, D. F., Chen, Y., *et al.* (2005). Growth hormone resistance in uremia, a role for impaired JAK/STAT signaling. *Pediatr Nephrol*, 20(3), 313–18.

Rabkin, R., Unterhalter, S. A., and Duckworth, W. C. (1979). Effect of prolonged uremia on insulin metabolism by isolated liver and muscle. *Kidney Int*, 16(4), 433–9.

Ramirez, G., Bittle, P. A., Sanders, H., *et al.* (1992). Hypothalamo-hypophyseal thyroid and gonadal function before and after erythropoietin therapy in dialysis patients. *J Clin Endocrinol Metab*, 74(3), 517–24.

Ramirez, G., Brueggemeyer, C., and Ganguly, A. (1988). Counterregulatory hormonal response to insulin-induced hypoglycemia in patients on chronic hemodialysis. *Nephron*, 49(3), 231–6.

Ramirez, G., Butcher, D., Brueggemeyer, C. D., *et al.* (1987). Testicular defect: the primary abnormality in gonadal dysfunction of uremia. *South Med J*, 80(6), 698–701.

Ramirez, G., Gomez-Sanchez, C., Meikle, W. A., *et al.* (1982). Evaluation of the hypothalamic hypophyseal adrenal axis in patients receiving long-term hemodialysis. *Arch Intern Med*, 142(8), 1448–52.

Ramirez, G., O'Neill, W., Jr., Jubiz, W., *et al.* (1976). Thyroid dysfunction in uremia: evidence for thyroid and hypophyseal abnormalities. *Ann Intern Med*, 84(6), 672–6.

Ramirez, G., O'Neill, W. M., Jr., Bloomer, H. A., *et al.* (1977). Abnormalities in the regulation of prolactin in patients with chronic renal failure. *J Clin Endocrinol Metab*, 45(4), 658–61.

Ramirez, G., O'Neill, W. M., Bloomer, H. A., *et al.* (1978). Abnormalities in the regulation of growth hormone in chronic renal failure. *Arch Intern Med*, 138(2), 267–71.

Reckelhoff, J. F., Zhang, H., and Srivastava, K. (2000). Gender differences in development of hypertension in spontaneously hypertensive rats: role of the renin-angiotensin system. *Hypertension*, 35(1 Pt 2), 480–3.

Rini, B. I., Tamaskar, I., Shaheen, P., *et al.* (2007). Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst*, 99(1), 81–3.

Rodger, R. S., Dewar, J. H., Turner, S. J., *et al.* (1986). Anterior pituitary dysfunction in patients with chronic renal failure treated by hemodialysis or continuous ambulatory peritoneal dialysis. *Nephron*, 43(3), 169–72.

Rodger, R. S., Morrison, L., Dewar, J. H., *et al.* (1985). Loss of pulsatile luteinising hormone secretion in men with chronic renal failure. *Br Med J (Clin Res Ed)*, 291(6509), 1598–600.

Rodríguez-Puyol, D., Martín-Oar, J. E., Cachofeiro, M. V., *et al.* (1986). Molecular heterogeneity of circulating prolactin in chronic uremic men and renal transplant recipients. *J Clin Endocrinol Metab*, 62(2), 352–6.

Roelfsema, V. and Clark, R. G. (2001). The growth hormone and insulin-like growth factor axis: its manipulation for the benefit of growth disorders in renal failure. *J Am Soc Nephrol*, 12(6), 1297–306.

Rosman, P. M., Farag, A., Peckham, R., *et al.* (1982). Pituitary-adrenocortical function in chronic renal failure: blunted suppression and early escape of plasma cortisol levels after intravenous dexamethasone. *J Clin Endocrinol Metab*, 54(3), 528–33.

Rotondi, M., Netti, G. S., Rosati, A., *et al.*(2008). Pretransplant serum FT3 levels in kidney graft recipients are useful for identifying patients with higher risk for graft failure. *Clin Endocrinol (Oxf)*, 68(2), 220–5.

Rudolf, K., Kunkel, S., Rudolf, H., *et al.* (1988). [Basal and stimulated secretion of prolactin and growth hormone in patients with chronic uremia]. *Zentralbl Gynakol*, 110(11), 693–7.

Saha, M. -T., Saha, H. H. T., Niskanen, L. K., *et al.* (2002). Time course of serum prolactin and sex hormones following successful renal transplantation. *Nephron*, 92(3), 735–7.

Sakemi, T., Ohtsuka, N., Tomiyosi, Y., *et al.* (1997). Attenuating effect of castration on glomerular injury is age-dependent in unilaterally nephrectomized male Sprague-Dawley rats. *Nephron*, 75(3), 342–9.

Sanai, T., Inoue, T., Okamura, K., *et al.* (2008). Reversible primary hypothyroidism in Japanese patients undergoing maintenance hemodialysis. *Clin Nephrol*, 69(2), 107–13.

Santoro, A. and Mancini, E. (2010). Hemodialysis and the elderly patient: complications and concerns. *J Nephrol*, 23 Suppl 15, S80–89.

Santos, F., Moreno, M. L., Neto, A., *et al.* (2010). Improvement in growth after 1 year of growth hormone therapy in well-nourished infants with growth retardation secondary to chronic renal failure: results of a multicenter, controlled, randomized, open clinical trial. *Clin J Am Soc Nephrol*, 5(7), 1190–7.

Sari, F., Sari, R., Ozdem, S., *et al.* (2012). Serum prolactin and macroprolactin levels in diabetic nephropathy. *Clin Nephrol*, 78(1), 33–9.

Sasagawa, I., Tateno, T., Suzuki, Y., *et al.* (1998). Circulating levels of inhibin in hemodialysis males. *Arch Androl*, 41(3), 167–71.

Sato, K., Okamura, K., Yoshinari, M., *et al.* (1992). Reversible primary hypothyroidism and elevated serum iodine level in patients with renal dysfunction. *Acta Endocrinol*, 126(3), 253–9.

Schaefer, F., Chen, Y., Tsao, T., *et al.* (2001). Impaired JAK-STAT signal transduction contributes to growth hormone resistance in chronic uremia. *J Clin Invest*, 108(3), 467–75.

Schaefer, F., Seidel, C., Mitchell, R., *et al.* (1991). Pulsatile immunoreactive and bioactive luteinizing hormone secretion in adolescents with chronic renal failure. The Cooperative Study Group on Pubertal Development in Chronic Renal Failure (CSPCRF). *Pediatr Nephrol*, 5(4), 566–71.

Schaefer, F., Veldhuis, J. D., Stanhope, R., *et al.* (1994). Alterations in growth hormone secretion and clearance in peripubertal boys with chronic renal failure and after renal transplantation. Cooperative Study Group of Pubertal development in Chronic Renal Failure. *J Clin Endocrinol Metab*, 78(6), 1298–306.

Schalch, D. S., Gonzalez-Barcena, D., Kastin, A. J., *et al.* (1975). Plasma gonadotropins after administration of LH-releasing hormone in patients with renal or hepatic failure. *J Clin Endocrinol Metab*, 41(5), 921–5.

Schmitz, O. and Møller, J. (1983). Impaired prolactin response to arginine infusion and insulin hypoglycaemia in chronic renal failure. *Acta Endocrinol*, 102(4), 486–91.

Seikaly, M. G., Waber, P., Warady, B. A., *et al.* (2009). The effect of rhGH on height velocity and BMI in children with CKD: a report of the NAPRTCS registry. *Pediatr Nephrol*, 24(9), 1711–17.

Shahidi, N. T. (1973). Androgens and erythropoiesis. *N Engl J Med*, 289(2), 72–80.

Sharma, K., Considine, R. V., Michael, B., *et al.* (1997). Plasma leptin is partly cleared by the kidney and is elevated in hemodialysis patients. *Kidney Int*, 51(6), 1980–5.

Sharp, N. A., Devlin, J. T., and Rimmer, J. M. (1986). Renal failure obfuscates the diagnosis of Cushing's disease. *JAMA*, 256(18), 2564–5.

Siamopoulos, K. C., Eleftheriades, E. G., Pappas, M., *et al.* (1988). Ovine corticotropin-releasing hormone stimulation test in patients with chronic renal failure: pharmacokinetic properties, and plasma

adrenocorticotropic hormone and serum cortisol responses. *Horm Res*, 30(1), 17–21.
Sievertsen, G. D., Lim, V. S., Nakawatase, C., *et al.* (1980). Metabolic clearance and secretion rates of human prolactin in normal subjects and in patients with chronic renal failure. *J Clin Endocrinol Metab*, 50(5), 846–52.
Silbiger, S. and Neugarten, J. (2008). Gender and human chronic renal disease. *Gend Med*, 5 Suppl A, S3–10.
Silverberg, D. S., Ulan, R. A., Fawcett, D. M., *et al.* (1973). Effects of chronic hemodialysis on thyroid function in chronic renal failure. *Can Med Assoc J*, 109(4), 282–6.
Singh, P. A., Bobby, Z., Selvaraj, N., *et al.* (2006). An evaluation of thyroid hormone status and oxidative stress in undialyzed chronic renal failure patients. *Indian J Physiol Pharmacol*, 50(3), 279–84.
Soffer, O., Chary, K. R., and Hall, W. D. (1980). Clinical hyperthyroidism in a patient receiving long-term hemodialysis. *Arch Intern Med*, 140(5), 708–9.
Sohmiya, M., Ishikawa, K., and Kato, Y. (1998). Stimulation of erythropoietin secretion by continuous subcutaneous infusion of recombinant human GH in anemic patients with chronic renal failure. *Eur J Endocrinol*, 138(3), 302–6.
Soules, M. R., Steiner, R. A., Clifton, D. K., *et al.* (1984). Progesterone modulation of pulsatile luteinizing hormone secretion in normal women. *J Clin Endocrinol Metab*, 58(2), 378–83.
Spark, R. F., Wills, C. A., O'Reilly, G., *et al.* (1982). Hyperprolactinaemia in males with and without pituitary macroadenomas. *Lancet*, 2(8290), 129–32.
Stanley, H. L., Schmitt, B. P., Poses, R. M., *et al.* (1991). Does hypogonadism contribute to the occurrence of a minimal trauma hip fracture in elderly men? *J Am Geriatr Soc*, 39(8), 766–71.
Stewart-Bentley, M., Gans, D., and Horton, R. (1974). Regulation of gonadal function in uremia. *Metab Clin Exp*, 23(11), 1065–72.
Swamy, A. P., Woolf, P. D., and Cestero, R. V. (1979). Hypothalamic-pituitary-ovarian axis in uremic women. *J Lab Clin Med*, 93(6), 1066–72.
Tauchmanovà, L., Carrano, R., Musella, T., *et al.* (2006). Thyroid function and morphology after a successful kidney transplantation. *J Endocrinol Invest*, 29(7), 625–32.
Teruel, J. L., Marcén, R., Navarro, J. F., *et al.* (1995). Evolution of serum erythropoietin after androgen administration to hemodialysis patients: a prospective study. *Nephron*, 70(3), 282–6.
Tönshoff, B., Blum, W. F., and Mehls, O. (1995a). Insulin-like growth factors (IGF) and IGF binding proteins in children with chronic renal failure. *Prog Growth Factor Res*, 6(2–4), 481–91.
Tönshoff, B., Blum, W. F., and Mehls, O. (1996). Serum insulin-like growth factors and their binding proteins in children with end-stage renal disease. *Pediatr Nephrol*, 10(3), 269–74.
Tönshoff, B., Mehis, O., Heinrich, U., *et al.* (1990). Growth-stimulating effects of recombinant human growth hormone in children with end-stage renal disease. *J Pediatr*, 116(4), 561–6.
Tönshoff, B., Veldhuis, J. D., Heinrich, U., *et al.* (1995b). Deconvolution analysis of spontaneous nocturnal growth hormone secretion in prepubertal children with preterminal chronic renal failure and with end-stage renal disease. *Pediatr Res*, 37(1), 86–93.
Traish, A. M., Saad, F., Feeley, R. J., *et al.* (2009). The dark side of testosterone deficiency: III. Cardiovascular disease. *J Androl*, 30(5), 477–94.
Ulinski, T., Mohan, S., Kiepe, D., *et al.* (2000). Serum insulin-like growth factor binding protein (IGFBP)-4 and IGFBP-5 in children with chronic renal failure: relationship to growth and glomerular filtration rate. The European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. German Study Group for Growth Hormone Treatment in Chronic Renal Failure. *Pediatr Nephrol*, 14(7), 589–97.
Umemoto, S., Izumi, K., and Kanno, H. (2007). [Two cases of hyperthyroidism induced by interferon-alpha therapy for renal cell carcinoma]. *Hinyokika Kiyo*, 53(4), 225–9.
Van den Heijkant, S., Hoorweg-Nijman, G., Huisman, J., *et al.* (2011). Effects of growth hormone therapy on bone mass, metabolic balance, and well-being in young adult survivors of childhood acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*, 33(6), e231–8.
Van Leusen, R. and Meinders, A. E. (1982). Cyclical changes in serum thyroid hormone concentrations related to hemodialysis: movement of hormone into and out of the extravascular space as a possible mechanism. *Clin Nephrol*, 18(4), 193–9.
Vaziri, N. D. (2004). Oxidative stress in uremia: nature, mechanisms, and potential consequences. *Semin Nephrol*, 24(5), 469–73.
Veldhuis, J. D., Iranmanesh, A., Wilkowski, M. J., *et al.* (1994). Neuroendocrine alterations in the somatotropic and lactotropic axes in uremic men. *Eur J Endocrinol*, 131(5), 489–98.
Veldhuis, J. D., Wilkowski, M. J., Zwart, A. D., *et al.* (1993). Evidence for attenuation of hypothalamic gonadotropin-releasing hormone (GnRH) impulse strength with preservation of GnRH pulse frequency in men with chronic renal failure. *J Clin Endocrinol Metab*, 76(3), 648–54.
Verger, M. F., Verger, C., Hatt-Magnien, D., *et al.* (1987). Relationship between thyroid hormones and nutrition in chronic renal failure. *Nephron*, 45(3), 211–15.
Verzola, D., Villaggio, B., Procopio, V., *et al.* (2009). Androgen-mediated apoptosis of kidney tubule cells: role of c-Jun amino terminal kinase. *Biochem Biophys Res Commun*, 387(3), 531–6.
Vimalachandra, D., Craig, J. C., Cowell, C. T., *et al.* (2001). Growth hormone treatment in children with chronic renal failure: a meta-analysis of randomized controlled trials. *J Pediatr*, 139(4), 560–7.
Wallace, E. Z., Rosman, P., Toshav, N., *et al.* (1980). -adrenocortical function in chronic renal failure: studies of episodic secretion of cortisol and dexamethasone suppressibility. *J Clin Endocrinol Metab*, 50(1), 46–51.
Wang, L. -C., Tsai, W. -Y., Yang, Y. -H., *et al.* (2003). Methimazole-induced lupus erythematosus: a case report. *J Microbiol Immunol Infect*, 36(4), 278–81.
Warren, M. P. (1983). Effects of undernutrition on reproductive function in the human. *Endocr Rev*, 4(4), 363–77.
Weetman, A. P., Weightman, D. R., and Scanlon, M. F. (1981). Impaired dopaminergic control of thyroid stimulating hormone secretion in chronic renal failure. *Clin Endocrinol (Oxf)*, 15(5), 451–6.
Weissel, M., Stummvoll, H. K., Kolbe, H., *et al.* (1979). Basal and TRH-stimulated thyroid and pituitary hormones in various degrees of renal insufficiency. *Acta Endocrinol*, 90(1), 23–32.
Wheatley, T., Clark, P. M., Clark, J. D., *et al.* (1989). Abnormalities of thyrotrophin (TSH) evening rise and pulsatile release in haemodialysis patients: evidence for hypothalamic-pituitary changes in chronic renal failure. *Clin Endocrinol (Oxf)*, 31(1), 39–50.
Wheatley, T., Clark, P. M., Clark, J. D., *et al.* (1987). Pulsatility of luteinising hormone in men with chronic renal failure: abnormal rather than absent. *Br Med J (Clin Res Ed)*, 294(6570), 482.
White, H. D., Ahmad, A. M., Durham, B. H., *et al.* (2005). Growth hormone replacement is important for the restoration of parathyroid hormone sensitivity and improvement in bone metabolism in older adult growth hormone-deficient patients. *J Clin Endocrinol Metab*, 90(6), 3371–80.
White, H. D., Ahmad, A. M., Durham, B. H., *et al.* (2007). PTH circadian rhythm and PTH target-organ sensitivity is altered in patients with adult growth hormone deficiency with low BMD. *J Bone Miner Res*, 22(11), 1798–807.
Whitworth, J. A., Stewart, P. M., Burt, D., *et al.* (1989). The kidney is the major site of cortisone production in man. *Clin Endocrinol (Oxf)*, 31(3), 355–61.
Wiederkehr, M. R., Kalogiros, J., and Krapf, R. (2004). Correction of metabolic acidosis improves thyroid and growth hormone axes in haemodialysis patients. *Nephrol Dial Transplant*, 19(5), 1190–7.
Williams, G. H., Bailey, G. L., Hampers, C. L., *et al.* (1973). Studies on the metabolism of aldosterone in chronic renal failure and anephric man. *Kidney Int*, 4(4), 280–8.
Witzke, O., Wiemann, J., Patschan, D., *et al.* (2007). Differential T4 degradation pathways in young patients with preterminal and terminal renal failure. *Horm Metab Res*, 39(5), 355–8.

Workman, R. J., Vaughn, W. K., and Stone, W. J. (1986). Dexamethasone suppression testing in chronic renal failure: pharmacokinetics of dexamethasone and demonstration of a normal hypothalamic-pituitary-adrenal axis. *J Clin Endocrinol Metab*, 63(3), 741–6.

Yakar, S., Liu, J. L., Stannard, B., *et al*. (1999). Normal growth and development in the absence of hepatic insulin-like growth factor I. *Proc Natl Acad Sci U S A*, 96(13), 7324–9.

Yilmaz, M. I., Sonmez, A., Qureshi, A. R., *et al*. (2011). Endogenous testosterone, endothelial dysfunction, and cardiovascular events in men with nondialysis chronic kidney disease. *Clin J Am Soc Nephrol*, 6(7), 1617–25.

Yu, F., Chen, M., Gao, Y., *et al*. (2007). Clinical and pathological features of renal involvement in propylthiouracil-associated ANCA-positive vasculitis. *Am J Kidney Dis*, 49(5), 607–14.

Zadeh, J. A., Koutsaimanis, K. G., Roberts, A. P., *et al*. (1975). The effect of maintenance haemodialysis and renal transplantation on the plasma testosterone levels of male patients in chronic renal failure. *Acta Endocrinol*, 80(3), 577–82.

Zager, P. G., Spalding, C. T., Frey, H. J., *et al*. (1985). Low dose adrenocorticotropin infusion in continuous ambulatory peritoneal dialysis patients. *J Clin Endocrinol Metab*, 61(6), 1205–10.

Zhang, R., Alper, B., Simon, E., *et al*. (2008). Management of metabolic bone disease in kidney transplant recipients. *Am J Med Sci*, 335(2), 120–5.

Ziegler, T. R., Lazarus, J. M., Young, L. S., *et al*. (1991). Effects of recombinant human growth hormone in adults receiving maintenance hemodialysis. *J Am Soc Nephrol*, 2(6), 1130–5.

Zilker, T. R., Rebel, C., Kopp, K. F., *et al*. (1988). Kinetics of biosynthetic human proinsulin in patients with terminal renal insufficiency. *Horm Metab Res Suppl*, 18, 43–8.

Zoccali, C. and Mallamaci, F. (2012). Thyroid function and clinical outcomes in kidney failure. *Clin J Am Soc Nephrol*, 7(1), 12–4.

Zoccali, C., Mallamaci, F., Tripepi, G., *et al*. (2006). Low triiodothyronine and survival in end-stage renal disease. *Kidney Int*, 70(3), 523–8.

Zoccali, C., Tripepi, G., Cutrupi, S., et al. (2005). Low triiodothyronine: a new facet of inflammation in end-stage renal disease. J Am Soc Nephrol, 16(9), 2789–95.

CHAPTER 133

Sexual dysfunction

Tomas Thor Agustsson and Paul Carroll

Introduction

Sexual problems in patients with chronic renal failure are both common and varied and have been shown to significantly impair quality of life. Sexual dysfunction is found in at least two-thirds of both haemodialysis and peritoneal dialysis patients (Abram et al., 1975; Bommer et al., 1976; Diemont et al., 2000). Although interest in these problems has increased significantly in the last few decades it remains one of the least well-addressed complications of chronic renal failure.

Numerous factors may contribute. Physical factors include hormonal disturbances, side effects of drugs, altered penile smooth muscle function, reduced arterial blood flow and impaired penile blood pressure, venous leakage due to venous shunts, and neurological dysfunction. Psychological factors play an important role and to manage these issues effectively it is necessary to address all potential contributing factors. Sexual dysfunction in the majority of patients with chronic renal failure will be caused by a combination of physical and psychological factors.

Sexual dysfunction in men with chronic renal failure

Patients treated with haemodialysis often describe several problems relating to sexual function. The most common include loss of libido, erectile dysfunction (ED), impaired sense of satisfaction, ejaculatory problems, and concerns about fertility. Older studies found that ED affects 40–80% of all men on haemodialysis (Abram et al., 1975; Bommer et al., 1976; Toorians et al., 1997; Diemont et al., 2000), and at least half describe reduced libido (Toorians et al., 1997). More recent studies confirm this high prevalence at 9% in predialysis patients to 70–80% in those receiving dialysis (Palmer, 1999, 2004). Some studies from the 1970s showed that libido and sexual function had already declined in the majority of uraemic men before starting dialysis, with little or no change during dialysis therapy (Abram et al., 1975; Salvatierra et al., 1975; Sherman, 1975; Procci et al., 1981; Handelsman and Dong, 1993; Handelsman and Liu, 1998). If psychological factors around this step in treatment are effectively addressed, improvement after initiation of dialysis is more likely (Bommer et al., 1976). Sexual dysfunction is less prevalent in transplant patients, but still affects at least half (Diemont et al., 2003), although there is often substantial improvement after successful transplantation.

Erectile dysfunction and its treatment

Several disease mechanisms can lead to ED in uraemia. The most important causes include vascular insufficiency, neurogenic causes, psychogenic problems, complications of drug therapy, and hormonal factors. Identifying these factors can guide tailored treatment.

Several tests have been developed to differentiate between ED caused by vascular, neurogenic, or psychogenic causes. Measurements of nocturnal penile tumescence can be used to differentiate between psychogenic and organic causes of ED. This can be done by the 'stamp test', snap gauge band, or special strain transducers, which register the intensity and frequency of tumescence during the night. A normal result indicates psychogenic ED (Karacan et al., 1977). The visual sexual stimulation test, with and without vibrotactile stimulation of the penis, is another laboratory-based test which can be used for the same purposes (Slob et al., 1990; Janssen et al., 1994). For a more detailed vascular diagnosis, measurements of systolic pressure in the penile artery can be used. This can be achieved using a small sphygmomanometer cuff and Doppler sonography. Significant discrepancy (penile blood pressure index < 0.6) indicates arteriogenic impotence. Intracavernosal injection of a vasodilating agent, such as 10 micrograms of prostaglandin E1 (PGE1), is perhaps a more accurate test of penile vasculature. In normal subjects this is followed by a full rigid erection within 10–15 minutes lasting for at least 30 minutes. Such injections closely mimic normal penile haemodynamic changes during erection and if the patient responds normally, vascular problems can be excluded and neurological or psychological causes should be addressed. If a vascular problem is suspected then further imaging with duplex ultrasound or angiography is indicated, especially if surgical repair is being considered.

Several simple tests can indicate whether severe neurological problems are present. Latency of the bulbus cavernous reflex can indicate damage to the pudendal nerve. Autonomic dysfunction can, for example, be assessed by measuring orthostatic hypotension, Valsalva ratio, and cold pressure hand tests.

Vascular causes for erectile dysfunction

Arterial blood flow

Adequate arterial blood flow and pressure in penile arteries are necessary for correct penile erection. An intercavernosal arterial blood pressure > 80 mmHg is essential for erection that is sufficient to allow penetration. During erection, the intercavernosal pressure is around 20 mmHg lower than the pressure in the pelvic arteries. Systemic systolic pressure of at least 80–100 mmHg is therefore required to achieve an erection. Arterial occlusive disease will cause a greater gradient and insufficient penile pressures. It is interesting and clinically a very important observation that intermittent claudication in the lower limbs develops at peripheral pressures of around 70 mmHg. ED can therefore be an earlier marker of significant atherosclerotic disease (Jackson et al., 2010).

Vascular disease is thought to contribute to at least 60% of ED in non-uraemic patients (Virag et al., 1985a, 1985b). Considering the higher prevalence of atherosclerotic changes in the uraemic population this is likely to be even higher. This relationship and the precise aetiological significance of renal insufficiency in arterial vascular ED is complex and somewhat difficult to define. Advancing age, diabetes mellitus, smoking, hypertension, hyperlipidaemia, homocysteinaemia, and disturbed calcium/phosphate metabolism are probably the main factors favouring arterial causes of ED in this population, just like in patients without renal insufficiency. A large proportion of dialysis patients also have diabetes mellitus which is known to cause ED through many related processes including micro-and macroangiopathy and neuropathy (McConnell et al., 1982).

Venous leakage

Smooth muscle dysfunction followed by impaired veno-occlusion is a common cause for incomplete or insufficiently persisting erection in dialysis patients. During penile erection, venous efflux is reduced by the expansion of penile smooth muscle against the inflexible tunica albuginea, resulting in a compression of subtunical veins. Impaired relaxation of penile smooth muscle is the main reason for insufficient reduction of venous efflux from the cavernosal space, resulting in ED. Several causes for this impairment have been postulated. Precocious ageing and enhanced fibrosis which impacts smooth muscle function is common in dialysis patients (Sell and Monnier, 1990). Neural and neurohumoral factors are also likely to play a significant role.

Erectile dysfunction caused by drugs

Many commonly used drugs can affect libido and erectile function (Box 133.1). Some therapeutic agents interfere with central pathways involved in erectile function. These often affect libido at the same time. Monoamine oxidase (MAO) inhibitors and tricyclic antidepressants have been reported to inhibit both erection and ejaculation. Tobacco and alcohol impair sexual function significantly, both in subjects with and without renal failure (Mannino et al., 1994). In patients with significant arterio-occlusive disease, a direct correlation between erectile potency and blood pressure lowering can be observed with antihypertensive treatment.

Box 133.1 Drugs associated with erectile dysfunction

- Hormones: antiandrogens, oestrogen, progesterone
- β-blockers: propranolol, atenolol, pindolol
- Sympatholytics: methyldopa, clonidine, guanethidine, phenoxybenzamine, reserpine
- Vasodilators: hydralazine
- Diuretics: thiazides, spironolactone
- Lipid-lowering drugs: clofibrate, gemfibrozil
- Sedatives: various barbiturates, bromides
- Psychotropic drugs: lithium with benzodiazepines, benzodiazepines, phenothiazine, tricyclic antidepressants, monoamine oxidase inhibitors, diazepam with opiates
- Others: immunomodulatory agents, digoxin, cimetidine, ranitidine, anticholinergic drugs.

Drugs commonly used in dialysis patients with negative effects on erectile function include sympatholytics (e.g. methyldopa, clonidine), some adrenergic receptor blocking agents (e.g. prazosin), β-blockers (propranolol), and vasodilators (e.g. hydralazine); α-adrenergic agents such as clonidine may also act via constriction of the cavernosal artery regulated by α_2-adrenergic receptors (Hedlund and Andersson, 1985). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers affect erectile function to a lesser degree and are therefore often the preferred agents in men with ED requiring antihypertensive treatment.

Neurogenic causes for erectile dysfunction

Normal penile erection is a complex process influenced by several humoral, neural, and local substances in addition to central effects. Different neurogenic processes are involved in this cascade of effects and can be affected in chronic renal failure. Direct nerve destruction, for example, after prostate surgery, proctocolectomy, or other pelvic surgery, can cause neurogenic ED. Autonomic neuropathy is a much more common cause of ED in chronic renal failure. Intact parasympathetic activity is required for initiation and maintenance of normal erection. Studies have shown high prevalence of parasympathetic dysfunction in dialysis patients. Jassal et al. described parasympathetic dysfunction in 65.9% of older dialysis patients (> 65 years of age) and 33.3% of younger dialysis patients and in 11.8% and 0% of the older and younger control subjects, respectively. Combined parasympathetic and sympathetic dysfunction was seen in 41.5% and 11.9% of older and younger dialysis patients but not in any of the control groups (Jassal et al., 1998a, 1998b). Some improvement in autonomic function has been observed after starting haemodialysis (Röckel et al., 1979; Zucchelli et al., 1985; Solders et al., 1986). When assessing causes of ED, autonomic neuropathy related to diabetes mellitus and alcohol excess should always be considered.

Psychogenic causes for erectile dysfunction

The importance of psychological factors cannot be overestimated in any patient, male or female, presenting with sexual dysfunction. The correlation between depression and ED is well recognized. In the Massachusetts Male Aging Study, out of non-uraemic men with severe depression, 90% had ED, while 25% with minimal depression described ED (Feldman et al., 1994). The exact neuropsychiatric pathways involved in this disturbance are not entirely known, but a variety of cortical centres, hypothalamic nuclei, and peripheral sympathetic and parasympathetic nerve fibres are involved. Psychogenic stimuli to the sacral cord may inhibit reflex erections. Excessive sympathetic stimulation, elevated blood catecholamine, or both, can also increase penile smooth muscle tone, opposing the smooth muscle relaxation necessary for erection.

Overall, patients with chronic renal failure suffer from many physical and psychological stresses, which are likely to affect erectile function. Depression is more common in patients receiving dialysis treatment than in healthy controls and transplant patients. The time lost to dialysis treatment, whether haemodialysis, chronic ambulatory peritoneal dialysis, or intermittent peritoneal dialysis, and the physical and psychological implications of such a severe disease and its therapy produce problems and increased stress at home and at work. Alternative social roles at home and in marriage

may influence self-confidence and increase performance anxiety (Glass et al., 1987).

Hormonal factors

The different hormonal abnormalities associated with sexual dysfunction in men are discussed in detail in Chapter 132. These include hypogonadism, which is very common in CKD, end-stage renal disease (ESRD), and in dialysis patients, and affects both libido and erectile function significantly. Hyperprolactinaemia related to uraemia is also associated with hypogonadism and sexual dysfunction. Hypothyroidism can also be a contributing factor.

Treatment options for erectile dysfunction and hypogonadism in renal failure

Because of the multifactorial causes of ED and hypogonadism in renal failure some general principles apply and a holistic approach must be used. Optimal delivery of renal replacement therapy and adequate nutritional intake is important. Implicated drugs must be removed, but appropriate therapy for depression or other psychological factors must be considered along with correction of anaemia (Palmer, 1999) (Box 133.2).

Phosphodiesterase type 5 inhibitors

A number of phosphodiesterase type 5 (PDE5) inhibitors are now available on the market and have undoubtedly become the most commonly used therapy for ED. These include sildenafil, tadalafil, and vardenafil. By inhibiting cGMP-specific PDE5, they reduce cGMP clearance and enhance, but do not initiate, the erectile response of erotic stimuli. They do therefore not cause a spontaneous erection, and the appropriate stimulation is required to assess their efficacy. They do also depend on the integrity of local nerve supply as a source of nitric oxide (NO). Reduced arterial function on the other hand does not exclude beneficial effects of PDE5 inhibitors. Sixty per cent of men with diabetes, for example, report at least one successful attempt at intercourse after sildenafil (Rendell et al., 1999). PDE5 inhibitors are generally well tolerated and are cleared by hepatic metabolism. Their pharmacokinetics in renal failure are similar to healthy subjects and their efficacy has been shown to be good with around 50–60% of men on dialysis reporting an erection with sildenafil (Ayub and Fletcher, 2000; Türk et al., 2001; Sharma et al., 2006). Side effects in dialysed patients are not markedly different from non-renal patients (Goldstein et al., 1998; Siegel and Grossman, 2001).

The most common side effects with PDE5 inhibitors include headache, dizziness, nasal congestion, and facial flushing (Goldstein et al., 1998; Siegel and Grossman, 2001). Several issues around this warrant special attention in the patient with renal failure. PDE5 inhibitors are contraindicated in hypotensive patients, which may have implications for timing of treatment around dialysis and other drug therapy. PDE5 inhibitors should never be used with any form of nitrate drug, or NO donor drug as simultaneous therapy could cause severe hypotension. PDE5 inhibitors are metabolized by cytochrome P450, and simultaneous treatment with other drugs affecting this enzyme system must be considered. Tacrolimus can, for example, prolong the effects of these drugs.

The different PDE5 inhibitors available differ mainly in their onset of action and half-life, which have important implications for timing of treatment. Sildenafil is rapidly absorbed after oral administration and an erection can be expected after 15–20 minutes lasting for up to 2–3 hours (Rosas et al., 2001). Vardenafil reaches peak plasma concentrations after around 40–55 minutes, lasting a little longer than sildenafil (Montorsi et al., 2003). Tadalafil has a much longer half-life of 17.5 hours, and a later onset of action of 2 hours. It is therefore possible to use tadalafil as a chronic drug, even as a once-daily dose, which gives much more scope for spontaneity regarding sexual activity (Porst et al., 2003).

Vacuum devices and penile prosthesis

Lederer first described a vacuum constrictor device to treat ED in 1917. This simple mechanical method involved placing the penis in a cylindrical chamber, applying a vacuum of 100–180 mmHg, and then a rubber band or ring is placed around the base of the penis. The success rate of this type of treatment is good at around 70–80% with a relatively low drop-out rate of < 20% in most studies (Lawrence et al., 1998). Patients receiving anticoagulation are at increased risk of developing bruising and bleeding in association with this treatment.

Various forms of penile prosthesis have been used, including semi-flexible prostheses and inflatable penile prostheses with two silicone or polyurethane cylinders and a fluid reservoir at the cavum Retzii and a small pump at the scrotum. If an arterial or venous cause has been identified and characterized various corrective vascular procedures have been used with somewhat variable results.

Intracavernous injections and urethral suppositories

Intracavernosal injection of various drugs results in smooth muscle relaxation and can be used to treat ED. Papaverin has been used for this purpose, but now the drug of choice is the PGE1 analogue alprostadil. This acts on specific surface receptors on smooth muscle cells and the adenylate cyclase system to cause relaxation and opening of both the vascular spaces of the erectile tissue and the feeding vascular arterioles (Linet and Ogrinc, 1996). Erection occurs after around 5–10 minutes and can last for up to 2 hours. This type of therapy is very effective, with 75–80% of men achieving

Box 133.2 Potentially useful therapeutic options in hypogonadism and erectile dysfunction in chronic renal failure

- Antioestrogens: clomiphene citrate
- Dopaminergic agonists: bromocriptine
- Erythropoiesis-stimulating factors: erythropoietin
- Vitamins and essential trace elements: zinc and vitamin E
- Stimulators of endogenous testicular testosterone production: human chorionic gonadotropin
- Sildenafil and other phosphodiesterase type 5 inhibitors
- Intracavernous injection of alprostadil
- Vacuum devices
- Urethral suppositories containing alprostadil
- Penile prosthesis
- Control of secondary hyperparathyroidism
- Renal transplantation
- Androgens: testosterone.

an erection, but poorly tolerated with a high and early drop-out rate in most studies.

Prostaglandin may also be administered intraurethrally. PGE2 can be administered as a pellet through a specific delivery device prior to intercourse. Here larger doses are required, and success rate is somewhat lower (40–65%). This method tends to be better tolerated than intracavernous injections.

Antioestrogens: clomiphene citrate

In 1976, Lim and Fang showed that long-term clomiphene treatment can increase pituitary gonadotropin secretion and testosterone production in men with chronic renal failure (Lim and Fang, 1976). Effects on spermatogenesis were inconclusive. A more recent study confirmed these findings in men receiving haemodialysis and in successful transplants subjects (Martin-Malo et al., 1993). These findings indicate that clomiphene may partially correct some of the hormonal disturbances of the gonadal axis in uraemic patients.

Dopaminergic agonists

Experimental data suggests that bromocriptine can improve Leydig cell function and sperm production in CKD (Yamamoto et al., 1997). Studies on human subjects receiving haemodialysis showed improvement in libido, erectile function, an increase in serum testosterone, and normalization of serum prolactin without changes in gonadotropins (Ramirez et al., 1985; Vircburger et al., 1985). Other studies have not confirmed effects of bromocriptine on libido or sexual potency (Gómez et al., 1980; Stegmayr and Skogström, 1985).

Table 133.1 Favourable and unfavourable effects of testosterone replacement therapy in ESRD patients (Barton et al., 1982; Lawrence et al., 1998; Bhasin et al., 2010)

Favourable effects	Unfavourable effects
Restoration of physiological levels of circulating serum testosterone	Erythrocytosis
Anabolic effects	Acne and oily skin
Androgenic effects	Detection of subclinical prostate cancer
Increased sense of well-being	Growth of metastatic prostate cancer
Restoration of sexual function to normal (3–10%)	Reduced sperm production and fertility
Improvement in sexual function (50–70%)	Gynaecomastia
Erythropoiesis stimulation	Growth of breast cancer
Reduction of erythropoietin requirements	Obstructive sleep apnoea
	Fluid retention
	Pain at injection site for intramuscular injections
	Skin reactions for transdermal patches
	Testosterone transfer to another person with transdermal gel
	Alteration in taste or irritation of gums for buccal testosterone tablets
	Infection from pellets and implants
	Effects on liver and lipid profile for oral tablets

Adapted from Iglesias et al. (2012).

Erythropoiesis-stimulating factors

Studies have confirmed that effective treatment with recombinant human erythropoietin (rhEPO) in uraemic men receiving haemodialysis is associated with improved testosterone concentrations, reduced gonadotropins, normalization of prolactin levels, and a reduction of exaggerated response of LH to exogenous administration of gonadotropin-releasing hormone (GnRH) (Schaefer et al., 1988; Schaefer et al., 1989; Kokot et al., 1990; Ramirez et al., 1992; Yeksan et al., 1992b; Díez et al., 1997). These changes may be associated with the improved sexual activity reported in rhEPO-treated patients (Schaefer et al., 1989; Tokgöz et al., 2001; Wu et al., 2001).

Vitamins and essential trace elements

There is some experimental evidence to suggest that vitamin E has some protective effect on Leydig cell function (Verma and Nair, 2002; Chen et al., 2005; Chandra et al., 2010). Studies in human subjects on haemodialysis showed some reduction in prolactin levels but no other significant effect (Yeksan et al., 1992a).

Zinc deficiency is common in uraemic patients and has been linked to the development of hypogonadism (Mahajan et al., 1979; Nishi et al., 1984; Prasad, 1985). Zinc supplementation in men on haemodialysis has been shown to improve libido, sexual function, and raise serum testosterone levels in some studies (Antoniou et al., 1977; Mahajan et al., 1982), but not all (Del Río Vázquez et al., 1986).

Human chorionic gonadotropin

As previously described, uraemia is associated with marked testicular dysfunction and resistance to gonadotropin stimulation. It is therefore not surprising that treatment with human chorionic gonadotropin produces limited testosterone response and clinical effect (Rager et al., 1975; Ramirez et al., 1987). Some authors have reported normalization of testosterone levels, but only with prolonged use of large doses (Bundschu et al., 1976).

Renal transplantation

Successful renal transplantation is in many ways an effective treatment for uraemic hypogonadism and associated sexual dysfunction. A number of studied have confirmed normalization of hormonal profiles and significant improvement in libido and sexual function (Chopp and Mendez, 1978; Procci et al., 1981; Van Coevorden et al., 1986; Ramirez et al., 1987; Akbari et al., 2003). This effect seems most pronounced in younger patients (Tsujimura et al., 2002).

Testosterone replacement therapy

Testosterone could be an attractive therapeutic option in uraemia. It has both anabolic and androgenic properties, which could be of benefit, and may improve some of the pathophysiological pathways related to increased mortality in ESRD (Iglesias et al., 2012) (Table 133.1).

Relatively little work has been done around the safety, benefits, and efficacy of testosterone replacement therapy (TRT) in ESRD. The evidence available is rather limited to draw solid conclusions. Several pharmacokinetic studies have suggested that metabolic clearance rates of exogenous testosterone are similar in ESRD and

healthy subjects, and TRT can be administered using the same guidelines as in healthy men (Stewart-Bentley et al., 1974; Barton et al., 1982; De Vries et al., 1984; Van Coevorden et al., 1986; Lawrence et al., 1998; Singh et al., 2001; Johansen, 2004a, 2004b; Bhasin et al., 2010).

Spermatogenesis/fertility

Male fertility is significantly reduced in uraemia. Spermatogenesis is often impaired, even at relatively moderated degree of renal failure. Sperm counts are markedly decreased in men on dialysis, sperm abnormalities are frequent, and sperm motility is reduced. Ejaculatory volume is also reduced with diminished fructose and acid phosphatase content. Thus normospermia is observed in a minority of men on haemodialysis (Lim and Fang, 1975; Holdsworth et al., 1978; Tharandt et al., 1980). Testicular biopsies show arrest of maturation, which is indicative of lack of hormonal stimuli rather than toxic effects which typically effect earlier stages of spermatogenesis (De Kretser, 1974; Lim and Fang, 1975; Holdsworth et al., 1977). Other authors have described atrophy of Sertoli cells and seminiferous tubules, interstitial fibrosis, and calcification and thickening of tubular basement membrane (Lim and Fang, 1975). There is evidence to suggest that these morphological changes and decreased spermatogenesis do improve after successful renal transplantation (Toorians et al., 1997; De Celis et al., 1999; Malavaud et al., 2000).

Generally there is little evidence that any type of hormonal treatment increases male fertility in chronic renal failure. Studies using clomiphene have shown limited effect on spermatogenesis. There is limited correlation between gonadotropin concentrations and testosterone and spermatogenesis, although the higher the level of follicle stimulating hormone, the worse the prognosis for recovery of spermatogenic function with improvement of renal function. Management of reduced fertility in male patients with chronic renal failure should therefore focus on optimizing the nutritional state, optimizing renal replacement therapy, planning with intercourse planned around ovulation, avoiding excessive testicular temperatures, and other practical measures. Family planning can also be postponed until after successful renal transplantation if possible.

Sexual dysfunction in women with chronic renal failure

Although less is known about sexual dysfunction in women than men with chronic renal disease, sexual behaviour and function is likely to be no less affected. For example, in an older study on dialysis patients, 33% reported no sexual activity at all and 44% only one episode of intercourse per week or less (Levy, 1973). This study and later work have also showed marked deterioration in sexual function after commencing dialysis. Prior to this the majority of women report regularly having orgasm during intercourse, but after starting dialysis this falls to around 30% (Levy, 1973; Toorians et al., 1997; Diemont et al., 2000). This field does warrant further research.

Vaginal and menstrual problems

In around half of dialysed women, low plasma oestrogen is associated with atrophic vaginitis, pruritus, and reduced pubic hair growth. Vaginal cytology documents disturbed hormonal status. The normal midcyclic increase of karyopyknosis index is absent. The presence of malignant cells is not increased. The prevalence and spectrum of vaginal infections are not considered to be different in preuraemic or dialysis patients.

Menstrual irregularities develop along with uraemia. Amenorrhoea has been reported in 50–100% of female patients with end-stage renal failure (Goodwin et al., 1968; Huriet et al., 1974; Espersen et al., 1988). In many patients, amenorrhoea changes to irregular menstruation during maintenance haemodialysis, but the majority of patients suffer from continuous amenorrhoea. Of those patients who do menstruate, 50–80% suffer from hypermenorrhoea, menorrhagia, or oligomenorrhoea (Rice, 1973; Huriet et al., 1974; Morley et al., 1979).

In the early years of dialysis, the midcycle increase in basal body temperature, which is normally an indicator of ovulation, was not observed in 95% of female dialysis patients. More recently studies have indicated more frequent ovulatory cycles, perhaps related to better correction of renal anaemia with erythropoietin (Schaefer et al., 1989). In women with anovulatory cycles, progesterone deficiency results in incomplete maturation of the endometrium, followed by hypermenorrhoea and dysfunctional bleeding, that is, the menstrual abnormalities common in many dialysed women result predominantly from disturbed hypothalamic–pituitary regulation and gonadal dysfunction. Uraemic coagulopathy and heparinization during haemodialysis may intensify menstrual bleeding. In uraemic women, menstrual abnormalities may also be the consequence of hyper- and hypothyroidism, severe diabetes mellitus, Addison disease, or severe disease such as carcinoma, tuberculosis, and immunological disorders.

Fertility

Basal body temperature, vaginal cytology, and luteal endometrial biopsies indicate that anovulatory cycles are common in women on maintenance haemodialysis (Huriet et al., 1974). However, general infertility cannot be assumed. Ovulation in 45% of cycles has been reported, although with a slightly atypical hormonal pattern. More frequent ovulatory cycles have been reported only with bromocriptine therapy (Wass et al., 1978), but also with rhEPO therapy. In dialysed patients, some authors also reported a reduction of hyperprolactinaemia on rhEPO, but this was not confirmed by others. It is recommended that during the reproductive age sexually active dialysis women should use contraception to avoid unwanted pregnancies.

If improved fertility is desired, bromocriptine therapy (2.5–5 mg) can induce resumption of menstrual bleeding and ovulatory cycles in some patients (Wass et al., 1978). Disappearance of amenorrhoea and the onset of ovulation have also been reported when anaemia was improved after rhEPO therapy (Schaefer et al., 1989).

Moderate ovarian hyperstimulation syndrome occurred with a GnRH agonist (leuprolide acetate) in an anephric dialysis woman (Hampton et al., 1991). Information is lacking about the efficacy of pulsatile GnRH given subcutaneously or intravenously in dialysis patients, although this is a successful therapy in non-uraemic women with hypogonadotropic hypogonadism.

For further reading on pregnancy in patients receiving dialysis or following transplantation, see Chapter 294.

Treatment of menstrual problems and fertility

Before rhEPO was available, amenorrhoea and oligomenorrhoea were welcome symptoms in many anaemic female patients on

maintenance haemodialysis. If menstrual bleeding is required, the common failure of follicle luteinization can be treated with cyclical progesterone. This induces endometrial transformation and normal menstruation. In view of the increased risk of endometrial cancer in patients with anovulation and corpus luteum insufficiency, application of such intermittent progesterone therapy around three times a year should be considered. Alternatively, regular monthly oestrogen/progesterone combination therapy can be used, as in non-uraemic patients. Low-oestrogen-containing preparations are preferred to avoid potential effects on blood pressure. Oestrogen/progesterone combinations are beneficial for bone disease in dialysis patients.

Hypermenorrhoea can be stopped within 1 or 2 days by application of high doses of progesterone. In patients with chronic hypermenorrhoea, or if menstruation in general is undesired, perhaps due to anaemia, endometrial atrophy can be induced by continuous administration of high doses of progesterone. Alternatively, intermittent intramuscular injection of progesterone may prevent menstrual bleeding. However, such long-term exclusive progesterone therapy increases bone problems in dialysis patients. For this reason intermittent oestrogen therapy or oestrogen/progesterone combinations for some months are particularly recommended. As a last resort, a hysterectomy can be performed.

Contraception and pregnancy in CKD

These are discussed in Chapters 293 and 295.

References

Abram, H. S., Hester, L. R., Sheridan, W. F., *et al.* (1975). Sexual functioning in patients with chronic renal failure. *J Nerv Ment Dis*, 160(3), 220–6.

Akbari, F., Alavi, M., Esteghamati, A., *et al.* (2003). Effect of renal transplantation on sperm quality and sex hormone levels. *BJU Int*, 92(3), 281–3.

Antoniou, L. D., Shalhoub, R. J., Sudhakar, T., *et al.* (1977). Reversal of uraemic impotence by zinc. *Lancet*, 2(8044), 895–8.

Ayub, W. and Fletcher, S. (2000). End-stage renal disease and erectile dysfunction. Is there any hope? *Nephrol Dial Transplant*, 15(10), 1525–8.

Barton, C. H., Mirahmadi, M. K., and Vaziri, N. D. (1982). Effects of long-term testosterone administration on pituitary-testicular axis in end-stage renal failure. *Nephron*, 31(1), 61–4.

Bhasin, S., Cunningham, G. R., Hayes, F. J., *et al.* (2010). Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*, 95(6), 2536–59.

Bommer, J., Tschöpe, W., Ritz, E., *et al.* (1976). Sexual behaviour of hemodialyzed patients. *Clin Nephrol*, 6(1), 315–8.

Bundschu, H. D., Rager, K., Heller, S., *et al.* (1976). [Effects of long-term HCG administration on testicular function in hemodialysis patients (author's transl)]. *Klin Wochenschr*, 54(21), 1039–46.

Chandra, A. K., Chatterjee, A., Ghosh, R., *et al.* (2010). Vitamin E-supplementation protect chromium (VI)-induced spermatogenic and steroidogenic disorders in testicular tissues of rats. *Food Chem Toxicol*, 48(3), 972–9.

Chen, H., Liu, J., Luo, L., *et al.* (2005). Vitamin E, aging and Leydig cell steroidogenesis. *Exp Gerontol*, 40(8–9), 728–36.

Chopp, R. T. and Mendez, R. (1978). Sexual function and hormonal abnormalities in uremic men on chronic dialysis and after renal transplantation. *Fertil Steril*, 29(6), 661–6.

De Celis, R. and Pedrón-Nuevo, N. (1999). Male fertility of kidney transplant patients with one to ten years of evolution using a conventional immunosuppressive regimen. *Arch Androl*, 42(1), 9–20.

De Kretser, D. M., Atkins, R. C., Hudson, B., *et al.* (1974). Disordered spermatogenesis in patients with chronic renal failure undergoing maintenance haemodialysis. *Aust N Z J Med*, 4(2), 178–81.

Del Río Vázquez, A., Rico Lenza, H., Romero Burgos, R., *et al.* (1986). [Zinc supplements in uremic hypogonadism: absence of beneficial effects]. *Rev Clin Esp*, 178(8), 373–6.

De Vries, C. P., Gooren, L. J., and Oe, P. L. (1984). Haemodialysis and testicular function. *Int J Androl*, 7(2), 97–103.

Diemont, W. L., Vruggink, P. A., Meuleman, E. J., *et al.* (2000). Sexual dysfunction after renal replacement therapy. *Am J Kidney Dis*, 35(5), 845–51.

Díez, J. J., Iglesias, P., Bajo, M. A., *et al.* (1997). Effects of erythropoietin on gonadotropin responses to gonadotropin-releasing hormone in uremic patients. *Nephron*, 77(2), 169–75.

Espersen, T., Schmitz, O., Hansen, H. E., *et al.* (1988). Ovulation in uremic women: the reproductive cycle in women on chronic hemodialysis. *Int J Fertil*, 33(2), 103–6.

Feldman, H. A., Goldstein, I., Hatzichristou, D. G., *et al.* (1994). Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol*, 151(1), 54–61.

Glass, C. A., Fielding, D. M., Evans, C., *et al.* (1987). Factors related to sexual functioning in male patients undergoing hemodialysis and with kidney transplants. *Arch Sex Behav*, 16(3), 189–207.

Goldstein, I., Lue, T. F., Padma-Nathan, H., *et al.* (1998). Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl J Med*, 338(20), 1397–404.

Gómez, F., De la Cueva, R., Wauters, J. P., *et al.* (1980). Endocrine abnormalities in patients undergoing long-term hemodialysis. The role of prolactin. *Am J Med*, 68(4), 522–30.

Goodwin, N. J., Valenti, C., Hall, J. E., *et al.* (1968). Effects of uremia and chronic hemodialysis on the reproductive cycle. *Am J Obstet Gynecol*, 100(4), 528–35.

Hampton, H. L., Whitworth, N. S., and Cowan, B. D. (1991). Gonadotropin-releasing hormone agonist (leuprolide acetate) induced ovarian hyperstimulation syndrome in a woman undergoing intermittent hemodialysis. *Fertil Steril*, 55(2), 429–31.

Handelsman, D. J. and Dong, Q. (1993). Hypothalamo-pituitary gonadal axis in chronic renal failure. *Endocrinol Metab Clin North Am*, 22(1), 145–61.

Handelsman, D. J. and Liu, P. Y. (1998). Androgen therapy in chronic renal failure. *Baillieres Clin Endocrinol Metab*, 12(3), 485–500.

Hedlund, H. and Andersson, K. E. (1985). Comparison of the responses to drugs acting on adrenoreceptors and muscarinic receptors in human isolated corpus cavernosum and cavernous artery. *J Auton Pharmacol*, 5(1), 81–8.

Holdsworth, S., Atkins, R. C., De Kretser, D. M. (1977). The pituitary-testicular axis in men with chronic renal failure. *N Engl J Med*, 296(22), 1245–9.

Holdsworth, S. R., De Kretser, D. M., Atkins, R. C. (1978). A comparison of hemodialysis and transplantation in reversing the uremic disturbance of male reproductive function. *Clin Nephrol*, 10(4), 146–50.

Huriet, C., Mire, F., Kessler, M., *et al.* (1974). [Proceedings: Clinical and cytological profile of women in hemodialysis]. *J Urol Nephrol (Paris)*, 80(4–5), 369–75.

Iglesias, P., Carrero, J. J., and Díez, J. J. (2012). Gonadal dysfunction in men with chronic kidney disease: clinical features, prognostic implications and therapeutic options. *J Nephrol*, 25(1), 31–42.

Jackson, G., Montorsi, P., Adams, M. A., *et al.* (2010). Cardiovascular aspects of sexual medicine. *J Sex Med*, 7(4 Pt 2), 1608–26.

Janssen, E., Everaerd, W., Van Lunsen, R. H., *et al.* (1994). Visual stimulation facilitates penile responses to vibration in men with and without erectile disorder. *J Consult Clin Psychol*, 62(6), 1222–8.

Jassal, S. V., Allen, J. A., Douglas, J. F., *et al.* (1998a). Autonomic function in patients on continuous ambulatory peritoneal dialysis. *Perit Dial Int*, 18(1), 46–51.

Jassal, S. V., Douglas, J. F., and Stout, R. W. (1998b). Prevalence of central autonomic neuropathy in elderly dialysis patients. *Nephrol Dial Transplant*, 13(7), 1702–8.

Johansen, K. L. (2004a). Testosterone metabolism and replacement therapy in patients with end-stage renal disease. *Semin Dial*, 17(3), 202–8.

Johansen, K. L. (2004b). Treatment of hypogonadism in men with chronic kidney disease. *Adv Chronic Kidney Dis*, 11(4), 348–56.
Karacan, I., Scott, F. B., Salis, P. J., *et al*. (1977). Nocturnal erections, differential diagnosis of impotence, and diabetes. *Biol Psychiatry*, 12(3), 373–80.
Kokot, F., Wiecek, A., Grzeszczak, W., *et al*. (1990). Influence of erythropoietin treatment on follitropin and lutropin response to luliberin and plasma testosterone levels in haemodialyzed patients. *Nephron*, 56(2), 126–9.
Lawrence, I. G., Price, D. E., Howlett, T. A., *et al*. (1998). Correcting impotence in the male dialysis patient: experience with testosterone replacement and vacuum tumescence therapy. *Am J Kidney Dis*, 31(2), 313–19.
Levy, N. B. (1973). Sexual adjustment to maintenance hemodialysis and renal transplantation: national survey by questionnaire: preliminary report. *Trans Am Soc Artif Intern Organs*, 19, 138–43.
Lim, V. S. and Fang, V. S. (1975). Gonadal dysfunction in uremic men. A study of the hypothalamo-pituitary-testicular axis before and after renal transplantation. *Am J Med*, 58(5), 655–62.
Lim, V. S. and Fang, V. S. (1976). Restoration of plasma testosterone levels in uremic men with clomiphene citrate. *J Clin Endocrinol Metab*, 43(6), 1370–7.
Linet, O. I. and Ogrinc, F. G. (1996). Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. The Alprostadil Study Group. *N Engl J Med*, 334(14), 873–7.
Mahajan, S. K., Abbasi, A. A., Prasad, A. S., *et al*. (1979). Relationship between uremic hypogonadism and zinc? *Proc Clin Dial Transplant Forum*, 9, 165–9.
Mahajan, S. K., Abbasi, A. A., Prasad, A. S., *et al*. (1982). Effect of oral zinc therapy on gonadal function in hemodialysis patients. A double-blind study. *Ann Intern Med*, 97(3), 357–61.
Malavaud, B., Rostaing, L., Rischmann, P., *et al*. (2000). High prevalence of erectile dysfunction after renal transplantation. *Transplantation*, 69(10), 2121–4.
Mannino, D. M., Klevens, R. M., and Flanders, W. D. (1994). Cigarette smoking: an independent risk factor for impotence? *Am J Epidemiol*, 140(11), 1003–8.
Martin-Malo, A., Benito, P., Castillo, D., *et al*. (1993). Effect of clomiphene citrate on hormonal profile in male hemodialysis and kidney transplant patients. *Nephron*, 63(4), 390–4.
McConnell, J., Benson, G. S., and Wood, J.,G. (1982). Autonomic innervation of the urogenital system: adrenergic and cholinergic elements. *Brain Res Bull*, 9(1–6), 679–94.
Montorsi, F., Salonia, A., Deho', F., *et al*. (2003). Pharmacological management of erectile dysfunction. *BJU Int*, 91(5), 446–54.
Morley, J. E., Distiller, L. A., Epstein, S., *et al*. (1979). Menstrual disturbances in chronic renal failure. *Horm Metab Res*, 11(1), 68–72.
Nishi, Y., Hatano, S., Aihara, K., *et al*. (1984). Role of zinc in testicular function of chronic renal failure. *Pediatrics*, 73(5), 740–1.
Palmer, B. F. (1999). Sexual dysfunction in uremia. *J Am Soc Nephrol*, 10(6), 1381–8.
Palmer, B. F. (2004). Outcomes associated with hypogonadism in men with chronic kidney disease. *Adv Chronic Kidney Dis*, 11(4), 342–7.
Porst, H., Young, J. M., Schmidt, A. C., *et al*. (2003). Efficacy and tolerability of vardenafil for treatment of erectile dysfunction in patient subgroups. *Urology*, 62(3), 519–23.
Prasad, A. S. (1985). Clinical manifestations of zinc deficiency. *Annu Rev Nutr*, 5, 341–63.
Procci, W. R., Goldstein, D. A., Adelstein, J., *et al*. (1981). Sexual dysfunction in the male patient with uremia: a reappraisal. *Kidney Int*, 1919(2), 317–23.
Rager, K., Bundschu, H., and Gupta, D. (1975). The effect of HCG on testicular androgen production in adult men with chronic renal failure. *J Reprod Fertil*, 42(1), 113–20.
Ramirez, G., Bittle, P. A., Sanders, H., *et al*. (1992). Hypothalamo-hypophyseal thyroid and gonadal function before and after erythropoietin therapy in dialysis patients. *J Clin Endocrinol Metab*, 74(3), 517–24.
Ramirez, G., Butcher, D., Brueggemeyer, C. D., *et al*. (1987). Testicular defect: the primary abnormality in gonadal dysfunction of uremia. *South Med J*, 80(6), 698–701.
Ramirez, G., Butcher, D. E., Newton, J. L., *et al*. (1985). Bromocriptine and the hypothalamic hypophyseal function in patients with chronic renal failure on chronic hemodialysis. *Am J Kidney Dis*, 6(2), 111–18.
Rendell, M. S., Rajfer, J., Wicker, P. A., *et al*. (1999). Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. *JAMA*, 281(5), 421–6.
Rice, G. G. (1973). Hypermenorrhea in the young hemodialysis patient. *Am J Obstet Gynecol*, 116(4), 539–43.
Röckel, A., Hennemann, H., Sternagel-Haase, A., *et al*. (1979). Uraemic sympathetic neuropathy after haemodialysis and transplantation. *Eur J Clin Invest*, 9(1), 23–7.
Rosas, S. E., Wasserstein, A., Kobrin, S., *et al*. (2001). Preliminary observations of sildenafil treatment for erectile dysfunction in dialysis patients. *Am J Kidney Dis*, 37(1), 134–7.
Salvatierra, O., Jr., Fortmann, J. L., and Belzer, F. O. (1975). Sexual function of males before and after renal transplantation. *Urology*, 5(1), 64–6.
Schaefer RM, Kokot F, Kuerner B, *et al*. (1989). Normalization of serum prolactin levels in hemodialysis patients on recombinant human erythropoietin. *Int J Artif Organs*, 12(7), 445–9.
Schaefer RM, Kokot F, Kürner B, *et al*. (1988). Normalization of elevated prolactin levels in hemodialysis patients on erythropoietin. *Nephron*, 50(4), 400–1.
Schaefer RM, Kokot F, Wernze H, *et al*. (1989). Improved sexual function in hemodialysis patients on recombinant erythropoietin: a possible role for prolactin. *Clin Nephrol*, 31(1), 1–5.
Sell, D. R. and Monnier, V. M. (1990). End-stage renal disease and diabetes catalyze the formation of a pentose-derived crosslink from aging human collagen. *J Clin Invest*, 85(2), 380–4.
Sharma, R. K., Prasad, N., Gupta, A., *et al*. (2006). Treatment of erectile dysfunction with sildenafil citrate in renal allograft recipients: a randomized, double-blind, placebo-controlled, crossover trial. *Am J Kidney Dis*, 48(1), 128–33.
Sherman, F. P. (1975). Impotence in patients with chronic renal failure on dialysis: its frequency and etiology. *Fertil Steril*, 26(3), 221–3.
Siegel, R. and Grossman, E. (2001). Timing of sildenafil therapy in dialysis patients. *Nephrol Dial Transplant*, 16(8), 1719–20.
Singh, A. B., Norris, K., Modi, N., *et al*. (2001). Pharmacokinetics of a transdermal testosterone system in men with end stage renal disease receiving maintenance hemodialysis and healthy hypogonadal men. *J Clin Endocrinol Metab*, 86(6), 2437–45.
Slob, A. K., Blom, J. H., and Van der Werff ten Bosch, J. J. (1999). Erection problems in medical practice: differential diagnosis with relatively simple method. *J Urol*, 143(1), 46–50.
Solders, G., Persson, A., and Wilczek, H. (1986). Autonomic system dysfunction and polyneuropathy in nondiabetic uremia. A one-year follow-up study after renal transplantation. *Transplantation*, 41(5), 616–19.
Stegmayr, B. and Skogström, K. (1985). Hyperprolactinaemia and testosterone production. Observations in 2 men on long-term dialysis. *Horm Res*, 21(4), 224–8.
Stewart-Bentley, M., Gans, D., and Horton, R. (1974). Regulation of gonadal function in uremia. *Metab Clin Exp*, 23(11), 1065–72.
Tharandt, L., Graben, N., Schäfer, R., *et al*. (1980). Effects of prolactin suppression on hypogonadism im patients on maintenance haemodialysis. *Proc Eur Dial Transplant Assoc*, 17, 323–7.
Tokgöz, B., Utaş, C., Dogukan, A., *et al*. (2001). Effects of long-term erythropoietin therapy on the hypothalamo-pituitary-testicular axis in male CAPD patients. *Perit Dial Int*, 21(5), 448–54.
Toorians, A. W., Janssen, E., Laan, E., *et al*. (1997). Chronic renal failure and sexual functioning: clinical status versus objectively assessed sexual response. *Nephrol Dial Transplant*, 12(12), 2654–63.
Tsujimura, A., Matsumiya, K., Tsuboniwa, N., *et al*. (2002). Effect of renal transplantation on sexual function. *Arch Androl*, 48(6), 467–74.

Türk, S., Karalezli, G., Tonbul, H. Z., *et al*. (2001). Erectile dysfunction and the effects of sildenafil treatment in patients on haemodialysis and continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant*, 16(9), 1818–22.

Van Coevorden, A., Stolear, J. C., Dhaene, M., *et al*. (1986). Effect of chronic oral testosterone undecanoate administration on the pituitary-testicular axes of hemodialyzed male patients. *Clin Nephrol*, 26(1), 48–54.

Verma, R. J. and Nair, A. (2002). Effect of aflatoxins on testicular steroidogenesis and amelioration by vitamin E. *Food Chem Toxicol*, 40(5), 669–72.

Virag, R., Bouilly, P., and Frydman, D. (1985a). About arterial risk factors and impotence. *Lancet*, 1(8437), 1109–10.

Virag, R., Bouilly, P., and Frydman, D. (1985b). Is impotence an arterial disorder? A study of arterial risk factors in 440 impotent men. *Lancet*, 1(8422), 181–4.

Vircburger, M. I., Prelević, G. M., Perić, L. A., *et al*. (1985). Testosterone levels after bromocriptine treatment in patients undergoing long-term hemodialysis. *J Androl*, 6(2), 113–16.

Wass, V. J., Wass, J. A., Rees, L., *et al*. (1978). Sex hormone changes underlying menstrual disturbances on haemodialysis. *Proc Eur Dial Transplant Assoc*, 15, 178–86.

Wu, S. C., Lin, S. L., and Jeng, F. R. (2001). Influence of erythropoietin treatment on gonadotropic hormone levels and sexual function in male uremic patients. *Scand J Urol Nephrol*, 35(2), 136–40.

Yamamoto, Y., Sofikitis, N., and Miyagawa, I. (1997). Effects of erythropoietin, bromocryptine and hydralazine on testicular function in rats with chronic renal failure. *Andrologia*, 29(3), 141–4.

Yeksan, M., Polat, M., Türk, S., *et al*. (1992a). Effect of vitamin E therapy on sexual functions of uremic patients in hemodialysis. *Int J Artif Organs*, 15(11), 648–52.

Yeksan, M., Tamer, N., Cirit, M., *et al*. (1992b). Effect of recombinant human erythropoietin (r-HuEPO) therapy on plasma FT3, FT4, TSH, FSH, LH, free testosterone and prolactin levels in hemodialysis patients. *Int J Artif Organs*, 15(10), 585–9.

Zucchelli, P., Sturani, A., Zuccalà, A., *et al*. (1985). Dysfunction of the autonomic nervous system in patients with end-stage renal failure. *Contrib Nephrol*, 45, 69–81.

CHAPTER 134

Health-related quality of life and the patient with chronic kidney disease

Fredric O. Finkelstein and Susan H. Finkelstein

Introduction

The compromised health-related quality of life (HRQOL) of patients with end-stage renal disease (ESRD) is now well documented (Evans et al., 1985; Kimmel et al., 2000, 2003; Lopes et al., 2002, 2004; Mapes et al., 2003; Kutner et al., 2004, 2005; Reynolds et al., 2004; Wu et al., 2004; Hedayati et al., 2005, 2008; Fukuhara et al., 2007; Finkelstein et al., 2009; Jaber et al., 2010; 2011; Lacson 2010, 2012; Finkelstein et al., 2012). Clinicians were aware of these difficulties from the time dialysis treatments became readily available for patients with ESRD (Evans et al., 1985). A challenge for the nephrology community then became how to systematically document the difficulties presented by both the disease itself as well as the treatment of the disease. A variety of well-validated instruments, thus, were developed to examine the problems encountered by the chronic kidney disease (CKD) patient. More recently, research has focused on how to not only document the impaired HRQOL of ESRD patients but also on how to develop treatment strategies to help the patients better cope with, understand, and work with their illness and its problems (Finkelstein et al., 2009).

It is important that the terms 'quality of life' and 'HRQOL' be understood so that clinicians are aware of implications of the active, ongoing research in these areas. Quality of life can be defined as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns (Finkelstein et al., 2009). HRQOL can be defined as the extent to which one's usual or expected physical, social, or emotional well-being (*quality of life*) is affected by a medical condition *or* its treatment (Finkelstein et al., 2009). Thus, there are various domains that all impact on patient perceptions of their quality of life.

Assessing HRQOL

The assessment of the HRQOL of patients can be thought of as involving three classes of measurement. Generic instruments, which have been developed for use in the general population with a variety of diseases (e.g. SF-36® health survey (Medical Outcomes Trust, Boston, MA); Health Utility Index) cover a wide variety of generic domains. Disease-specific instruments focus on symptoms related to a specific disease or interventions directed at that disease (e.g. Kidney Disease Quality of Life) and symptom-specific instruments focus on specific symptoms produced by or associated with a particular disease or its condition and/or treatment (e.g. time to recovery after a dialysis session).

These instruments rely on objective and/or subjective assessments. Objective assessments involve obtaining precise measurements in various domains, such as examining physical functioning with a 6-minute walk or other easily recorded measurement (Painter et al., 2002) or cognitive abilities with an instrument such as the Trailmaking Test or standard recall test (Suri et al., 2001). Subjective measures rely on the ability of the patients to report the presence and severity of symptoms and can be referred to as patient-reported outcomes (PROs). PROs can be defined as a measurement based on a report that comes directly from the patient about the status of his/her health condition without amendment or interpretation of the patient's response by a clinician (Concato and Feinstein, 1997; Food and Drug Administration, 2009).

Outcomes relate to HRQOL

It seems obvious that healthcare providers would have a keen interest in improving the HRQOL of any patient. But, certainly interest in developing treatment algorithms to improve the HRQOL of ESRD patients was given an impetus by studies demonstrating an association between reduced HRQOL measurements with mortality and hospitalization rates in CKD patients after correction for the standard variables that were known to impact on patient outcomes. These studies helped underscore the importance of understanding how patients perceive their illness. The validity and reliability of many of these associations have now been confirmed. For example, the strong associations between the physical component score (PCS) and mental component score (MCS) of the SF-36® and depressive symptoms with mortality and hospitalization rates of ESRD patients, first noted in the Dialysis Outcomes and Practice Pattern Studies (DOPPS), has been confirmed in larger studies from the databases of large dialysis organizations. Thus, patients with lower PCS scores (< 25), indicating poorer reported quality of life, have a nearly twofold higher 1-year mortality rate than patients with scores > 46 (Lopes et al., 2002, 2004; Mapes et al., 2003; Lacson et al., 2010). Similarly, patients with higher levels of depressive symptoms had dramatically higher mortality rates than

patients with lower scores (Lopes et al., 2004; Hedayati et al., 2005, 2008; Lacson et al., 2012). For example, patients in the DOPPS who had Centre for Epidemiologic Studies Depression (CES-D) scores of 15–30 (indicating the presence of prominent depressive symptoms) had a nearly twofold greater mortality than patients with scores of 0–4. Furthermore, the response to even a single question ('How would you say your health is in general?') is an important predictor of mortality after correcting for the standard variables; patients who reported a poor state of health had a > 3.5 greater mortality rate than patients who rated their general health as very good or excellent (Thong et al., 2008).

Routine recording

One of the problems therefore is how to document patients' perceptions of their quality of life. Importantly, studies have shown that clinical staff, despite seeing haemodialysis (HD) patients three times per week, do not fully comprehend the symptoms which patients experience and the severity of these symptoms as perceived by the patient (Weisbord et al., 2007). Thus, developing strategies to capture patients' perceptions of their quality of life is now being incorporated into routine patient care of ESRD patients and is in being mandated by the Centre for Medicare and Medicaid Services in the United States (Finkelstein et al., 2009). The notion of closely monitoring patients' perceptions of their health has been attracting considerable attention recently and the National Institutes of Health in the United States is in the process of developing a battery of PRO assessment tools that can be used in clinical trials and patient care (<http://www.nihpromis.org>). The selection of instruments to be used to monitor ESRD patients routinely are in the process of being developed but will certainly need to include generic, disease-, and symptom-specific instruments since the measurement of all these areas can impact on outcomes and give insights to healthcare providers about how to help assist and manage patients (Finkelstein et al., 2009).

Improving HRQOL

How then can healthcare providers improve patients' perceptions of their quality of life? First, it is important to examine the areas of difficulty perceived by the patient. Defining these areas permits the exploration of different approaches and treatment algorithms to be pursued. Depression, as an example, is a domain that has attracted considerable interest. This interest has been stimulated both by the strong association of depressive symptoms with poor outcomes and by the various treatment options that have been described to improve patients' depressive symptomatology (Kimmel et al., 2000; Lopes et al., 2002, 2004; Hedayati et al., 2005, 2008; 2012). Hedayati et al. have recently proposed a systematic approach to both diagnosing and treating depression in ESRD patients (Hedayati et al., 2012). Treatments that have been shown in randomized trials to improve depressive symptoms include cognitive behavioural therapy and exercise programmes (Levendoglu et al., 2004; Duarte et al., 2009; Ouzouni et al., 2009). Changes in the dialysis treatment regimen have resulted in improvement in symptoms in cohort studies (Reynolds et al., 2004; Chertow et al., 2010; Jaber et al., 2010). And, pharmacological therapy with or without counselling can result in an improvement in depressive symptoms (Hedayati et al., 2012). However, whether treating depression or not improves hospitalizations or mortality remains to be determined.

The impact of the dialysis treatment regimen on patient perceptions is attracting much more attention recently. This has occurred for two reasons. First is the recognition that as the length of time of renal replacement therapy increases, patients' perceptions of their quality of life tends to deteriorate (Paniagua et al., 2005). For example, the HRQOL scores reported by patients enrolled in both the control and intervention group in the ADEMEX study demonstrated a progressive decline in both the physical and mental component scores of the SF-36® despite receiving a standard and 'acceptable' peritoneal dialysis (PD) treatment regimen (Paniagua et al., 2005). Second, recent studies have focused attention on the impact of changes in the dialysis treatment regimens on HRQOL (Reynolds et al., 2004; Cullerton et al., 2007; Manns et al., 2009; Chertow et al., 2010; Jaber et al., 2010; Jaber et al., 2011; Unruh et al., 2011; Finkelstein et al., 2012). Thus, changing from conventional three times per week HD to six times per week home or in-centre dialysis can be associated with improvements in restless legs, sleep disturbances, depressive symptoms, time to recovery after a dialysis session, and various domains on the SF-36® questionnaire (Reynolds et al., 2004; Cullerton et al., 2007; Manns et al., 2009; Chertow et al., 2010; Jaber et al., 2010; Jaber et al., 2011; Unruh et al., 2011; Finkelstein et al., 2012). Patients' perceptions of and satisfactions with their care with PD are generally better with PD than with HD (Rubin et al., 2004; Juergensen et al., 2006). Patients maintained on PD reported that their therapy had less of a negative impact on their lives than did HD patients and that they were more satisfied with the care provided to them by the dialysis centres (Rubin et al., 2004; Juergensen et al., 2006). Thus, paying attention to the impact of the dialysis treatment regimen on patients' perceptions of their HRQOL is particularly important. Patients need to be monitored over time and changes in dialysis treatment regimens should be considered if there are deteriorations in various HRQOL measures and/or patients perceive that the therapy is having too much of a negative impact on their lives.

Explaining prognosis

The importance of evaluating HRQOL needs particular emphasis when considering the treatment options available to elderly patients with various co-morbidities. Preliminary work done thus far has suggested that elderly patients are not well informed about palliative care options or about the actual impact of ESRD therapy on their HRQOL (Davison, 2010). Many elderly patients who have started dialysis report regretting this decision (Davison, 2010). Data in fact suggests that elderly patients with two or more co-morbidities managed with a palliative care approach do not have a longer survival or improved HRQOL compared to patients treated with dialysis therapy (Murtagh et al., 2007; Chandna et al., 2011). Thus, it is important to not only inform elderly patients carefully about their treatment options but also to monitor their HRQOL and the impact of dialysis on their HRQOL and adjust treatments accordingly.

References

Chandna, S. M., Silva-Gane, M., Marshall, C., *et al.* (2011). Survival of elderly patients with stage 5 CKD: comparison of conservative management and renal replacement therapy. *Nephrol Dial Transplant*, 26(5), 1608–14.

Chertow, G. M., Levin, N. W., Beck, G. J., *et al.* (2010). In-center hemodialysis six times per week versus three times per week. *N Engl J Med*, 363, 2287–300.

Concato, J. and Feinstein, A. R. (1997). Asking patients what they like: overlooked attributes of patient satisfaction with primary care. *Am J Med* 102, 399–406.

Cullerton, B., Walsh, M., Klarenbach, S. W., *et al.* (2007). Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. *JAMA*, 298, 1291–9.

Davison, S. N. (2010). End-of-life care preferences and needs: perceptions of patients with chronic kidney disease. *Clin J Am Soc Nephrol*, 5, 195–204.

Duarte, P. S., Miyasaki, M. C., Blay, S. L., *et al.* (2009). Cognitive- behavioral group therapy is an effective treatment for major depression in hemodialysis patients. *Kidney Int*, 76, 414–21.

Evans, R. W., Manninen, D. L., Garrison, L. P. Jr., *et al.* (1985). The quality of life of patients with end-stage renal disease. *N Engl J Med*, 312, 553–9.

Finkelstein, F. O., Schiller, B., Daoui, R., *et al.* (2012). Effect of at-home short daily hemodialysis on health-related quality of life: interim report from the FREEDOM Study. *Kidney Int*, 82(5), 561–9.

Finkelstein, F. O., Wuerth, D., and Finkelstein, S. H. (2009). Health related quality of life and the CKD patient: challenges for the nephrology community. *Kidney Int*, 76, 946–52.

Food and Drug Administration (2009). Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Washington, DC: Food and Drug Administration. <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282>

Fukuhara, S., Yamazaki, S., Hayashino, Y., *et al.* (2007). Measuring health-related quality of life in patients with end-stage renal disease: why and how. *Nat Clin Pract Nephrol*, 3, 352–3.

Hedayati, S. S., Bosworth, H., Briley, L., *et al.* (2008). Death or hospitalization of patients on chronic hemodialysis is associated with a physician-based diagnosis of depression. *Kidney Int*, 74, 930–6.

Hedayati, S. S., Grambow, S. C., Szczech, L. A., *et al.* (2005). Physician-diagnosed depression as a correlate of hospitalizations in patients receiving long-term hemodialysis. *Am J Kidney Dis*, 46, 642–9.

Hedayati, S. S., Yalamanchili, V., and Finkelstein, F. O. (2012). A practical approach to the treatment of depression in patients with chronic kidney disease and end-stage renal disease. *Kidney Int*, 81, 247–55.

Jaber, B. L., Lee, Y., Collins, A. J., *et al.* Effect of daily hemodialysis on depressive symptoms and postdialysis recovery time: interim report from the FREEDOM study. *Am J Kidney Dis*, 56, 531–9.

Jaber, B. L., Schiller, B., Burkart, J. M., *et al.* (2011). Impact of at-home short daily hemodialysis on restless legs symptoms and sleep disturbances. *Clin J Am Soc Nephrol*, 6, 1049–56.

Juergensen, E., Wuerth, D., Finkelstein, S. H., *et al.* (2006). Hemodialysis and peritoneal dialysis: patients' assessment of their satisfaction with therapy and the impact of the therapy on their lives. *Clin J Am Soc Nephrol*, 1, 1191–6.

Kimmel, P. L., Emont, S. L., Newmann, J. M., *et al.* (2003). ESRD patient quality of life: symptoms, spiritual beliefs, psychosocial factors, and ethnicity. *Am J Kidney Dis*, 42, 713–21.

Kimmel, P. L., Peterson, R. A., Weihs, K. L., *et al.* (2000). Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. *Kidney Int*, 57, 2093–8.

Kutner, N., Zhang, R., Barnhart, H., *et al.* (2005). Health status and quality of life reported by incident patients after 1 year on haemodialysis or peritoneal dialysis. *Nephrol Dial Transplant*, 20, 2159–67.

Kutner, N. G. (2004). Quality of life and daily hemodialysis. *Semin Dial*, 17, 92–8.

Lacson, E., Jr., Li, N. C., Guerra-Dean, S., *et al.* (2012). Depressive symptoms associate with high mortality risk and dialysis withdrawal in incident hemodialysis patients. *Nephrol Dial Transplant*, 27(7), 2921–8.

Lacson, E., Jr., Xu, J., Lin, S. F., *et al.* (2010). A comparison of SF-36 and SF-12 composite scores and subsequent hospitalization and mortality risks in long-term dialysis patients. *Clin J Am Soc Nephrol*, 5(2), 252–60

Levendoglu, F., Altintepe, L., Okudan, N., *et al.* (2004). A twelve week exercise program improves the psychological status, quality of life and work capacity in hemodialysis patients. *J Nephrol*, 17, 826–32.

Lopes, A. A., Albert, J. M., Young, E. W., *et al.* (2004). Screening for depression in hemodialysis patients: associations with diagnosis, treatment, and outcomes in the DOPPS. *Kidney Int*, 66, 2047–53.

Lopes, A. A., Bragg, J., Young, E., *et al.* (2002). Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe. *Kidney Int*, 62, 199–207.

Manns, B. J., Walsh, M. W., Culleton, B. F., *et al.* (2009). Nocturnal hemodialysis does not improve overall measures of quality of life compared to conventional hemodialysis. *Kidney Int*, 75, 542–9.

Mapes, D., Lopes, A. A., Satayathum, S., *et al.* (2003). Health-related quality of life as a predictor of mortality and hospitalization: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int*, 64, 339–49.

Murtagh, F. E., Marsh, J. E., Donohoe, P., *et al.* (2007). Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. *Nephrol Dial Transplant*, 22, 1955–62.

Ouzouni, S., Kouidi, E., Sioulis, A., *et al.* (2009). Effects of intradialytic exercise training on healthrelated quality of life indices in haemodialysis patients. *Clin Rehabil*, 23, 53–63.

Painter, P., Moore, G., Carlson, L., *et al.* (2002). Effects of exercise training plus normalization of hematocrit on exercise capacity and health-related quality of life. *Am J Kidney Dis*, 39, 257–65.

Paniagua, R., Amato, D., Vonesh, E., *et al.* (2005). Mexican Nephrology Collaborative Study Group. Mexican Nephrology Collaborative Study Group. Health-related quality of life predicts outcomes but is not affected by peritoneal clearance: the ADEMEX trial. *Kidney Int*, 67, 1093–104.

Reynolds, J., Homel, P., Cantey, L., *et al.* (2004). A one year trial of in-center daily hemodialysis with an emphasis on quality of life. *Blood Purification*, 22, 320–8.

Rubin, H. R., Fink, N. E., Plantinga, L. C., *et al.* (2004). Patient ratings of dialysis care with peritoneal dialysis vs hemodialysis. *JAMA*, 291, 697–703.

Suri, R., Garg, A. X., Chertow, G. M., *et al.* (2007). Frequent Hemodialysis Network Trial Group. Frequent Hemodialysis Network (FHN) randomized trials: study design. *Kidney Int*, 71, 349–59.

Thong, M. S., Kaptein, A. A., Benyamini, Y., *et al.* (2008). Association between a self-rated health question and mortality in young and old dialysis patients: a cohort study. *Am J Kidney Dis*, 52, 111–17.

Unruh, M., Larive, B., Chertow, G., *et al.* (2011). Effects of six versus three times per week hemodialysis on depressive symptoms and mental health: Frequent Hemodialysis Network (FHN) Trials Abstract. *ASNL*, 2011, 36.

Weisbord, S. D., Fried, L. F., Mor, M. K., *et al.* (2007). Renal provider recognition of symptoms in patients on maintenance hemodialysis. *Clin J Am Soc Nephrol*, 2, 960–7.

Wu, A. W., Fink, N. E., Marsh-Manzi, J. V., *et al.* (2004). Changes in quality of life during hemodialysis and peritoneal dialysis treatment: generic and disease specific measures. *J Am Soc Nephrol*, 15, 743–53.

CHAPTER 135

Coagulopathies in chronic kidney disease

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Introduction

Abnormalities of coagulation are common in patients with chronic kidney disease (CKD). These can be divided into two categories: those secondary to uraemia or treatments for CKD and those in which a coagulopathy or its treatment contributes to the cause of CKD. In the former, both bleeding and thrombosis are seen at higher incidences than in the general population, whilst in the latter, thrombosis of the renal vasculature is the most common underlying pathology causing CKD.

Secondary coagulation abnormalities in chronic kidney disease

Haemorrhage

Bleeding in patients with CKD is more common than in the general population with an overall incidence of bleeding episodes of 2.5–11% per year (Holden et al., 2008). The highest risks are in those with lower glomerular filtration rates (GFRs) and those receiving anticoagulation. Bleeding is most commonly from the upper gastrointestinal tract, with gastric ulcer representing approximately 35% of cases (Gheissari et al., 1990). Intracranial haemorrhage is the next most common with an incidence of 0.6–0.87% per year (fivefold higher than in the general population). Postoperative bleeding is also more common in CKD; for example, the risk of significant bleeding post coronary artery bypass grafting doubles from 3% to 6% in patients with a serum creatinine > 130 mmol/L. There is significant mortality and morbidity associated with bleeding in these patients; hospital stays are up to twofold longer and mortality is twice as high compared to those with normal renal function, with a case fatality rate of 60% following an intracranial bleed (Sohal et al., 2006).

Aside from the fact that patients with CKD are more likely to have epidemiological risk factors predisposing to bleeding, including older age and cardiovascular co-morbidities, there are multiple pathophysiological changes, caused by uraemia, which contribute to the increased bleeding risk in these patients (see Table 135.1) (Gangji et al., 2005; Pavord and Myers, 2011). Additionally, a high proportion of patients with CKD are on anticoagulant therapy: 8–25% of patients on haemodialysis (HD) are receiving vitamin K antagonists (VKAs), 40% are on antiplatelet therapies, and most will receive either unfractionated or low-molecular weight-heparin (LMWH) during dialysis (Chan et al., 2009). The risk of bleeding in uraemic patients on anticoagulation is increased two- to threefold with an increased mortality risk compared to those not on anticoagulants (Thorevska et al., 2004; Hetzel and Sucker, 2005; Nolin, 2010; Saltiel, 2010) (see Table 135.2).

Thrombosis

The annual risk of venous thromboembolic events (VTEs) in the general population is 0.1% with individual risk increasing from 0.001% in childhood to 1% in the elderly (Anderson et al., 1991). The overall risk of arterial thromboembolic events (ATEs) is 0.18%.

CKD is an independent risk factor for both. Risk correlates inversely with GFR, so patients with an estimated GFR (eGFR) < 60 mL/min have a twofold higher incidence (0.45%) of VTE compared to eGFR > 60 mL/min (Wattanakit et al., 2008; Wattanakit and Cushman, 2009, Folsom et al., 2010) and a 30–40% increase in fatal and non-fatal cardiovascular ATEs including myocardial infarction and stroke (Go et al., 2004; Di Angelantonio et al., 2007; Chronic Kidney Disease Prognosis Consortium, 2010; Lee et al., 2010). For instance, the baseline risk of stroke in non-anticoagulated patients with atrial fibrillation and eGFR > 60 mL/min is 1.63 per 100 patient years, rising by 13% when eGFR is 45–60 mL/min and by 39% when < 45 mL/min.

Albuminuria is an independent risk factor for VTEs and mortality (Go et al., 2009). The risk of VTE in patients with nephrotic syndrome is eight times higher than in the general population (Mahmoodi et al., 2008), with an annual incidence of 1.02%. Historical data, based on venography, suggested a high incidence of renal vein thromboses in these patients of up to 22% but modern data using venous ultrasound suggest rates of < 0.5% (Kayali et al., 2008). The annual incidence of ATEs in nephrotic syndrome is 1.48%, with myocardial infarction accounting for almost 60%. For both ATE and VTE the risk is greatest in the first 6 months following diagnosis of nephrotic syndrome when the incidence is 5.52% and 9.85%, respectively.

As well as an increased prevalence of traditional risk factors such as diabetes mellitus, obesity, and older age, there are also specific prothrombotic changes in CKD. First, reductions in the physiological anticoagulants protein C, protein S, and antithrombin are seen in CKD, with prevalence rates of 12%, 4%, and 13.5% respectively,

Table 135.1 Factors contributing to increased risk of bleeding

	Defect in:	
	Endothelial-platelet adhesion	**Platelet aggregation**
Uraemia	Small peptides (e.g. Arg–Gly–Asp) in serum competitively antagonize vWF and fibrinogen Increased levels of nitric oxide (NO)	Presence of increased PTH, phenol and guanethidine in serum reduces platelet aggregation
Anaemia	Reduced PCV alters pattern of laminar flow and disrupts platelet interactions with endothelium Increased levels of NO (Hb scavenges NO)	Reduced haematocrit → less ADP and thromboxane A2
Platelet	Conformational change in glycoprotein IIa–IIIb receptor (alteration in vWF interaction)	Reduced levels of ADP in platelet granules

Table 135.2 Anticoagulation considerations in CKD

	Metabolism	Effects due to kidney impairment	Notes
Unfractionated heparin	Hepatic (mainly) but renal excretion important when high doses given	Accumulation only in severe kidney impairment	Short half-life Easy to monitor with activated partial thromboplastin time ratio Antagonist available
Low-molecular-weight heparin	Mainly renally excreted	Half-life increased in kidney impairment	Long acting Monitor with anti-factor Xa levels Protamine only partially reverses effect
Vitamin K antagonists (e.g. warfarin)	Mainly non-renal excretion Traditionally drug labelled as not requiring dose adjustment but 25% less warfarin dose required than those with normal kidney function	Patients with eGFR < 30 mL/min spend less time with INR in therapeutic range and have higher risk of over anticoagulation	Inhibition of vitamin K-dependent matrix Gla protein suggested as link between warfarin and vascular calcification.

compared to < 0.5% in the general population. Secondly, increased levels of factor VIIIc and antiphospholipid (lupus anticoagulant and anticardiolipin) antibodies are more common (Ghisdal et al., 2011). In addition, patients with CKD have elevated levels of circulating microparticles, released by activated or apoptotic cells, which are procoagulant by virtue of their negatively charged phospholipid composition (Faure et al., 2006). Additionally, platelets in CKD have been shown to be in a state of chronic activation, with an outer membrane expressing increased amounts of the negatively charged phosphatidylserine, promoting increased assembly of the prothrombinase complex (Bonomini et al., 2004). This is due, at least in part, to increased caspase activity in uraemic platelets. CKD and nephrotic syndrome are also associated with abnormalities of fibrin formation and fibrinolysis, although the mechanisms underlying these changes are not precisely defined (Undas et al., 2008).

Finally, there is an increased incidence of heparin-induced thrombocytopenia (HIT) in patients on HD, characterized by thrombocytopenia developing 4–10 days after starting unfractionated heparin (and less commonly LMWH). It is due to antibodies against the heparin-platelet factor 4 (PF4) and heparin complex, which activate platelets and endothelial cells. These develop in up to 4% of patients on HD, though only 10% have platelet activating activity. Overdiagnosis of HIT can be minimized with use of a HIT clinical scoring system and platelet activation assays, which are superior to the enzyme immunoassay in discerning clinically relevant anti-PF4 antibodies (Warkentin, 2011). Management includes the discontinuation of heparin and initiation of an alternative anticoagulant such as fondaparinux, danaparoid, or a direct thrombin inhibitor such as argatroban.

Although high plasma levels of homocysteine in CKD have been weakly associated with ATEs, recent interventional studies using vitamin B supplementation, to reduce plasma homocysteine levels, have failed to show a reduction in ATEs, emphasizing the limited value of measuring and treating increased levels. (Bostom et al 2011).

Coagulation abnormalities contributing to chronic kidney disease

Antiphospholipid syndrome

Antiphospholipid syndrome (APLS; see Chapter 164) is defined by the presence of antiphospholipid antibodies (aPLs) associated with VTE or ATE and/or specific types of pregnancy morbidity. Thrombosis can affect vessels of any size, and a large spectrum of renal thrombotic manifestations have been described, including renal artery stenosis, renal vein thrombosis, renal infarction, and thrombotic microangiopathies (TMAs); the latter may produce an acute or

chronic haemolytic uraemic syndrome (HUS). aPLs can occur alone or in association with other autoimmune disease, especially systemic lupus erythematosus (SLE), in which they are found in approximately one-third of patients. SLE-related kidney disease has a worse prognosis in patients with aPLs. Overall, renal abnormalities (defined by the presence of renal insufficiency and/or proteinuria with or without microscopic haematuria) are present in 8–10% of patients with APLS (Sinico et al., 2010). The mainstay of treatment of established thrombosis in APLS is anticoagulation, usually a VKA running an international normalized ratio (INR) of 2–3 after a VTE. There is considerable debate and uncertainty about the appropriate INR for those with ATE, but many favour an INR of 3–4. Protocols for bridging and postoperative thromboprophylaxis at our institution can be obtained from a free iPhone app (<http://itunes.apple.com/gb/app/thrombosis-guidelines/id448736238?mt=8>). Immunosuppression has no effect on thrombotic risk, although there are anecdotal reports of the beneficial role of plasma exchange, steroids, and cyclophosphamide in catastrophic APLS (Joseph et al., 2001).

Thrombotic microangiopathies

TMA is used to describe a spectrum of disorders characterized by a microangiopathic haemolytic anaemia, with prominent red cell fragmentation (due to red cells passing over fibrin strands), thrombocytopenia, and thrombosis in the microvasculature (see Chapter 174). The term encompasses patients with thrombotic thrombocytopenic purpura (TTP), HUS, and a variety of disorders in which TMA may be primary or secondary to another disorder such as malignant hypertension. The histological renal lesion is characterized by thrombosis (mainly of the arterioles and capillaries) and the thrombus is due to a mix of platelets and fibrin except for TTP where the thrombus is almost purely platelets. Injury to the endothelium is the central factor in the sequence of events leading to most TMAs such as D+ HUS caused by *Shiga* toxins and hereditary forms of complement dysregulation including factor H deficiency in atypical HUS, but in TTP there is a deficiency of von Willebrand factor (vWF) cleaving protease or ADAMTS13. ADAMTS13 is responsible for breaking down large multimers of vWF. In the absence of ADAMTS13, large multimers of vWF cause spontaneous aggregation of platelets under high shear pressures seen in the microvasculature. TTP is a medical emergency with up to 90% of patients benefitting from urgent plasma exchange (Ruggenenti et al., 2001).

References

Anderson, F. A., Wheeler, H. B., Goldberg, R. J., *et al.* (1991). A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT study. *Arch Intern Med*, 151, 933–8.

Bonomini, M., Dottori, S., Amoroso, L., *et al.* (2004). Increased platelet phosphatidylserine exposure and caspase activation in chronic uraemia. *J Thromb Haemost*, 2, 1275–81.

Bostom, A. G., Carpenter, M. A., Kusek J. W., *et al.* (2011). Homocysteine-lowering and cardiovascular disease outcomes in kidney transplant recipients primary results from folic acid for vascular outcome reduction in transplantation trial. *Circulation*, 123, 1763–70.

Chan, K. E., Lazarus, J. M., Thadhani, R., *et al.* (2009) Anti-coagulation and antiplatelet usage associates with mortality among haemodialysis patients. *J Am Soc Nephrol*, 20, 872–81.

Chronic Kidney Disease Prognosis Consortium (2010). Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*, 375, 2073–81.

Di Angelantonio, E., Danesh, J., Eiriksdottir, G., *et al.* (2007). Renal function and risk of coronary heart disease in general populations: new prospective study and systematic review. *PLoS Med*, 4, e270.

Faure, V., Sabatier, F., Cerini, C., *et al.* (2006). Elevation of circulating endothelial microparticles in patients with chronic renal failure. *J Thromb Haemost*, 4, 566–73.

Folsom, A. R., Lutsey, P. L., Astor, B. C., *et al.* (2010). Chronic kidney disease and venous thromboembolism: a prospective study. *Nephrol Dial Transplant*, 25, 3296–301.

Gangji, A. S., Sohal, A. S., Treleavan, D., *et al.* (2005). Bleeding in patients with renal insufficiency: a practical guide to clinical management. *Thromb Res*, 118, 423–8.

Gheissari, A., Rajyaguru, V., Kumashiro, R., *et al.* (1990). Gastrointestial haemorrhage in end stage renal disease patients. *Int Surg*, 75, 93–5.

Ghisdal, L., Broeders, N., Wissing, K. M., *et al.* (2011). Thrombophilic factors in stage V chronic kidney disease patients are corrected by renal transplantation. *Nephrol Dial Transplant*, 26, 2700–5.

Go, A. S., Chertow, G. M., Fan, D., *et al.* (2004). Chronic kidney disease and the risks of death, cardiovascular events and hospitalzsation. *N Engl J Med*, 351, 1296–305.

Go, A. S., Fang, M. C., Udaltsova, N., *et al.* (2009). Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation*, 119, 1363–9.

Hetzel, G. R. and Sucker, C. (2005). The heparins: all a nephrologist should know. *Nephrol Dial Transplant*, 20, 2036–42.

Holden, R. M., Harman, G. J., Wang, M., *et al.* (2008). Major bleeding in haemodialysis patients. *Clin J Am Soc Nephrol*, 3, 105–10.

Joseph, R. E., Radhakrishnan, J., and Apel, G. (2001). Antiphospholipid antibody syndrome and renal disease. *Curr Opin Nephrol Hypertens*, 10, 175–81.

Kayali, F., Najjar, R., Aswad, F., *et al.* (2008). Venous thromboembolism in patients hospitalised with nephrotic syndrome. *Am J Med*, 121, 226–30.

Lee, M., Saver, J. L., Chang, K., *et al.* (2010). Low glomerular filtration rate and risk of stroke: meta-analysis. *BMJ*, 341, c4249.

Mahmoodi, B. K., Kate, M. K., Waanders, F., *et al.* (2008). High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: results from a large retrospective cohort study. *Circulation*, 117, 224–30.

Nolin, T. D. (2010). On warfarin use in kidney disease: a therapeutic window of opportunity. *Am J Kidney Dis*, 56, 805–8.

Pavord, S. and Myers, B. (2011). Bleeding and thrombotic complications of kidney disease. *Blood Rev*, 25, 271–8.

Ruggenenti, P., Noris, M., and Remuzzi, G. (2001). Thrombotic microangiopathy, haemolytic uraemic syndrome, and thrombotic thrombocytopenia purpura. *Kidney Int*, 60, 831–46.

Saltiel, M. (2010). Dosing low molecular weight heparins in kidney disease. *J Pharm Pract*, 23, 205–9.

Sinico, R. A., Cavazzana, I., Nuzzo, M., *et al.* (2010). Renal involvement in primary antiphospholipid syndrome; retrospective analysis of 160 patients. *Clin J Am Soc Nephrol*, 5, 1211–17.

Sohal, A. S., Gangji, A. S., Crowther, M. A., *et al.* (2006). Uraemic bleeding; pathophysiology and clinical risk factors. *Thromb Res*, 118, 417–22.

Thorevska, N., Amoateng-Adjepong, Y., Sabahi, R., *et al.* (2004). Anti-coagulation in hospitalised patients with renal insufficiency. *Chest*, 125, 856–63.

Undas, A., Kolarz, M., Kopec, G., *et al.* (2008). Altered fibrin clot properties in patients on long term haemodialysis: relation to cardiovascular mortality. *Nephrol Dial Transplant*, 23, 2010–15.

Warkentin, T. E. (2011). How I diagnose and manage HIT. *Haematology Am Soc Haematol Educ Program*, 2011, 143–9.

Wattanakit, K. and Cushman, M. (2009). Chronic kidney disease and venous thromboembolism: epidemiology and mechanisms. *Curr Opin Pulm Med*, 15, 408–12.

Wattanakit, K., Cushman, M., Stehman-Breen, C., *et al.* (2008). Chronic kidney disease increases risk for venous thromboembolism *J Am Soc Nephrol*, 19, 135–40.

CHAPTER 136

Mechanisms of progression of chronic kidney disease: overview

Neil Turner

Introduction

Patients at high risk of progressive renal disease leading to end-stage renal failure include some with continuing activity of the disease that first caused their kidney injury, but in many cases the injury is historic, the disease or insult that caused the injury having long passed. Patients at high risk form a minority of the very large numbers of patients in the population with chronic kidney disease (CKD), most of whom are elderly and have very slowly progressive or stable disease. The hallmarks of high renal risk and its management are discussed in Chapter 99, but it is interesting that the markers of high risk are to a large extent independent of the initiating renal condition. They can be summarized as

1. more severe existing injury (current glomerular filtration rate (GFR))
2. proteinuria
3. blood pressure
4. having a specific renal diagnosis
5. younger age (which may relate to (4)).

Explanations for progressive kidney disease need to bear in mind:

- the very close association between proteinuria and outcome, regardless of the cause of proteinuria (with the notable exception of minimal change disease)
- the regenerative capacity of parts of the nephron, versus the tendency of injury to resolve or lead to scarring
- the protective effect of blood pressure reduction, and in particular of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

Three major current hypotheses attempt to explain the progression of CKD. They are not mutually exclusive. In addition, differences in healing versus scarring at the time of injury mechanisms may be important in determining whether amplifying mechanisms become established and whether or how fast they progress.

Hyperfiltration (nephron loss) hypothesis

Loss or 'deficiency' of nephrons leads to hyperfiltration in the remaining ones. By a mechanism that may involve static hydrodynamic pressure and stretching, damage is done to the structure of the glomerulus—perhaps particularly to podocytes. There is evidence for an association between nephron number at birth and CKD (see Chapter 138) in addition to the evidence that low GFRs are more likely to be associated with progression after renal damage. Proteinuria is presumed to be a sign of 'glomerular distress' in hyperfiltration. The protective effect of ACEIs is assumed to be simply haemodynamic; the reduction in glomerular filtration pressure reduces the stress on the glomerulus. It is interesting then that ACEIs can lead to complete remission of proteinuria in a number of circumstances (see Chapter 46).

However this explanation copes less well with the observation that glomerular diseases are more likely to progress than other types.

Toxicity of proteinuria hypothesis

Proteinuria caused by glomerular lesions leads to exposure of tubular cells to serum proteins, or substances bound to these proteins, and these are toxic to tubular cells, or other cells in the tubulointerstitium. This injury leads to cell death and directly or indirectly triggers tubulointerstitial fibrosis (see Chapters 137 and 140). It has been repeatedly observed that the extent of tubulointerstitial fibrosis is one of the strongest predictors of long-term outcome, even in glomerular diseases. There is also a large body of evidence from *in vitro* studies of renal tubular cells in tissue culture. In this hypothesis, the protective effect of ACEIs and ARBs is through reducing proteinuria at the glomerulus, and/or by altering the inflammatory/reparative response in the tubulointerstitium.

Podocyte loss hypothesis

Podocytes are the final common pathway of most proteinuria (see Chapters 45, 50). This hypothesis postulates that these cells are themselves key to progression of glomerular disease. The degree of proteinuria is a marker of the degree of podocyte injury, and severe podocyte injury causes podocyte death (see Chapters 45, 60). There

is experimental evidence that 20% podocyte loss per glomerulus may be recoverable, but after 40% loss progressive renal failure is the norm (see Chapter 59). Podocytes are known to have limited ability to replace themselves and it is uncertain whether stem cells could be making a significant contribution to replacement in a disease setting. In this hypothesis, the protective effects of ACEIs could be attributable to direct effects on podocytes that leads to them adapting or signalling in a way that is 'podocyte protective'. There are receptors for angiotensin (and many other mediators) on podocytes and good reason to believe that they may directly normalize podocyte phenotype, including slit diaphragm structure, and improve podocyte survival.

An extension of this hypothesis argues that proteinuria may be toxic to podocytes, which would help to explain the 'vicious cycle' of progressive renal disease, and give an additional indirect mechanism for the protective effect of ACEIs.

Healing versus scarring hypothesis

The nature and timing of a renal injury, and genetic factors, and age, may determine whether or not a renal injury leads to continuing progression or stable CKD.

Alternatively, following glomerular damage (for example caused by podocyte loss), the scarring we see is merely a secondary consequenc of nephron loss (see Chapter 139).

It is possible that current protective therapies bias these processes towards healing rather than scarring, and that there may be new ways to amend outcomes by influencing these pathways (see Chapter 140).

These mechanisms could be pertinent to both mechanisms of tubulointerstitial fibrosis in response to proteinuria, and to the ability of a glomerulus to survive with a reduced complement of podocytes without progressing to glomerulosclerosis.

CHAPTER 137

Proteinuria as a direct cause of progression

Jeremy Hughes

Introduction

Normal urine contains a small amount of protein (< 150 mg/day) but increased urinary protein excretion accompanies many renal diseases (see Chapter 50). There is a close association between the level of proteinuria and disease outcome in chronic kidney diseases irrespective of the cause of proteinuria and this raises the possibility that, in addition to being a marker of renal disease, proteinuria may exert independent detrimental effects upon the kidney.

This is one of the competing hypotheses to explain the tendency of renal diseases, and particular glomerular diseases, to progress long after the initial injury (see Chapter 136).

This hypothesis does not attempt to explain the progression of chronic kidney disease in all scenarios. Other mechanisms could also be involved including glomerular hyperfiltration and nephron number, excessive loss of podocytes and resultant glomerulosclerosis, and chronic tissue hypoxia consequent to rarefaction of the microvascular capillary network (see Chapter 136). It has also been suggested that, as a result of age or other factors, the kidneys of individuals may differ in their capacity to repair renal damage following acute or chronic injury and may thus be at more risk of subsequent scarring and loss of renal function. All of these factors might affect the extent of injury and the rate of progression of chronic kidney disease so that these hypotheses and concepts are not mutually exclusive but may play differential roles in different diseases.

In this chapter we will consider the following questions:

- What happens to filtered protein under normal circumstances?
- What is the prima facie evidence that a high level of protein in tubular fluid is actually nephrotoxic?
- What is the impact of proteinuria in human disease?
- What filtered proteins or protein-associated substances are detrimental and what is the mechanism of their nephrotoxic effects?

How much protein is filtered and what happens to it?

In order to gain access to the glomerular filtrate, protein must pass through the glomerular endothelium, glomerular basement membrane, and across the podocyte slit diaphragm and damage to any of these structures may result in proteinuria (see Chapter 50). The passage of proteins across these barriers is related to molecular size, configuration, and electrical charge. In health it is believed that there is very limited filtration of proteins of intermediate molecular weight such as albumin and almost no filtration of high-molecular-weight proteins such that tubular cells are not exposed to high levels of protein in tubular fluid (reviewed in (D'Amico and Bazzi, 2003). This area, however, has become more controversial in recent years.

Experimental work using two-photon microscopy in non-proteinuric live rats tracked and quantified the filtration and tubular handling of fluorescently labelled albumin (Russo et al., 2007). These experiments indicated that the glomerular sieving coefficient for albumin was approximately 50-fold higher than previously thought from micropuncture studies. Also, the data suggested that the high level of filtered labelled albumin was rapidly taken up by proximal tubular cells and passed into peritubular capillaries by a process termed transcytosis involving cytoplasmic vesicles containing albumin. This 'albumin retrieval pathway' appeared to be the predominant route of albumin absorption by proximal tubular cells and involved albumin binding to the apical cell surface receptors megalin and cubulin. Albumin binding to proximal tubular cells may also result in targeting to the lysosomal degradation pathway. The study of rats treated with the drug puromycin aminonucleoside that induces the nephrotic syndrome indicated that the glomerular filtration of albumin was not different in nephrotic rats compared to untreated control rats so that the authors concluded that the resultant albuminuria was secondary to a failure of tubular reabsorption of albumin. Further studies by the same group extended this work and suggested that impaired tubular reabsorption of albumin is partly responsible for the albuminuria found in rats with early diabetic nephropathy (Russo et al., 2009).

Although these studies using modern imaging tools are provocative, other studies (Tanner, 2009) have been unable to confirm these findings so that further work is undoubtedly required in this area (reviewed in Comper et al., 2008; Jarad and Miner, 2009; Nielsen and Christensen, 2010). However, the view that albuminuria may reflect, at least in part, a failure to reabsorb filtered albumin secondary to tubular pathophysiology and disease may need to be taken into account in future experimental and clinical studies. In addition, although this suggests that proximal tubular cells may be more actively engaged in filtered protein reabsorption under normal conditions than previously thought, it does not change the potential for elevated tubular levels of proteins not normally filtered (e.g.

high-molecular-weight proteins) and accompanying diverse molecules (e.g. cytokines, growth factors, and lipids) to exert adverse effects upon proximal tubular cells during proteinuric disease associated with podocyte injury and loss.

Can proteins within tubular fluid lead to tubular cell injury and fibrosis?

A key question is whether an elevated level of protein in tubular fluid is injurious to tubular cells in the absence of any glomerular pathology or inflammation. Seminal studies used the atypical renal anatomy of the amphibian axolotl (Fig. 137.1) to address this question. The kidneys of the axolotl have both 'open' and 'closed' nephrons. The 'open' nephrons access the peritoneal cavity via ciliated funnels termed nephrostomes whilst the 'closed' nephrons are supplied by glomeruli. This unique architecture allowed the daily intraperitoneal injection of fetal calf serum to result in high levels of tubular fluid protein within the open nephrons but not the closed nephrons so that the effect of tubular proteinuria in the absence of any upstream glomerular pathology could be examined (Gross et al., 2002). Histological assessment clearly indicated proteinaceous droplets within proximal tubular cells that were associated with upregulation of the pro-fibrotic cytokine transforming growth factor beta (TGF-β) and the presence of peritubular interstitial fibrosis with collagen I and fibronectin deposition. Similar results were found in studies involving the injection of human transferrin, human low-density lipoprotein, and human immunoglobulin suggesting that the nature of the protein present within the nephron lumen was not a critical factor. This work provided prima facie evidence that the presence of an abnormally high level of protein within the tubular fluid may be cytotoxic and pro-fibrotic.

Such an experiment is not feasible in rodents or humans but the tubular damage that may occur in patients with plasma cell dyscrasias and high levels of urinary free light chains is of interest. Affected patients may present with the Fanconi syndrome, acute kidney injury, or progressive renal disease and this indicates that the presence of a high level of a filtered protein, in this case free light chains, within the tubular fluid may be cytotoxic. Furthermore, the *in vitro* treatment of proximal tubular cells with free light chains may induce oxidative stress, cell activation (Ying et al., 2011), or apoptosis (Ying et al., 2012) (reviewed in Sanders, 2012).

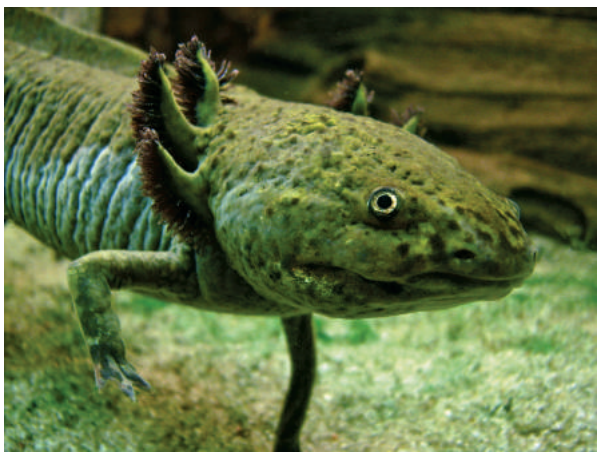

Fig. 137.1 The axolotl, *Ambystoma mexicanum*.
Wikimedia Commons, <http://commons.wikimedia.org/wiki/File:Axolotl_Portrait.jpg>

What is the impact of proteinuria in human disease?

The severity of proteinuria at presentation or during clinical follow-up is a robust predictor of outcome in patients with diverse glomerular diseases including immunoglobulin (Ig)-A nephropathy, membranous nephropathy, and focal segmental glomerulosclerosis (reviewed in Erkan, 2013; and Chapter 50). In addition, the degree of proteinuria predicts outcome in diseases that do not primarily affect the glomerulus as in patients with congenital anomalies of the kidney and urinary tract (Litwin, 2004).

Indirect evidence for a causative role for proteinuria in the progression of disease comes from interventional studies using antiproteinuric angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). For example, patients treated with ramipril in the REIN study had a comparable blood pressure to patients in the control group but had a reduction in proteinuria and a better outcome (GISEN Group, 1997). Also, the Reduction of End Points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study demonstrated that patients with the greatest reduction in proteinuria exhibited more renoprotection at comparable levels of blood pressure control (Brenner et al., 2001). A study of 542 patients with IgA nephropathy demonstrated that the level of proteinuria during follow-up was the strongest predictor of the rate of fall in glomerular filtration rate (GFR) (Reich et al., 2007). In this study, the rate of decline in GFR was 90% slower than the mean rate if the proteinuria was < 1 g per day.

Other agents that reduce proteinuria do not have a proven record in reducing the progression of human renal disease (though are often effective in animal models). It remains possible that the consistent association of a reduction in proteinuria with improved renal outcome is an epiphenomenon. In this scenario, the reduction in proteinuria could represent some other potentially renoprotective biological action of ACEIs and ARBs upon key cells such as podocytes, tubular cells, fibroblasts, etc. However, further evidence in support for a pathogenic role of proteinuria in the progression of kidney disease is derived from a combination of experimental *in vitro* and *in vivo* studies.

What filtered proteins or protein-associated substances are detrimental and what is the mechanism of their nephrotoxic effects?

Selective versus non-selective proteinuria

Although persistent proteinuria is a strong predictor of progressive renal disease, previous work suggested that highly selective proteinuria, as in cases of minimal change disease (see Chapters 50 and 55), is associated with less severe tubulointerstitial disease on renal biopsy (Bazzi et al., 2000). It has been proposed that this might reflect the detrimental effects of high-molecular-weight proteins such as immunoglobulin and complement factors in patients with non-selective proteinuria. However, patients with selective

proteinuria may also exhibit a different clinical course with a better response to treatment with steroids etc. so that the duration of disease is more limited. It should also be noted that patients with minimal change disease can progress to end-stage renal failure (Waldman et al., 2007) and further study of patients with selective versus non-selective proteinuria is merited.

Proteomics reveals the complexity of urine protein

Many studies have examined the effect of albumin upon rodent or human proximal tubular cell biology as it is found in abundance in proteinuric diseases but other proteins such as immunoglobulin, transferrin, and serum fractions have also been studied. Recent developments in proteomic methodologies indicate the tremendous range of proteins and peptides present in both normal urine and the urine of proteinuric patients (reviewed in Bonomini et al., 2012; see Chapter 50) such that tubular cells will be undoubtedly be exposed to many more molecules than can be tested *in vitro* in cell culture studies. Some of these proteins/peptides may be a consequence of renal injury, represent a biomarker of disease activity, or be actively involved in disease pathogenesis such as pro-inflammatory cytokines or growth factors.

A real example of this is believed to be the activation of ENaC by filtered proteases in nephrotic syndrome, leading to the avid sodium retention that characterizes the syndrome (described in Chapter 53).

Exogenous proteins may activate tubular cells

A significant body of *in vitro* work accumulated over a number of years indicates that exogenous protein interacts with the receptors megalin and cubulin on the apical cell surface of proximal tubular cells (reviewed in Birn and Christensen, 2006; Baines and Brunskill, 2008). Although cell surface-bound protein may be endocytosed and degraded, this is not necessarily required for the well-described activation of tubular cells by protein (reviewed in Zoja et al., 2003; Zandi-Nejad et al., 2004; Abbate et al., 2006). Exposure to proteins may result in activation of key transcription factors such as nuclear factor kappa B (NF-κB) and members of the signal transducers and activation of transcription (STAT) family. In addition, it has been shown that factors associated with or bound to proteins such as free fatty acids and other lipids may also be biologically active and exert activatory effects upon tubular cells. Tubular cell activation may result in the production of many bioactive mediators such as endothelin-1 or the pro-fibrotic cytokine TGF-β.

Activated tubular cells link proteinuria to interstitial inflammation

Although *in vitro* experiments do not reflect the complexity of the intrarenal microenvironment, an interesting finding was that the exposure of the apical or luminal cell surface to protein resulted in the secretion of mononuclear cell chemokines such as chemokine (C-C motif) ligand 2 (CCL2—previously known as monocyte chemoattractant protein-1) and CCL5 from the basolateral aspect of the cell (Fig. 137.2). These studies indicate that proximal tubular cells may first act as a sensor to detect proteins that either should not be present at all in the tubular fluid or are present at abnormally high levels. Second, the resultant cell activation may then amplify and focus the pro-inflammatory stimulus towards the interstitium via basolateral chemokine-mediated recruitment of pro-inflammatory mononuclear cells such as monocytes and T cells. Following exposure to protein, tubular cells may also express adhesion molecules such as osteopontin (also a monocyte/macrophage chemoattractant) and intercellular adhesion molecule 1 (ICAM-1) that promotes the retention of recruited cells to the tubulointerstitium.

Proteinuria may induce tubular cell death

In addition to being activated by exposure to proteins, tubular cells may also be injured and undergo apoptosis by the induction of oxidative stress (Matsui et al., 2010). Recent studies indicate that various physiological or pathological stresses can lead to the accumulation of abnormal misfolded proteins in the endoplasmic reticulum (ER). This ER stress induces the unfolded protein response (UPR) that upregulates the capacity of the ER to process these abnormal proteins. Although the UPR may be protective, prolonged or severe ER stress may lead to cell death by apoptosis. Albumin treatment of rat proximal tubular cells resulted in ER stress-induced apoptosis *in vitro* with cellular markers of ER stress being clearly demonstrated *in vivo* in the renal tubules of proteinuric rats (Ohse et al., 2006). ER stress is becoming increasingly recognized as playing an important role in renal disease including diabetic nephropathy in humans (reviewed in Cybulsky, 2010).

Complement activation and synthesis

The complement pathway is involved in many diseases affecting native or transplanted kidneys. Activation of complement in proteinuric urine has been shown to mediate tubular injury in several experimental proteinuric models including passive Heymann nephritis (a model of membranous nephropathy) and nephrotoxic glomerulonephritis with complement depletion or genetic deficiency of complement factor 6 being markedly renoprotective (reviewed in Hsu and Couser, 2003). In addition to the presence of filtered complement components in the urine, proteinuria may stimulate the active synthesis of pro-inflammatory complement factors by tubular cells (Abbate et al., 2006).

Tissue biopsy studies support a role for proteinuria in tubulointerstitial disease

Cell culture studies indicate that proteins may activate tubular cells and induce the production of chemokines and mediators capable of promoting mononuclear cell recruitment and retention as well as interstitial fibrosis. Additional supportive data has been demonstrated in experimental models of chronic proteinuria including the protein overload model, puromycin nephrosis, passive Heymann nephritis, and Adriamycin® nephropathy. Pertinent experimental findings including increased NF-κB activity of tubular epithelial cells that increases further with the duration of proteinuria (reviewed in Abbate et al., 2006). Also, the tubular expression of CCL2 and osteopontin precedes the accumulation of a mononuclear cell infiltrate comprising T cells and monocytes/macrophages. These findings have been shown to have human relevance with increased activation of proximal tubular cell NF-κB as well as increased expression of CCL2, CCL5, osteopontin, and TGF-β evident in renal biopsies from patients with progressive membranous nephropathy (Mezzano et al., 2001). Interestingly, in this study, although there was evidence of robust proximal tubular

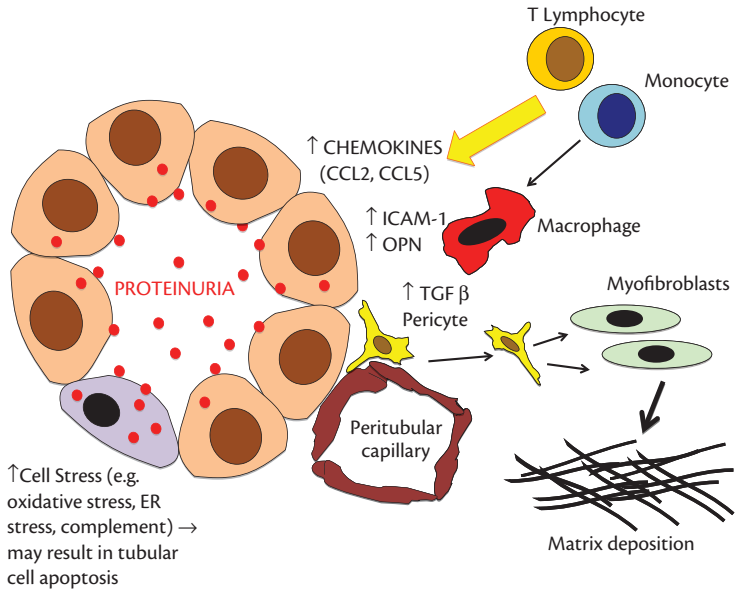

Fig. 137.2 Proteinuria results in the binding of proteins such as albumin to megalin and cubulin at the apical cell surface of proximal tubular cells. Cell activation leads to upregulation of transcription factors such as NF-κB resulting in increased expression of chemokines (e.g. CCL2) and adhesion molecules (e.g. ICAM-1, VCAM-1, and osteopontin). This results in the recruitment and retention of mononuclear cells such as T lymphocytes and monocytes that subsequently mature into tissue macrophages. The exact mechanistic link to the development of interstitial fibrosis is unclear at present but is likely to involve the production and activation of TGF-β. TGF-β may activate normally quiescent pericytes to detach from interstitial capillary endothelial cells and adopt a myofibroblast phenotype with resultant production and deposition of extracellular matrix. Proteinuria may result in significant cytotoxic injury to some tubular cells as a result of cell surface complement activation, oxidative stress, or endoplasmic reticulum stress. This may lead to cell death by apoptosis if severe. CCL2 = chemokine (C-C motif) ligand 2; ICAM-1 = intercellular adhesion molecule 1; NF-κB = nuclear factor kappa B; TGF-β = transforming growth factor beta; VCAM-1 = vascular cell adhesion molecule 1.

cell NF-κB activation in renal biopsies from patients with minimal change disease this was not accompanied by expression of CCL2, CCL5, osteopontin, or TGF-β (Fig. 137.2). Lastly, a strong association between proteinuria, urinary CCL2 levels, interstitial macrophage infiltration, and tissue injury on renal biopsy was evident in a cohort of 215 patients with chronic kidney disease of diverse aetiology (Eardley et al., 2006).

Conclusion

In summary, proteinuric urine contains myriad proteins and peptides as well as other molecules that are capable of exerting important biological effects upon tubular cells and many studies have demonstrated the activatory or cytotoxic effect of proteinuria upon proximal tubular cells *in vitro* and *in vivo*. The recruitment of pro-inflammatory mononuclear cells by activated proximal tubular cells leads to tubulointerstitial inflammation that can result in the activation of pericytes to adopt a myofibroblast phenotype and promote fibrotic scarring. Thus, the totality of the accumulated experimental and clinical data strongly indicates that although proteinuria is undoubtedly the result of glomerular disease it also represents a potentially important cause of progression in patients with chronic kidney disease associated with proteinuria.

References

Abbate, M., Zoja, C., and Remuzzi, G. (2006). How does proteinuria cause progressive renal damage? *J Am Soc Nephrol*, 17, 2974–84.

Baines, R. J. and Brunskill, N. J. (2008). The molecular interactions between filtered proteins and proximal tubular cells in proteinuria. *Nephron Exp Nephrol*, 110, e67–71.

Barbour, S. J. and Reich, H. N. (2012). Risk stratification of patients with IgA nephropathy. *Am J Kidney Dis*, 59, 865–73.

Bazzi, C., Petrini, C., Rizza, V., *et al.* (2000). A modern approach to selectivity of proteinuria and tubulointerstitial damage in nephrotic syndrome. *Kidney Int*, 58, 1732–41.

Birn, H. and Christensen, E. I. (2006). Renal albumin absorption in physiology and pathology. *Kidney Int*, 69, 440–9.

Bonomini, M., Sirolli, V., Magni, F., *et al.* (2012). Proteomics and nephrology. *J Nephrol*, 25, 865–71.

Brenner, B. M., Cooper, M. E., De Zeeuw, D., *et al.* (2001). Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*, 345, 861–9.

Breyer, J. A., Bain, R. P., Evans, J. K., *et al.* (1996). Predictors of the progression of renal insufficiency in patients with insulin-dependent diabetes and overt diabetic nephropathy. The Collaborative Study Group. *Kidney Int*, 50, 1651–8.

Comper, W. D., Hilliard, L. M., Nikolic-Paterson, D. J., *et al.* (2008). Disease-dependent mechanisms of albuminuria. *Am J Physiol Renal Physiol*, 295, F1589–600.

Cybulsky, A. V. (2010). Endoplasmic reticulum stress in proteinuric kidney disease. *Kidney Int*, 77, 187–93.

D'amico, G. and Bazzi, C. (2003). Pathophysiology of proteinuria. *Kidney Int*, 63, 809–25.

De Zeeuw, D., Remuzzi, G., Parving, H. H., *et al.* (2004). Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. *Kidney Int*, 65, 2309–20.

Eardley, K. S., Zehnder, D., Quinkler, M., *et al.* (2006). The relationship between albuminuria, MCP-1/CCL2, and interstitial macrophages in chronic kidney disease. *Kidney Int*, 69, 1189–97.

Erkan, E. (2013). Proteinuria and progression of glomerular diseases. *Pediatr Nephrol*, 28, 1049–58.

Gross, M. L., Hanke, W., Koch, A., *et al.* (2002). Intraperitoneal protein injection in the axolotl: the amphibian kidney as a novel model to study tubulointerstitial activation. *Kidney Int*, 62, 51–9.

Hsu, S. I. and Couser, W. G. (2003). Chronic progression of tubulointerstitial damage in proteinuric renal disease is mediated by complement activation: a therapeutic role for complement inhibitors? *J Am Soc Nephrol*, 14, S186–91.

Jarad, G. and Miner, J. H. (2009). Update on the glomerular filtration barrier. *Curr Opin Nephrol Hypertens*, 18, 226–32.

Litwin, M. (2004). Risk factors for renal failure in children with non-glomerular nephropathies. *Pediatr Nephrol*, 19, 178–86.

Matsui, T., Yamagishi, S., Ueda, S., *et al*. (2010). Irbesartan inhibits albumin-elicited proximal tubular cell apoptosis and injury in vitro. *Protein Pept Lett*, 17, 74–7.

Mezzano, S. A., Barria, M., Droguett, M. A., *et al*. (2001). Tubular NF-kappaB and AP-1 activation in human proteinuric renal disease. *Kidney Int*, 60, 1366–77.

Nielsen, R. and Christensen, E. I. (2010). Proteinuria and events beyond the slit. *Pediatr Nephrol*, 25, 813–22.

Ohse, T., Inagi, R., Tanaka, T., *et al*. (2006). Albumin induces endoplasmic reticulum stress and apoptosis in renal proximal tubular cells. *Kidney Int*, 70, 1447–55.

Reich, H. N., Troyanov, S., Scholey, J. W., *et al*. (2007). Remission of proteinuria improves prognosis in IgA nephropathy. *J Am Soc Nephrol*, 18, 3177–83.

Russo, L. M., Sandoval, R. M., Campos, S. B., *et al*. (2009). Impaired tubular uptake explains albuminuria in early diabetic nephropathy. *J Am Soc Nephrol*, 20, 489–94.

Russo, L. M., Sandoval, R. M., Mckee, M., *et al*. (2007). The normal kidney filters nephrotic levels of albumin retrieved by proximal tubule cells: retrieval is disrupted in nephrotic states. *Kidney Int*, 71, 504–13.

Sanders, P. W. (2012). Mechanisms of light chain injury along the tubular nephron. *J Am Soc Nephrol*, 23, 1777–81.

Tanner, G. A. (2009). Glomerular sieving coefficient of serum albumin in the rat: a two-photon microscopy study. *Am J Physiol Renal Physiol*, 296, F1258–65.

Waldman, M., Crew, R. J., Valeri, A., *et al*. (2007). Adult minimal-change disease: clinical characteristics, treatment, and outcomes. *Clin J Am Soc Nephrol*, 2, 445–53.

Ying, W. Z., Wang, P. X., Aaron, K. J., *et al*. (2011). Immunoglobulin light chains activate nuclear factor-kappaB in renal epithelial cells through a Src-dependent mechanism. *Blood*, 117, 1301–7.

Ying, W. Z., Wang, P. X., and Sanders, P. W. (2012). Pivotal role of apoptosis signal-regulating kinase 1 in monoclonal free light chain-mediated apoptosis. *Am J Pathol*, 180, 41–7.

Zandi-Nejad, K., Eddy, A. A., Glassock, R. J., *et al*. (2004). Why is proteinuria an ominous biomarker of progressive kidney disease? *Kidney Int Suppl*, S76–89.

Zoja, C., Morigi, M., and Remuzzi, G. (2003). Proteinuria and phenotypic change of proximal tubular cells. *J Am Soc Nephrol*, 14 Suppl 1, S36–41.

CHAPTER 138

Nephron numbers and hyperfiltration as drivers of progression

Valerie A. Luyckx

Introduction: the nephron number hypothesis

The core hypothesis underlying this explanation for progressive renal disease (see Chapter 136) is that there is a threshold number of nephrons, below which survival of surviving nephrons is threatened by 'hyperfiltration', or some corollary of that. The term 'programming' is used to define the process whereby long-term structural and functional changes occur as a consequence of environmental conditions experienced during critical growth periods (McMillen et al., 2005). In 1988, Brenner et al. suggested that an individual's nephron number, developmentally programmed *in utero*, may be a significant risk factor for hypertension and renal disease, and may explain the variable susceptibility to these diseases in individuals with similar exposures, for example, diabetes mellitus or sodium excess (Brenner et al., 1988).

This hypothesis extrapolated from the known relationship between surviving nephron mass and risk of renal disease progression in individuals with acquired nephron loss later in life, based on the concept of adaptive hyperfiltration in the remaining nephrons: a kidney with fewer nephrons would have a reduced sodium excretory capacity, thereby augmenting blood pressure, and have a reduced renal reserve to sustain hyperfiltration and adapt after renal injury (Fig. 138.1) (Brenner et al., 1988, 1996).

It was suggested that low birth weight (LBW) may be a surrogate marker for a reduced nephron number at birth (Brenner et al., 1988). Since then, diverse animal models of developmental programming have demonstrated an association of LBW with low nephron number and subsequent risk of hypertension and renal dysfunction (Luyckx and Brenner, 2010). Not all LBW animals have low nephron number, however, and not all animals with low nephron number develop hypertension, therefore nephron number alone, although important, does not capture all risk (Luyckx and Brenner, 2010).

In support of the nephron number hypothesis, humans born with severely reduced nephron number, for example, with unilateral renal agenesis, bilateral renal hypoplasia, or oligomeganephronia, develop proteinuria, glomerulosclerosis, and progressive renal failure over time (Schreuder et al., 2008). In contrast, uninephrectomy later in life for kidney donation is generally accepted to be safe, although hypertension, proteinuria, and occasional renal failure have been reported in some donors (Ibrahim et al., 2009). These observations raise the question whether renal adaptation to a nephron deficit may be different if nephron loss occurs during development or after completion of nephrogenesis (Luyckx and Brenner, 2010). Animal data suggests that glomerular maturation may be delayed when nephron loss occurs during development, which may have long-term implications increasing the risk of hypertension and renal disease (Nyengaard, 1993). Importantly, cardiovascular disease and diabetes are also developmentally programmed, which likely compound the risk of renal disease in LBW individuals (McMillen et al., 2005).

Nephron number in humans

Counting of nephrons in human kidneys can only be done post-mortem, and is a tedious and highly specialized process (Bertram et al., 2011). Thus far nephrons have been counted in < 1000 individuals worldwide, therefore data is limited. Bertram et al. have performed the most comprehensive studies in humans and have found that nephron numbers vary widely from 210,332 to 2,702,079 per kidney (Bertram et al., 2011). Nephron numbers do decline with age, however among 15 infants under 3 months of age, nephron number varied from 246,181 to 1,106,062, suggesting that developmental programming during early life is the major determinant of nephron number (Bertram et al., 2011). The up to 13-fold inter-individual variation in nephron number in these studies may reflect true differences between subjects, but given the magnitude, may also reflect confounding by the small sample sizes.

Renal development in humans begins during the 9th week and ends in the 36th week of gestation, therefore intrauterine conditions as well as gestational age determine nephron number at birth (Hinchliffe et al., 1993; Rodriguez et al., 2004). Nephrogenesis in humans is thought to cease at birth, however in a cohort of extremely premature infants, evidence of ongoing glomerulogenesis was observed until day 40 postnatally, although nephron numbers remained lower than in normal birth weight (NBW) full-term infants (Rodriguez et al., 2004). In contrast, other authors did not find any increase in nephrogenesis between kidneys from premature or full-term infants who died at birth or 1 year of age, stating that 'renal arrest' occurs after birth (Hinchliffe et al., 1993).

Determinants of nephron number in humans

An individual's nephron number is the result of complex life-long interactions between genetics, early development, and environment.

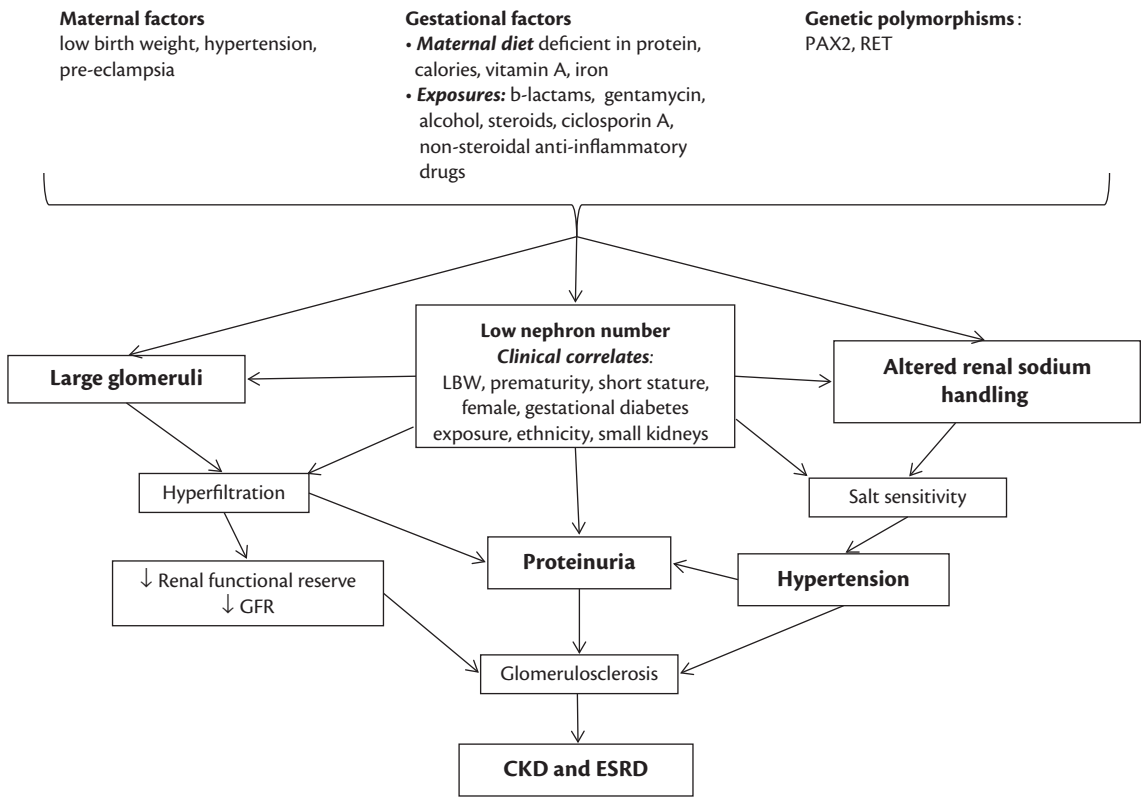

Fig. 138.1 Mechanisms and implications of developmental programming in the kidney.

Prenatal determinants of nephron number

Genetics

Major congenital and genetic abnormalities of kidney development contribute to approximately 40–60% of childhood end-stage renal disease (ESRD) (Kemper et al., 2001; Schreuder et al., 2008). Full or partial deletion of > 25 genes involved in nephrogenesis are associated with reduced nephron number and renal hypoplasia in mice (Moritz et al., 2008). Developmental abnormalities associated with more subtle genetic polymorphisms, however, may not present with childhood renal failure, but may impact nephron number and risk of future renal disease. Common polymorphisms of either *PAX2* or *RET*, genes participating in ureteric bud branching, were associated with a 10% reduction in renal volume in Caucasian infants (Quinlan et al., 2007; Zhang et al., 2008). When inherited together, these alleles were associated with a 23% reduction in kidney volume (Zhang et al., 2009). Newborn kidney volume is proportional to nephron number, therefore these polymorphisms are likely associated with reduced nephron number (Zhang et al., 2008). Conversely, newborn kidney size was increased by 22% if a common variant of the *ALHD1A2* gene, involved in retinoic acid metabolism, was present (El Kares et al., 2010). Such polymorphisms may therefore contribute to the observed variability in nephron number in the general population.

Intrauterine environment and gestational age

In humans, nephron number correlates linearly with birth weight, with an increase of around 260,000 nephrons per kilogram of birth weight (Bertram et al., 2011). Nephron numbers have not been counted in adults of known LBW, but were lower in LBW or premature infants compared to NBW full-term infants, demonstrating the impact of an adverse intrauterine environment on nephrogenesis (Manalich et al., 2000; Rodriguez et al., 2004). In animal models, LBW and/or low nephron number have been associated with a variety of prenatal insults that are prevalent in humans, which point to potential conditions amenable to intervention that could optimize nephron number in the offspring (Box 138.1) (Luyckx and Brenner, 2010).

Postnatal determinants of nephron number

Nutrition and catch-up growth

Protein energy malnutrition early in the postnatal period is associated with a reduced glomerular filtration rate (GFR) at age 7 years in premature infants (Bacchetta et al., 2009). Conversely, rapid growth within the first weeks to 2 years of life, especially after being born LBW, has been associated with increased risk of cardiovascular disease in adulthood (Luyckx et al., 2009). The pathophysiology underlying the latter observation has not been fully elucidated, but may be associated with accelerated renal and cardiovascular senescence resulting from rapid catch-up growth (Hales and Ozanne, 2003; Luyckx et al., 2009).

Nephron loss

Nephron number declines as a consequence of normal ageing, renal disease, and ongoing hyperfiltration (Brenner et al., 1996; Hoy et al., 2008; Bertram et al., 2011). Individuals born with fewer nephrons may therefore reach a critical low nephron number earlier than those born with higher nephron numbers and manifest with premature hypertension and renal disease.

Box 138.1 Factors associated with reduced nephron numbers in experimental models (Luyckx and Brenner, 2010)

- Maternal dietary deficiency:
  - low-protein diet
  - 50% calorie restriction
  - vitamin A deficiency
  - iron deficiency
- Uterine ischaemia:
  - uterine artery ligation or embolization
- Increased glucocorticoid exposure:
  - exogenous glucocorticoids
  - indirect via maternal low protein diet
- Maternal hyperglycaemia
- Gestational exposures:
  - gentamicin
  - beta-lactam antibiotics
  - ciclosporin
  - alcohol.

Clinical correlates of nephron number

Nephron number cannot be determined *in vivo*, therefore clinical surrogates are required to identify individuals at risk of low nephron number (Hoy et al., 2008; Luyckx and Brenner, 2010).

Anthropomorphic correlates

- LBW is the strongest clinical marker for low nephron number (Hoy et al., 2008; Luyckx and Brenner, 2010; Bertram et al., 2011). LBW is defined by the World Health Organization as a birth weight < 2.5 kg, and > 30 million LBW babies are born annually worldwide (<http://www.who.int>). LBW may occur with intrauterine growth restriction (IUGR), resulting in an infant who is small for gestational age (SGA), or from the premature birth of an infant at an appropriate weight for gestational age (AGA). Very low birth weight (VLBW) is defined as a birth weight < 1.5 kg, high birth weight (HBW) is defined as a birth weight > 4.5 kg.
- Prematurity is associated with reduced glomerulogenesis (Rodriguez et al., 2004).
- Nephron number increases by 28,000 glomeruli per centimetre increase in height in adult males (Hoy et al., 2008). LBW is associated with short stature.
- Nephron numbers vary by ethnicity. Aboriginal Australians have the lowest nephron numbers among the populations studied thus far (Hoy et al., 2008). LBW is highly prevalent in this population. Relative increase in nephron number per kilogram birth weight is higher among Caucasian compared with African American subjects (Bertram et al., 2011).
- Nephron number declines by 3676 nephrons per kidney per year after age 18 (Hoy et al., 2008).
- Females have 12% fewer nephrons than males (Hoy et al., 2008).

Kidney size

- Nephron number increases with increasing kidney mass in both neonates and adults, but is only measurable post-mortem or in the setting of kidney donation (Schmidt et al., 2004; Zhang et al., 2008).
- Renal volume can be calculated radiologically and is proportional to renal mass. Renal volume has been used as a surrogate for nephron endowment, and was found to be lower in SGA compared to AGA infants as well as Australian Aboriginal compared to Caucasian children (Spencer et al., 2001; Schmidt et al., 2004), although the relationship was weakened by correction for body size (Rakow et al., 2008). The confounding effect of renal hypertrophy or nephron loss on kidney volume in the setting of low nephron number cannot be controlled for in these studies.

Glomerular volume

- In all studies to date, glomerular volume has been found to increase as nephron number and birth weight decrease, although filtration surface area has been calculated to remain relatively constant irrespective of nephron number (Hoy et al., 2008; Bertram et al., 2011). This finding suggests that glomerular hypertrophy and hyperfiltration likely occur in compensation for low nephron number, which may maintain renal function initially, but as occurs in the setting of nephron loss, may not be sustainable over time and contribute to renal functional decline (Brenner et al., 2005). Consistent with this, increased glomerular size is a predictor of poorer outcomes among African American kidney donors, Aboriginal Australians, and Pima Indians (Luyckx and Brenner, 2010).
- Glomerular size correlates with body size, but in the absence of other possible causes should raise suspicion low nephron number (Hoy et al., 2008).

Birth weight and developmental programming of blood pressure and renal disease

Birth weight and blood pressure

The relationship between LBW and higher blood pressure has now been consistently demonstrated in diverse populations worldwide (Law and Shiell, 1996). The association tends to be less strong among adolescents, likely confounded by timing of growth spurts, and in some studies is absent in children of African American origin, though preserved in other children of African origin (Longo-Mbenza et al., 1999; Hemachandra et al., 2006). Importantly, in addition to LBW, superimposed rapid catch-up growth exacerbates the risk of higher blood pressures, demonstrating the long-term impact of early life nutrition (Huxley et al., 2000; Ben-Shlomo et al., 2008). Early blood pressure differences between subjects of LBW and NBW become greater with age, resulting in higher prevalence of overt hypertension in LBW subjects (Law et al., 1993). Prematurity has also been associated with higher blood pressures in young adults, however LBW for gestational age was a stronger predictor of later life blood pressure than LBW of prematurity (Keijzer-Veen et al., 2005; Schmidt et al., 2005).

Birth weight and salt sensitivity

The premise underlying the low nephron number hypothesis is that a reduction in filtration surface area would limit sodium excretion. Consistent with this hypothesis, salt sensitivity has been demonstrated in some, but not all, animal models of low nephron number (Gilbert et al., 2008; Luyckx and Mueller, 2012). Age appears to be an important modulator of salt sensitivity in developmentally programmed animals, possibly reflecting the impact of additional nephron loss with age, or loss of adaptive mechanisms over time (Gilbert, 2008; Salazar et al., 2008). In humans thus far, two small studies in children and adults have confirmed an inverse association between salt sensitivity and birth weight, independent of GFR, suggesting a programmed alteration in sodium handling per se (de Boer et al., 2008; Simonetti et al., 2008).

Recent data from animal models suggests other programmed changes in addition to a reduction in filtration surface area likely contribute to the higher blood pressure in LBW subjects, as shown in Box 138.2 and reviewed in detail elsewhere (Nuyt and Alexander, 2009; Luyckx and Brenner, 2010).

Birth weight and renal function

GFR, extrapolated from Amikacin clearance in newborns, was significantly lower in infants born either premature or with IUGR compared to NBW controls (Schreuder et al., 2009). In older children, serum creatinines were found to be higher, and clearances of cystatin C lower in those who had been of LBW (Rodriguez-Soriano et al., 2005; Franco et al., 2008). Similarly, in young adults who had been very premature, GFRs were lower and serum creatinine and albuminuria were higher in those with lower birth weights (Keijzer-Veen et al., 2005). Taken together, these results support the hypothesis that renal function may be subtly impaired in young subjects of LBW. Interestingly, GFRs measured by iothalamate clearance at age 7.6 years were found to be lower in VLBW children born with IUGR or who experienced poor early postnatal growth compared to those who were AGA with normal growth (Bacchetta et al., 2009). This study emphasizes the independent impact of poor postnatal nutrition and extrauterine growth restriction on renal development in premature infants, and demonstrates a potential window where nephrogenesis may be positively impacted postnatally.

A possible confounder in studies of LBW and blood pressure or renal function is genetic background. To examine the relative contributions of environment and genetic background to renal programming, GFR was measured at age 25 years in 265 twin pairs (Gielen et al., 2005). GFR was significantly lower in LBW compared to NBW twins, and within both dizygotic and monozygotic pairs, GFR was significantly lower in the twin of lower birth weight, demonstrating an independent role for environmental and fetoplacental factors in renal programming.

Box 138.2 Programmed factors contributing to increased blood pressure (Luyckx and Brenner, 2010)

- Low nephron number
- Salt sensitivity
- Increased expression/activity of renal sodium transporters
- Increased activity of renal renin–angiotensin system
- Altered renal and peripheral vascular reactivity
- Sympathetic nervous system hyperactivity
- Rapid catch-up growth
- Accelerated vascular senescence.

Birth weight and renal functional reserve

GFR was measured before and after dopamine infusion or an amino acid load, to assess renal functional reserve, in 20-year-old subjects who had been premature, either SGA or AGA, or full term and NBW (Keijzer-Veen et al., 2007). The relative increase in GFR tended to be lower in SGA compared to AGA and control subjects, suggesting a reduced renal reserve in kidneys of LBW and premature individuals, possibly as a result of reduced nephron number.

Birth weight and proteinuria

In an Australian aboriginal population, the odds ratio for macroalbuminuria was 2.8 (1.26–6.31) in subjects of LBW compared to those of NBW (Hoy et al., 1999). Since then, many other studies have supported an inverse relationship between urine protein excretion and birth weight (Painter et al., 2005; White et al., 2009). A U-shaped relationship was described among Pima Indians with type 2 diabetes, with birth weights < 2.5 kg or > 4.5 kg being associated with higher albuminuria (Nelson et al., 1998). In this cohort, exposure to maternal diabetes *in utero* was the strongest predictor of proteinuria in those of HBW. In a rat model, maternal diabetes was associated with reduced nephron numbers in the offspring, suggesting a possible relationship, which remains to be proven in humans, between gestational diabetes exposure and low nephron number (Amri et al., 1999).

Birth weight, chronic kidney disease, and end-stage renal disease

Low and high birth weight and short stature have been associated with increased prevalence of diabetic nephropathy in several cohorts (Rossing et al., 1995; Nelson et al., 1998). Other studies have shown a greater risk of progression of various primary renal diseases, for example, immunoglobulin A nephropathy and nephrotic syndromes in subjects who had been of LBW (Duncan et al., 1994; Zidar et al., 1998; Teeninga et al., 2008). A recent meta-analysis of 18 studies found an overall odds ratio of 1.73 (1.44–2.08) for risk of chronic kidney disease (CKD) with LBW (White et al., 2009). This study and others have also reported an increased odds ratio of ESRD in LBW subjects ranging from 1.4 to 1.7 (1.1–1.9) (Lackland et al., 2000; Vikse et al., 2008; White et al., 2009). Interestingly, some large cohorts have shown a U-shaped relationship between birth weight and risk of CKD, underscoring the importance of extremes of birth weight in renal risk (Nelson et al., 1998; Lackland et al., 2000; Li et al., 2008). Some studies have reported diverse associations of birth weight and renal disease in males and females; however, these findings require more investigation (Li et al., 2008; Vikse et al., 2008).

Nephron number and disease

Nephron number and blood pressure

Nephron number was found to be significantly lower in a cohort of adult Caucasians with essential hypertension compared to a

matched cohort without hypertension (Keller et al., 2003). Similarly, among Caucasian and Australian Aboriginal subjects, higher blood pressures were associated with lower nephron numbers, and conversely, higher nephron number appeared to protect against hypertension (Hoy et al., 2008). The relationship between blood pressure and nephron number is not as clear among African Americans, although glomerular size increases with increasing blood pressure (Hoy et al., 2008; Bertram et al., 2011).

Nephron number and renal pathology

In 140 human samples, nephron number was found to be inversely proportional to the percentage of glomeruli with obsolescent glomerulosclerosis and intimal thickening of interlobular arteries (Bertram et al., 2011). Secondary focal and segmental glomerulosclerosis, associated with large glomeruli, was described in a small cohort of subjects who had been born prematurely and presented with clinical renal disease in later life (Hodgin et al., 2009). These authors hypothesized that low nephron number was a likely contributor to the renal dysfunction in these subjects.

Kidney size and transplant outcomes

Several studies have examined the impact of donor kidney size relative to recipient size, as a predictor of long-term transplant outcomes. Although not always consistent, in general, smaller kidneys transplanted into larger recipients tend to have poorer outcomes, suggesting a deficiency of nephron 'dose', relative to recipient metabolic requirements, is a risk factor for functional decline over time (Luyckx and Brenner, 2010; Luyckx and Mueller, 2012).

Clinical implications and conclusions

The evidence that low nephron numbers are associated with adverse renal (among other) outcomes is strong. The mechanism behind its association with renal outcomes is the subject of some conjecture (see Chapter 136). The strand of evidence from low nephron numbers at birth helps to separate the question of nephron numbers from that of glomerular injury. Does it lead to podocyte stretch, injury and death (see Chapter 139)? Or is it a more direct consequence of barotrauma, as a result of hyperfiltration? What is the nature of the link to proteinuria, which may itself be nephrotoxic (see Chapter 137)?

At present we do not have methods to augment nephron number in humans, although several approaches are being explored experimentally (Luyckx and Mueller, 2012). The best proactive strategies to optimize nephron number in humans include adequate prenatal care and maternal nutrition, and careful management of premature infants, avoiding use of nephrotoxins and ensuring good postnatal nutrition.

With our current knowledge of clinical correlates of low nephron number, of which LBW is the most robust, we can identify individuals at risk for low nephron number. Many individuals are born with LBW around the globe. It is now clear that such individuals are at increased risk for later life hypertension, diabetes, cardiovascular and renal disease, which may be augmented by rapid weight gain or additional renal injury.

Avoidance of rapid catch-up growth and obesity in LBW infants, and education about nutrition and lifestyle choices in individuals at risk for low nephron number are clinically feasible strategies that will attenuate the progression of hypertension and programmed renal dysfunction over time, and may eventually impact the global epidemic of these non-communicable diseases.

References

Amri, K., Freund, N., Vilar, J., *et al.* (1999). Adverse effects of hyperglycemia on kidney development in rats: in vivo and in vitro studies. *Diabetes*, 48(11), 2240–5.

Bacchetta, J., Harambat, J., Dubourg, L., *et al.* (2009). Both extrauterine and intrauterine growth restriction impair renal function in children born very preterm. *Kidney Int*, 76(4), 445–52.

Barker, D. J. and Bagby, S. P. (2005). Developmental antecedents of cardiovascular disease: a historical perspective. *J Am Soc Nephrol*, 16(9), 2537–44.

Barker, D. J., Osmond, C., Forsen, T. J., *et al.* (2005). Trajectories of growth among children who have coronary events as adults. *N Engl J Med*, 353(17), 1802–9.

Ben-Shlomo, Y., McCarthy, A., Hughes, R., *et al.* (2008). Immediate postnatal growth is associated with blood pressure in young adulthood: the Barry Caerphilly Growth Study. *Hypertension*, 52(4), 638–44.

Bertram, J. F., Douglas-Denton, R. N., Diouf, B., *et al.* (2011). Human nephron number: implications for health and disease. *Pediatr Nephrol*, 26(9), 1529–33.

Brenner, B. M., Garcia, D. L., and Anderson, S. (1988). Glomeruli and blood pressure. Less of one, more the other? *Am J Hypertens*, 1(4 Pt 1), 335–47.

Brenner, B. M., Lawler, E. V., and Mackenzie, H. S. (1996). The hyperfiltration theory: a paradigm shift in nephrology. *Kidney Int*, 49(6), 1774–7.

De Boer, M. P., Ijzerman, R. G., de Jongh, R. T., *et al.* (2008). Birth weight relates to salt sensitivity of blood pressure in healthy adults. *Hypertension*, 51(4), 928–32.

Duncan, R. C., Bass, P. S., Garrett, P. J., *et al.* (1994). Weight at birth and other factors influencing progression of idiopathic membranous nephropathy. *Nephrol Dial Transplant*, 9(7), 875.

El Kares, R., Manolescu, D. C., Lakhal-Chaieb, L., *et al.* (2010). A human ALDH1A2 gene variant is associated with increased newborn kidney size and serum retinoic acid. *Kidney Int*, 78(1), 96–102.

Franco, M. C., Nishida, S. K., and Sesso, R. (2008). GFR estimated from cystatin C versus creatinine in children born small for gestational age. *Am J Kidney Dis*, 51(6), 925–32.

Gielen, M., Pinto-Sietsma, S. J., Zeegers, M. P., *et al.* (2005). Birth weight and creatinine clearance in young adult twins: influence of genetic, prenatal, and maternal factors. *J Am Soc Nephrol*, 16(8), 2471–6.

Gilbert, J. S. (2008). Sex, salt, and senescence: sorting out mechanisms of the developmental origins of hypertension. *Hypertension*, 51(4), 997–9.

Gilbert, J. S. and Nijland, M. J. (2008). Sex differences in the developmental origins of hypertension and cardiorenal disease. *Am J Physiol Regul Integr Comp Physiol*, 295(6), R1941–52.

Hales, C. N. and Ozanne, S. E. (2003). The dangerous road of catch-up growth. *J Physiol*, 547(Pt 1), 5–10.

Hemachandra, A. H., Klebanoff, M. A., and Furth, S. L. (2006). Racial disparities in the association between birth weight in the term infant and blood pressure at age 7 years: results from the collaborative perinatal project. *J Am Soc Nephrol*, 17(9), 2576–81.

Hinchliffe, S. A., Howard, C. V., Lynch, M. R., *et al.* (1993). Renal developmental arrest in sudden infant death syndrome. *Pediatr Pathol*, 13(3), 333–43.

Hodgin, J. B., Rasoulpour, M., Markowitz, G. S., *et al.* (2009). Very low birth weight is a risk factor for secondary focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol*, 4(1), 71–6.

Hoy, W. E., Bertram, J. F., Denton, R. D., *et al.* (2008). Nephron number, glomerular volume, renal disease and hypertension. *Curr Opin Nephrol Hypertens*, 17(3), 258–65.

Hoy, W. E., Rees, M., Kile, E., *et al.* (1999). A new dimension to the Barker hypothesis: low birthweight and susceptibility to renal disease. *Kidney Int*, 56(3), 1072–7.

Huxley, R. R., Shiell, A. W., and Law, C. M. (2000). The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hypertens*, 18(7), 815–31.

Ibrahim, H. N., Foley, R., Tan, L., *et al.* (2009). Long-term consequences of kidney donation. *N Engl J Med*, 360(5), 459–69.

Keijzer-Veen, M. G., Kleinveld, H. A., Lequin, M. H., *et al.* (2007). Renal function and size at young adult age after intrauterine growth restriction and very premature birth. *Am J Kidney Dis*, 50(4), 542–51.

Keijzer-Veen, M. G., Schrevel, M., Finken, M. J., *et al.* (2005). Microalbuminuria and lower glomerular filtration rate at young adult age in subjects born very premature and after intrauterine growth retardation. *J Am Soc Nephrol*, 16(9), 2762–8.

Keller, G., Zimmer, G., Mall, G., *et al.* (2003). Nephron number in patients with primary hypertension. *N Engl J Med*, 348(2), 101–8.

Kemper, M. J. and Muller-Wiefel, D. E. (2001). Renal function in congenital anomalies of the kidney and urinary tract. *Curr Opin Urol*, 11(6), 571–5.

Lackland, D. T., Bendall, H. E., Osmond, C., *et al.* (2000). Low birth weights contribute to high rates of early-onset chronic renal failure in the Southeastern United States. *Arch Intern Med*, 160(10), 1472–6.

Law, C. M., de Swiet, M., Osmond, C., *et al.* (1993). Initiation of hypertension in utero and its amplification throughout life. *BMJ*, 306(6869), 24–7.

Law, C. M. and Shiell, A. W. (1996). Is blood pressure inversely related to birth weight? The strength of evidence from a systematic review of the literature. *J Hypertens*, 14(8), 935–41.

Li, S., Chen, S. C., Shlipak, M., *et al.* (2008). Low birth weight is associated with chronic kidney disease only in men. *Kidney Int*, 73(5), 637–42.

Longo-Mbenza, B., Ngiyulu, R., Bayekula, M., *et al.* (1999). Low birth weight and risk of hypertension in African school children. *J Cardiovasc Risk*, 6(5), 311–4.

Luyckx, V. A. and Brenner, B. M. (2010). The clinical importance of nephron mass. *J Am Soc Nephrol*, 21(6), 898–910.

Luyckx, V. A., Compston, C. A., Simmen, T., *et al.* (2009). Accelerated senescence in kidneys of low-birth-weight rats after catch-up growth. *Am J Physiol Renal Physiol*, 297(6), F1697–705.

Luyckx, V. A. and Mueller, T. F. (2012). Clinical importance of nephron mass. In R. W. Schrier (ed.) *Schrier's Diseases of the Kidney and Urinary Tract* (9th ed.), pp. 46–73. Philadelphia, PA: Lippincott Williams & Wilkins.

Manalich, R., Reyes, L., Herrera, M., *et al.* (2000). Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. *Kidney Int*, 58(2), 770–3.

McMillen, I. C. and Robinson, J. S. (2005). Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol Rev*, 85(2), 571–633.

Moritz, K. M., Wintour, E. M., Black, M. J., *et al.* (2008). Factors influencing mammalian kidney development: implications for health in adult life. *Adv Anat Embryol Cell Biol*, 196, 1–78.

Nelson, R. G., Morgenstern, H., and Bennett, P. H. (1998). Birth weight and renal disease in Pima Indians with type 2 diabetes mellitus. *Am J Epidemiol*, 148(7), 650–6.

Nuyt, A. M. and Alexander, B. T. (2009). Developmental programming and hypertension. *Curr Opin Nephrol Hypertens*, 18(2), 144–52.

Nyengaard, J. R. (1993). Number and dimensions of rat glomerular capillaries in normal development and after nephrectomy. *Kidney Int*, 43(5), 1049–57.

Nyengaard, J. R. and Bendtsen, T. F. (1992). Glomerular number and size in relation to age, kidney weight, and body surface in normal man. *Anat Rec*, 232(2), 194–201.

Painter, R. C., Roseboom, T. J., van Montfrans, G. A., *et al.* (2005). Microalbuminuria in adults after prenatal exposure to the Dutch famine. *J Am Soc Nephrol*, 16(1), 189–94.

Quinlan, J., Lemire, M., Hudson, T., *et al.* (2007). A common variant of the PAX2 gene is associated with reduced newborn kidney size. *J Am Soc Nephrol*, 18(6), 1915–21.

Rakow, A., Johansson, S., Legnevall, L., *et al.* (2008). Renal volume and function in school-age children born preterm or small for gestational age. *Pediatr Nephrol*, 23(8), 1309–15.

Rodriguez, M. M., Gomez, A. H., Abitbol, C. L., *et al.* (2004). Histomorphometric analysis of postnatal glomerulogenesis in extremely preterm infants. *Pediatr Dev Pathol*, 7(1), 17–25.

Rodriguez-Soriano, J., Aguirre, M., Oliveros, R., *et al.* (2005). Long-term renal follow-up of extremely low birth weight infants. *Pediatr Nephrol*, 20(5), 579–84.

Rossing, P., Tarnow, L., Nielsen, F. S., *et al.* (1995). Short stature and diabetic nephropathy. *BMJ*, 310(6975), 296–7.

Salazar, F., Reverte, V., Saez, F., *et al.* (2008). Age- and sodium-sensitive hypertension and sex-dependent renal changes in rats with a reduced nephron number. *Hypertension*, 51(4), 1184–9.

Schmidt, I. M., Chellakooty, M., Boisen, K. A., *et al.* (2005). Impaired kidney growth in low-birth-weight children: distinct effects of maturity and weight for gestational age. *Kidney Int*, 68(2), 731–40.

Schmidt, I. M., Damgaard, I. N., Boisen, K. A., *et al.* (2004). Increased kidney growth in formula-fed versus breast-fed healthy infants. *Pediatr Nephrol*, 19(10), 1137–44.

Schreuder, M. F., Langemeijer, M. E., Bokenkamp, A., *et al.* (2008). Hypertension and microalbuminuria in children with congenital solitary kidneys. *J Paediatr Child Health*, 44(6), 363–8.

Schreuder, M. F., Wilhelm, A. J., Bokenkamp, A., *et al.* (2009). Impact of gestational age and birth weight on amikacin clearance on day 1 of life. *Clin J Am Soc Nephrol*, 4(11), 1774–8.

Simonetti, G. D., Raio, L., Surbek, D., *et al.* (2008). Salt sensitivity of children with low birth weight. *Hypertension*, 52(4), 625–30.

Spencer, J., Wang, Z., and Hoy, W. (2001). Low birth weight and reduced renal volume in Aboriginal children. *Am J Kidney Dis*, 37(5), 915–20.

Teeninga, N., Schreuder, M. F., Bokenkamp, A., *et al.* (2008). Influence of low birth weight on minimal change nephrotic syndrome in children, including a meta-analysis. *Nephrol Dial Transplant*, 23(5), 1615–20.

Vikse, B. E., Irgens, L. M., Leivestad, T., *et al.* (2008). Low birth weight increases risk for end-stage renal disease. *J Am Soc Nephrol*, 19(1), 151–7.

White, S. L., Perkovic, V., Cass, A., *et al.* (2009). Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. *Am J Kidney Dis*, 54(2), 248–61.

Zhang, Z., Quinlan, J., Grote, D., *et al.* (2009). Common variants of the glial cell-derived neurotrophic factor gene do not influence kidney size of the healthy newborn. *Pediatr Nephrol*, 24(6), 1151–7.

Zhang, Z., Quinlan, J., Hoy, W., *et al.* (2008). A common RET variant is associated with reduced newborn kidney size and function. *J Am Soc Nephrol*, 19(10), 2027–34.

Zidar, N., Cavic, M. A., Kenda, R. B., *et al.* (1998). Effect of intrauterine growth retardation on the clinical course and prognosis of IgA glomerulonephritis in children. *Nephron*, 79(1), 28–32.

CHAPTER 139

Podocyte loss as a common pathway to chronic kidney disease

Wilhelm Kriz

Introduction

Podocyte loss is one of the potential unifying mechanisms to explain the progressive nature of many renal diseases, particularly glomerular diseases, independently of the initiating injury (see Chapter 136).

The majority of kidney diseases that progress to chronic renal failure start in the glomerulus. This raises the question of why glomerular diseases are particularly prone to end up in chronic renal failure, independent of whether the initiating disease is still flourishing or not. The major challenge to glomeruli is the high intraglomerular pressure. Glomerular capillaries are constantly exposed to hydrostatic pressure gradients of 30–35 mmHg; elsewhere in the body only smooth muscle-armed arterioles tolerate such high pressure gradients. In addition, glomeruli are sensitive to immune attacks resulting in inflammatory diseases and, though it is not fully understood why, to the metabolic challenges associated with diabetes mellitus. On the other hand, and in contrast to tubules, glomerular cells tolerate ischaemic episodes well.

Compared to renal tubules, glomeruli have a very limited capacity for regeneration. Glomerular diseases are prone to enter self-sustained progression. This notable deficiency depends on one cell type of the glomerulus, namely, the *podocyte* (Pavenstadt et al., 2003). Podocytes are a kind of post-mitotic cells. It appears that lost podocytes cannot be replaced by proliferation of neighbouring undamaged cells. We are born with a certain number of podocytes, roughly 800 per glomerulus for 2 million nephrons, an estimated 1,600,000 in total. We constantly lose podocytes; however, without serious kidney disease we maintain a sufficient number until reaching an advanced age. Glomerular diseases accelerate the usual loss of podocytes, and to make matters worse, it is not the total number of podocytes that matters, it is the number in each individual glomerulus. If in a certain glomerulus the number of podocytes falls below a certain level (roughly < 60%; (Lemley et al., 2002)) the glomerulus will not survive and the glomerulus together with the entire nephron will be lost.

There is a stereotyped sequence of events that leads from podocyte insufficiency (a term first coined by Fries and colleagues (Fries et al., 1988)) and podocyte loss to the loss of the entire nephron (Kriz and Le Hir, 2005). This sequence is largely independent of the kind of disease present. Many glomerular diseases (e.g. immune diseases and diabetic glomerulopathy) start within the endocapillary compartment with the involvement of endothelial and mesangial cells. As long as the disease process remains confined within the endocapillary compartment, the damage will undergo recovery, or will be repaired by scarring. Progression of glomerular diseases always begins with this involvement, with damage of the podocyte. Clinically, damage to the podocyte is indicated by proteinuria, more precisely by albuminuria, which represents an alarming symptom of a glomerular disease.

The fine structure of the glomerulus is detailed in Chapter 43. The sequence of events from a glomerular disease to renal fibrosis may be subdivided into several steps:

Step 1: loss of podocytes from the tuft

Progression of glomerular diseases always starts with the failure and loss of podocytes. As already mentioned, we steadily lose podocytes during our lifetimes, the rate being tremendously increased during episodes of glomerular disease. It is widely believed that the way of losing podocytes is by apoptosis (Böttinger, 2007). There is little structural evidence for such a mechanism, however; instead there is abundant evidence that podocytes are lost as viable cells by detachment (Fig. 139.1).

Podocytes occupy a unique position on the outside of glomerular capillaries: they are fixed to the glomerular basement membrane (GBM) only by their processes, their cell bodies float within the filtrate in Bowman's space. This position is permanently challenged by the hydrostatic pressure gradient across the filtration barrier (Kriz and Endlich, 2005) and the shear stress (Friedrich et al., 2006) imposed on them by the flow of the filtrate in Bowman's space. These challenges will greatly increase under pathological conditions associated with hypertension and hyperfiltration. Under inflammatory conditions, the podocyte–GBM connections are challenged by complement factors and other inflammatory mediators. Thus, under disease conditions, podocytes are permanently in danger of detaching from the GBM and being excreted with the urine.

Hara, Nakamura, and colleagues (Hara et al., 1995, 1998; Nakamura et al., 2000a, 2000b, 2000c) were the first to find podocytes in urinary sediments of patients with a variety of kidney diseases, in quantities correlating with the severity of the disease. Vogelmann and colleagues (Vogelmann et al., 2003) showed that the majority of urinary podocytes are still viable, thus podocytes detach not due to undergoing necrosis or apoptosis. These authors

also found urinary podocytes in healthy individuals, even if in small amounts. Since then, several groups (Petermann et al., 2004; Yu et al., 2005; Aita et al., 2009; Weil et al., 2011) have presented strong evidence that shedding of podocytes is a regular mechanism in experimental and human glomerular diseases and represents the usual way of how we lose podocytes.

Podocytes have developed strategies against the danger of detaching from the GBM (Kriz et al., 2013). The mechanism of foot process effacement (FPE) may be interpreted as a process to reinforce podocyte adherence to the GBM in injurious situation, by retracting the foot processes to broader contact areas (Fig. 139.1), that is accompanied by a switch to obviously more resistant integrin connections (from α3/β1 to αv/β3) (Schordan et al., 2010; Greka and Mundel, 2012). These changes are associated with a partial loss of the barrier function for macromolecules, thus with protein leakage. FPE is generally thought to cause protein leakage. It entails disassembly of the slit diaphragm and is associated with protein leakage, but probably greatly decreases protein leakage compared to a situation with progressing detachments. In acute inflammatory conditions, FPE may prevent the 'supergau' (meltdown) of widespread detachments of podocytes.

FPE is not always successful, it may be futile. Detachment despite FPE indicates that the podocyte finally lost the struggle against detachment. If a majority of podocytes win, there is a chance for recovery—but only a chance. Even if a great majority in a certain glomerulus win, this does not guarantee the survival of the nephron. Even a single podocyte in its struggle against detachment may produce a fatal situation that initiates a development leading to the final loss of the nephron. A single podocyte may adhere to Bowman's capsule and thereby become the nidus of a tuft adhesion to Bowman's capsule.

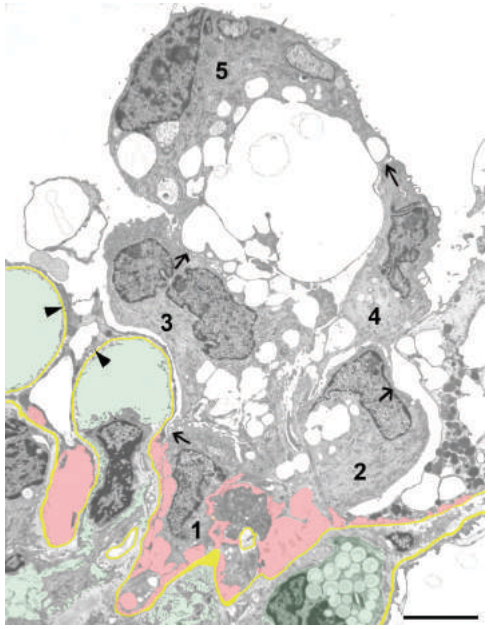

Fig. 139.1 Podocytes in the process of detachment from the GBM. Five podocytes (1–5) are seen that are in the process of disconnection from the tuft. Podocytes 1 and 2 have still partial contact to the GBM (highlighted in yellow), whereas podocytes 3 and 4 are connected by intercellular contacts (arrows) to podocytes 1 and 2 and podocyte 5 to podocytes 3 and 4. All podocytes look viable with cell nuclei that have a normal chromatin pattern. The spaces between naked GBM and detaching podocytes are shown in pink, capillary lumina in green. Note that areas with FPE are closely apposed to the GBM (arrowheads). (Transmission electron micrograph (TEM); rat after 8 weeks of growth stimulation by FGF2. Bar: 5 µm.)
Reproduced from Kriz et al. (1995) with permission.

Step 2: formation of a tuft adhesion to Bowman's capsule

At sites of severe podocyte damage and podocyte loss, cell bridges between the tuft and Bowman's capsule are established either by (1) parietal cells adhering to bare sites of GBM or by (2) adhering of podocytes to the parietal basement membrane (PBM; Fig. 139.2) (Kriz and Le Hir, 2005). The first mechanism is typical for degenerative diseases, for example, in experimental acute glomerular hypertension like in the deoxycorticosterone acetate–salt model (Kretzler et al., 1994).

The second mechanism, that is, podocytes adhering to Bowman's capsule, occurs much more frequently and has been found in a great variety of experimental glomerular diseases. This behaviour of podocytes is ubiquitously seen in inflammatory glomerular diseases (Le Hir et al., 2001) but is also widely found in degenerative diseases (author's observations (Nagata and Kriz, 1992; Kriz et al., 1995)). Podocytes in danger of detachment from the GBM seem to seek adhesion at other sites, by fixing to adjacent podocytes and parietal epithelial cells by formation of intercellular junctions and may finally penetrate through the parietal epithelium and adhere to the PBM (Le Hir et al., 2001). Here they seem to spread by pushing apart the parietal epithelial cells. Finally, a cell bridge between the tuft and the PBM becomes established.

Such individual cell bridges are the starting point for the formation of a firm tuft adhesion to Bowman's capsule, finally consisting of several bridging cells—podocytes and parietal cells—and interposed matrix, which generally is of parietal origin (Smeets et al., 2009).

No evidence has so far been presented that an adhesion can resolve. Therefore, a tuft adhesion may be regarded as the first committed lesion leading to progression (van Damme et al., 1990; Kriz et al., 1998).

Step 3: growing of an adhesion into a crescent

An adhesion generally initiates proliferative processes within Bowman's capsule that may spread from the site of adherence in any direction forming what is generally called a crescent (Fig. 139.3). An adhesion may progress to more severe damage by several mechanisms including further podocyte loss at the flanks of the adhesion followed either by expansion of the adherent area or by invasion of parietal cells along the adhesion onto the tuft leading to the spread of sclerosis at the tuft (Smeets et al., 2009). Most importantly, the damage spreads within Bowman's capsule by two mechanisms, by misdirected filtration or by cell proliferation, frequently a mixture of both (Kriz and Le Hir, 2005). Growing by misdirected filtration will occur in instances where the adhesion contains perfused glomerular capillaries. Such capillaries are devoid of any podocyte cover, allowing leakage of plasma proteins into the crescent resulting in a growing proteinaceous crescent. Proliferation of parietal cells and, to some extent, also podocytes (which in a dedifferentiated stage seem to have regained the capacity to multiplicate) will lead to a cellular crescent (Smeets et al., 2009). Most crescents are of a mixed type with a predominance of cell proliferation.

These processes within Bowman's capsule (i.e. inside the PBM) initiate a periglomerular response. Proliferation of local fibroblasts

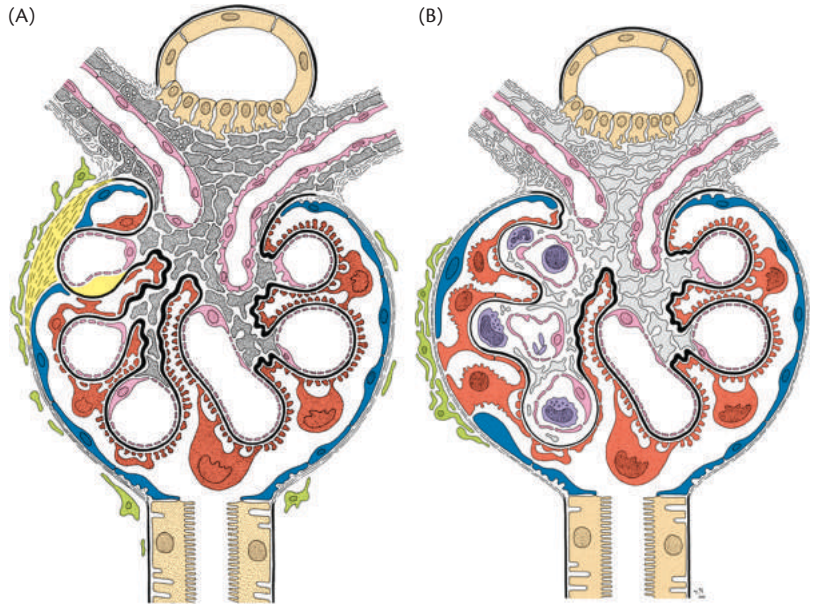

Fig. 139.2 Formation of connections between the tuft and Bowman's capsule. Schematics of injured glomeruli; the GBM is shown in black, mesangial cells in grey, endothelial cells in pink, podocytes in brown, parietal cells in blue, macrophages in violet, tubular cells in light brown, and interstitial cells in green. At sites of severe podocyte damage, cell bridges between the tuft and Bowman's capsule are established either by parietal cells attaching to the GBM (A) or by podocytes attaching to the parietal basement membrane (B). The first mechanism has been observed in degenerative diseases with early podocyte loss, for example, glomerular hypertension and is frequently associated with the accumulation of a protein rich filtrate within Bowman's capsule ('misdirected filtration', shown in yellow).The more frequent second mechanism is typical for inflammatory diseases but may be found in degenerative diseases, as well. Podocytes that appear to be in danger of detachment from the GBM may attach at other sites including at the parietal basement membrane (see text for further explanation).

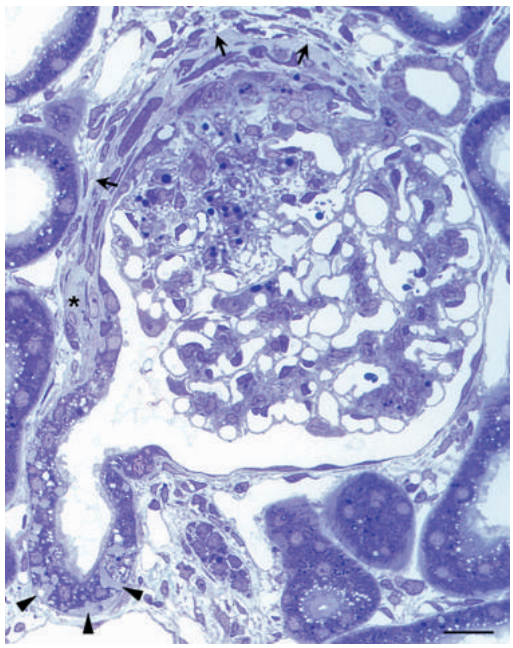

Fig. 139.3 Adhesion crescent. A tuft adhesion to Bowman's capsule is seen that has advanced to a crescent spreading within Bowman's capsule. The crescent is of a mixed cell-matrix type consisting of proliferating cells and a proteinaceous matrix (indicating misdirected filtration). Outside the parietal basement membrane (PBM; arrows) a cap of proliferating interstitial cells is seen. At the glomerular urinary pole the crescent encroaches on to the tubule along its outside, that is, in between the tubular cells and the tubular basement membrane (TBM; asterisks). At several sites, the penetration of the protein-rich matrix into the lateral spaces between proximal tubular cells is seen (arrowheads). (Thy-1 mediated glomerulonephritis, rat. Bar 10 µm.)
Unpublished light micrograph from Kriz et al. (2003).

turning into matrix producing myofibroblasts and invasion of macrophages establish the interstitial cap of a crescent. In advanced stages, the separating PBM will progressively be dissolved, leading to a mixing of the epithelial and interstitial portion of a growing crescent.

An advanced stage of this process is generally called focal segmental glomerulosclerosis (FSGS), formerly called focal segmental glomerulosclerosis and hyalinosis, wherein hyalinosis (resulting from misdirected filtration) indicates the progressive nature of the lesion. Quantitative assessments (Gotzmann et al., 2004) have clearly proven that a loss of podocytes underlies this pathogenetic process. As the term 'segmental' indicates, in the beginning this process is restricted to a glomerular lobule. In cases where the underlying disease resolves, there seems to be a certain chance for this process to develop into a segmental scar (synechia) with some stability, permitting the rest of the glomerulus to function for some time (Kriz and Le Hir, 2005). However, progression of the damage onto other segments of the glomerulus and/or onto the tubule remains an everlasting danger.

Step 4: encroachment of the glomerular lesion on the tubule

There is agreement that in cases of global glomerulosclerosis, the tubule—deprived of any filtrate—will undergo degeneration as well. In cases of segmental glomerular damage (with maintenance of some filtrate delivery to the tubule), there are two major hypotheses regarding how a glomerular lesion may be transferred to the tubulo-interstitium. First, the loss of barrier function in such glomeruli leads to massive leakage of albumin and other high-molecular-weight compounds that are toxic to the tubule

(Remuzzi and Bertani, 1998). In response, tubular cells produce a variety of factors (cytokines, e.g. transforming growth factor beta (TGF-β)), which initiate a peritubular inflammation that, in turn, is harmful to the tubule and may initiate its degeneration. So far, only correlative evidence has been offered for such a mechanism; direct structural observations showing the association of segmental glomerular damage with damage of the corresponding tubule have not been presented.

The second discussed mechanism relies on the observation that a growing crescent, as soon as it reaches the glomerulo-tubular junction, may directly encroach upon the tubule (Figs 139.4 and 139.5). There, the process will spread in between the tubular epithelium and the tubular basement membrane (TBM). The mechanisms are the same as for the spreading of a crescent within Bowman's capsule: misdirected filtration and cell proliferation, frequently a mixture of both. This will lead to a narrowing, eventually to a complete obstruction. As a consequence, the tubule will be partially or totally deprived from filtrate delivery. This will initiate the degeneration of the tubule; atrophy may be an intermediate stage (Kriz and Le Hir, 2005).

The evidence for the encroachment thesis of progression comes from consistent structural observations in a great variety of animal models and observations in human biopsy and autopsy material. Convincing quantitative evidence has been presented by LeHir and Besse-Eschmann (2003). In crescentic glomerulonephritis in mice, these authors examined 265 glomeruli in section series: 168 glomeruli were intact, did not show crescents, and all corresponding tubules exhibited a normal structure. Ninety-seven glomeruli had crescents, 57 of these crescents did not extend onto the glomerulo-tubular junction, and all corresponding tubules showed a normal structure. The remaining 40 glomeruli had crescents that encroached upon the glomerulo-tubular junction and in all these cases the corresponding tubules showed features of degeneration. These data strongly speak (1) in favour of the encroachment hypothesis (all crescent with involvement exhibited tubular damage) and (2) against the hypothesis that protein leakage causes the tubular damage (57 crescents without involvement of the urinary orifice had no tubular damage). Fig. 139.6 shows a heavily injured glomerulus with an open urinary orifice and a fully intact proximal tubule.

Step 5: degeneration of the tubule

The degeneration of the tubule after obstruction of the urinary orifice starts at the most proximal segment and proceeds distally (Fig. 139.7). Tubule cells degenerate inside the envelope of the TBM. As presented in detail in recent work (Koesters et al., 2010; Li et al., 2010), autophagy represents the major mechanism, fratricide may participate. This process may finally lead to almost cell-free collapsed structures enclosed by wrinkled but continuous TBM. Cells crossing the TBM border of degenerating tubules were not encountered, neither any macrophages entering, nor any tubular cells leaving. Thus, macrophages are not involved in the decomposition of tubular cells but may become engaged later in the removal of the TBM. Even in the case of a complete degeneration of a tubule and removal of its remnants, the glomerular remnants may survive for some time as an atubular inoperable structure (Marcussen, 1995; Kriz et al., 2003).

It is worth noting that direct toxic or hypoxic injuries to the tubule may lead to other forms of epithelial degeneration, to necrosis and early tubulorrhexis.

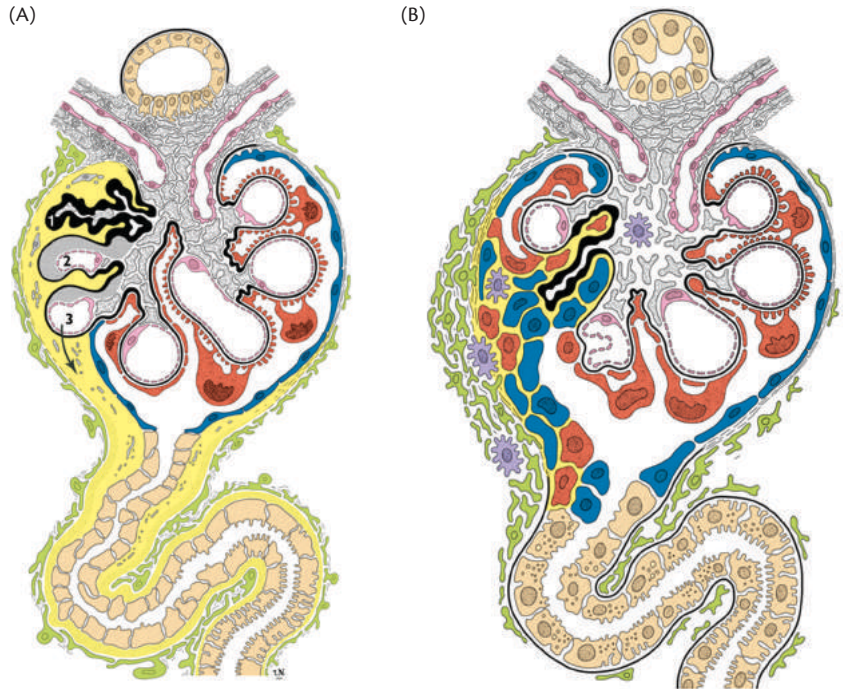

Fig. 139.4 Encroachment of a glomerular injury on the tubule. Schematics of injured glomeruli; the GBM is shown in black, mesangial cells in grey, endothelial cells in pink, podocytes in brown, parietal cells in blue, macrophages in violet, tubular cells in light brown, and interstitial cells in green. A progressing glomerular injury spreads within Bowman's capsule. If this process reaches the glomerulo-tubular junction, it may encroach upon the tubule either by spreading of a misdirected filtrate (A; arched arrow) and/or by cell proliferation (B). The first mechanism may be dominant in cases with perfused capillaries contained in the crescent (capillaries 2 and 3, 1 is shown being collapsed). In the majority of cases the second mechanism dominates: a proliferating crescent spreads within Bowman's capsule and may reach the glomerulo-tubular junction. In consequence of a narrowing (shown here), eventually of a complete obstruction of the urinary orifice the tubule will be deprived from any filtrate delivery.

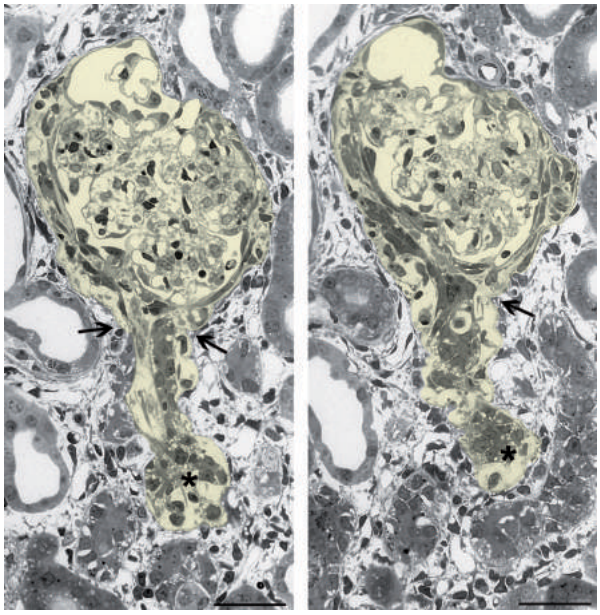

Fig. 139.5 Encroachment of a crescent on the tubule. Two consecutive pictures of a heavily injured glomerulus with encroachment of a crescent on the tubule (highlighted in yellow). The tubule is undergoing decomposition. The cells have separated from the tubular basement membrane (TBM) and joined to a single strand, the tubular lumen is lost. The cells contain large amounts of autophagic vacuoles (arrows). Cell nuclei (asterisks) look normal with no signs of apoptosis. Outside the TBM a vivid interstitial proliferation is seen. (Thy-1 mediated glomerulonephritis, rat, after 2 weeks. Bar: 20 µm.)
Reproduced from Kriz et al. (2003) with permission.

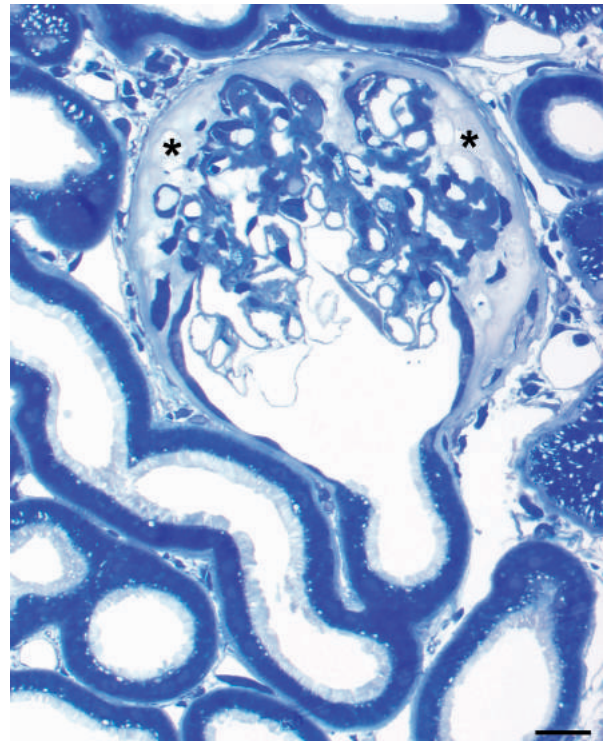

Fig. 139.6 Protein leakage versus damage encroachment. Severely damaged glomerulus associated with a giant proteinaceous crescent. It may readily be suggested that the filtrate from this glomerulus contains abundant albumin and other proteins. The tubular orifice is patent; the epithelium of the proximal tubule (asterisks) shows no abnormalities. (Angiotensin II receptor 1 (AT1) overexpression in rat podocytes after 16 month. Bar: 20 µm.)
Unpublished light micrograph from Hoffmann et al. (2004) with permission.

Step 6: development of fibrosis

The degenerating tubule cells initiate (by so far insufficiently understood signalling) a local peritubular inflammation, which will finally lead to the removal of all tubular remnants and the formation of a local area of fibrosis. The outstanding feature of the local inflammatory process surrounding a degenerating tubule consists of the massive accumulation of myofibroblasts (Fig. 139.7). According to our results, the only relevant source for these myofibroblasts are the residential interstitial cells, which are generally called fibroblasts, some authors call them pericytes (Humphreys et al., 2010). The proposal that myofibroblasts may also develop from injured tubular cells by a process called epithelial to mesenchymal transition (EMT) was based on questionable data and has not found supporting evidence (Humphreys et al., 2010; Kriz et al., 2011). Myofibroblasts organize the interstitial fibrosis by synthesizing type I collagen and finally by contraction of the affected area to a scar. The sum of such scars, each derived from the degeneration of a nephron, represents what is finally called renal fibrosis.

Fibrosis: consequence or cause?

(See also Chapter 140)

According to this sequence of progression, the progressive nature of kidney fibrosis is ultimately dependent on the progressing glomerular disease. There are two vicious cycles that account for the steadily ongoing progression of the disease in the glomerulus.

The first cycle concerns the podocytes in each individual glomerulus; the second cycle concerns the entirety of glomeruli in function.

If during a disease in a given glomerulus (first cycle) podocytes are lost, the remaining podocytes have to replace them and take over the tasks of the lost ones. They do this by undergoing hypertrophy covering an increased outer capillary surface including counteracting the pressure gradient in an increased segment of a capillary. This process has limits. Excessive degrees of hypertrophy clearly increase the vulnerability of podocytes to any further challenge, thereby closing the cycle. Quantitative assessments (Wharram et al., 2005) have clearly proven that a loss of podocytes below a certain level (roughly 60%) will lead to the loss of the nephron.

The second cycle starts with the loss of nephrons. A certain rate of nephron loss is probably tolerated without adverse consequences. However, sooner or later, a critical point will be reached where the remaining glomeruli are no longer able to cope with their task of producing an adequate volume of ultrafiltrate. They allow higher filtration pressures and, together with the podocytes, they in total undergo hypertrophy. Hypertrophy makes them more susceptible to damage. In particular, the exposure to higher pressures followed by hyperfiltration signifies a dramatically increased challenge. This vicious cycle is known as the glomerular overload hypothesis, first formulated by Barry Brenner (Hostetter et al., 1981; Brenner et al., 1996).

In addition, it is widely believed that the fibrosing process in the tubulo-interstitium may also acquire a progressive potential accounting for a self-sustained progression of the disease to end-stage renal failure—independent from any progression of

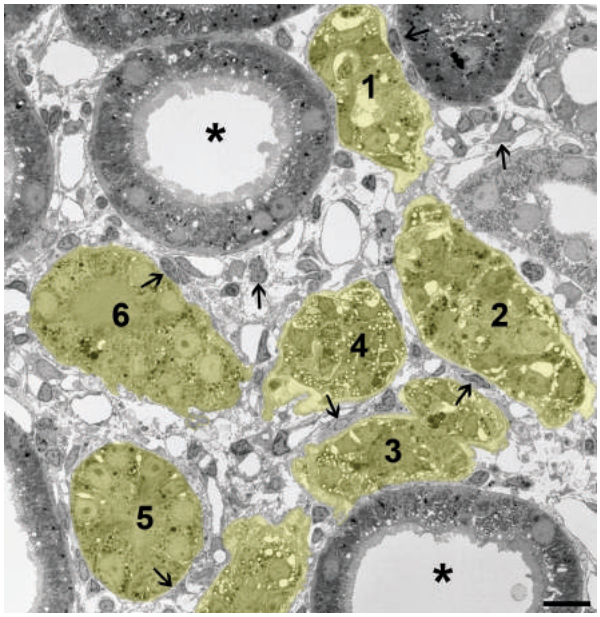

Fig. 139.7 Degeneration of tubules subsequent to obstruction of the glomerular urinary orifice. TEM of a group of degenerating proximal tubules as a consequence of obstruction of the glomerular urinary orifice. The severity of epithelial changes increases downstream; upstream segments (1, 2, 3, 4) exhibit epithelial decomposition with autophagy of tubular cells (arrows; note the abundant autophagic vacuoles), in downstream segments (5, 6) the epithelial integrity is still preserved. The surrounding interstitium is expanded, rich in cells (many myofibroblasts, arrows) and fluid, and contains ample capillaries. Proximal tubules of unaffected nephrons exhibit an intact epithelium (asterisks). (Thy-1 mediated glomerulonephritis, rat, after 2 weeks. Bar: 30μm.)
Reproduced from Kriz et al. (2003) with permission.

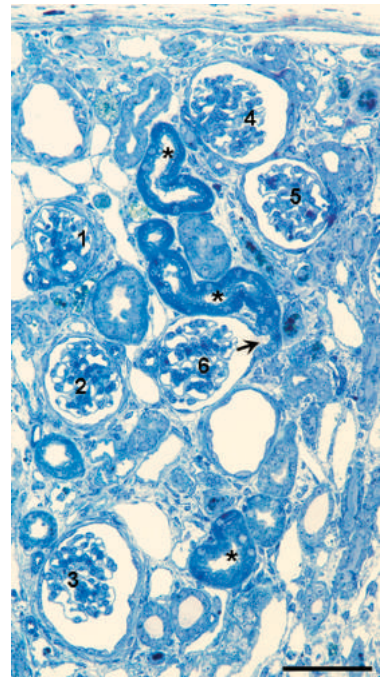

Fig. 139.8 A healthy nephron surrounded by tubulointerstitial fibrosis. Within an area of extensive nephron degeneration (glomeruli 1–5 appear as a tubular remnants) a single well-structured glomerulus (6) is seen that has an open urinary orifice (arrow) and intact tubules (asterisks) embedded into an area composed of degenerating tubules and surrounding fibrosis. (TGF-β-induced kidney fibrosis after six cycles of DOX. Bar: 100 μm.)
Unpublished light micrograph from Koesters et al. (2010) with permission.

the disease in glomeruli. Therefore, we have to discuss the question of whether fibrosis is merely a secondary process replacing lost nephrons or may fibrosis become harmful to so far healthy nephrons?

To address this we must first recognize that fibrosis may develop in different scenarios. Here, we have only considered fibrosis development subsequent to glomerular injury. Fibrosis formation in conjunction with a chronic allograft dysfunction has other causes and follows other pathways. This is not a focal process related to individually diseased nephrons but starts more or less ubiquitously in the interstitium. Therefore, we must narrow our question to the relevance of fibrosis that starts as a focal process subsequent to the degeneration of individual nephrons. Although this may affect many nephrons at one time, it is nevertheless a process, which occurs in relation to individual nephrons.

So, the crucial question reads: is fibrosis as it generally occurs subsequent to glomerular diseases harmful to intact nephrons? In most publications on this subject, this question is not explicitly raised: it is simply assumed, without explicit justification, that fibrosis is harmful. This assumption is essentially based on the observation that the decline in renal function in chronic renal disease correlates more closely with interstitial fibrosis than with glomerular fibrosis (Ridson et al., 1968; Bohle et al., 1977; Cameron, 1992; d'Amico et al., 1995).

This correlation is taken as an argument in favour of a genuine interstitial mechanism of progression. Thereby one overlooks a crucial fact: as animal models (Kriz and Le Hir, 2005) and studies in the ageing human kidney show (Kanwar, 1984; Yang and Morrison, 1980), the remnants of a degenerative nephron, including glomeruli, may be completely removed and replaced by fibrous tissue. Thus, the more nephrons degenerate, the more the interstitial damage score will increase, while the glomerular damage score will decrease due to the disappearance of sclerotic glomeruli. Recent studies clearly show that the decline in renal function in chronic renal disease correlates best with the number of remaining nephrons (Nyengaard and Bendtsen, 1992; Lubran, 1995; Bajema et al., 1999). Thus, the evidence for the fibrosis hypothesis from these studies is far from being conclusive.

Our own observations in a great variety of animal models do not support the hypothesis that fibrosis may become a self-sustained process that injures healthy nephrons. We consistently found that tubule segments of healthy nephrons, even if completely surrounded by degenerating tubules or being embedded in fibrotic tissue, preserve their normal structure—even in advanced stages. Fig. 139.8 shows an area of extensive nephron degeneration from an experimental fibrosis model (overexpression of TGF-β (Koesters et al., 2010) that contains a single structurally intact nephron fully surrounded by degenerating nephrons and fibrosing tissue. Thus, there is little evidence that the fibrosing process or the completed fibrosis are harmful to healthy nephrons.

The pathophysiological situation in a stage of advanced fibrosis consisting of fibrosing and fibrotic areas, deadly and partially

damaged and some intact (but hypertrophied) nephrons must be considered as extremely complex. The chance to clearly decipher profibrotic and antfibrotic mechanisms is small, at best, as is the chance for any successful therapeutic interventions. The fight against progression has to start earlier, and is most optimal at an early stage of the glomerular disease.

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References

Aita, K., Etoh, M., Hamada, H., *et al.* (2009). Acute and transient podocyte loss and proteinuria in preeclampsia. *Nephron Clin Pract*, 112, c65–70.

Bajema, I., Hagen, E. C., Hermans, J., *et al.* (1999). Kidney biopsy as a predictor for renal outcome in ANCA-associated necrotizing glomerulonephritis. *Kidney Int*, 56, 1751–8.

Bohle, A., Glomb, D., Grund, K., *et al.* (1977). Correlations between relative interstitial volume of the renal cortex and serum creatinine concentration in minimal changes with nephrotic syndrome and in focal sclerosing glomerulonephritis. *Virchows Arch*, 376, 221–32.

Böttinger, E. (2007). TGF-beta in renal injury and disease. *Semin Nephrol*, 3, 309–20.

Brenner, B., Lawler, E., and Mackenzie, H. (1996). The hyperfiltration theory: a paradigm shift in nephrology. *Kidney Int*, 49, 1774–7.

Cameron, J. (1992). Tubular and interstitial factors in the progression of glomerulonephritis. *Pediatr Nephrol*, 6, 292–303.

D'Amico, G., Ferrario, F., and Rastaldi, M. (1995). Tubulointerstitial damage in glomerular diseases: its role in the progression of renal damage. *Am J Kidney Dis*, 26, 124–32.

Friedrich, C., Endlich, N., Kriz, W., *et al.* (2006). Podocytes are sensitive to fluid shear stress in vitro. *Am J Physiol Renal Physiol*, 291, F856–F865.

Fries, J., Mendrick, D., and Rennke, H. (1988). Determinants of immune complex-mediated glomerulonephritis. *Kidney Int*, 34, 333–45.

Gotzmann, J., Mikula, M., Eger A., *et al.* (2004). Molecular aspects of epithelial cell plasticity: implications for local tumor invasion and metastasis. *Mutat Res*, 566, 9–20.

Greka, A. and Mundel, P. (2012). Cell biology and pathology of podocytes. *Annu Rev Physiol*, 74, 299–323.

Hara, M., Yamamoto, T., Yanagihara, T., *et al.* (1995). Urinary excretion of podocalyxin indicates glomerular epithelial cell injuries in glomerulonephritis. *Nephron*, 69, 397–403.

Hara, M., Yanagihara, T., Takada, T., *et al.* (1998). Urinary excretion of podocytes reflects disease activity in children with glomerulonephritis. *Am J Nephrol*, 18, 35–41.

Hoffmann, S., Podlich, D., Hähnel, B., *et al.* (2004). Angiotensin II type 1 receptor overexpression in podocytes induces glomerulosclerosis in transgenic rats. *J Am Soc Nephrol*, 15, 1475–87.

Hostetter, T., Olson, J. L., Rennke, H. G., *et al.* (1981). Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol*, 241, F85–F93.

Humphreys, B., Lin, S. L., Kobayashi, A., *et al.* (2010). Fate tracing reveals the pericyte and not epithelial origin of myofibroblasts in kidney fibrosis. *Am J Pathol*, 176, 85–97.

Kanwar, Y. (1984). Biology of disease. Biophysiology of glomerular filtration and proteinuria. *Lab Invest*, 51, 7–21.

Koesters, R., Kaissling, B., Lehir, M., *et al.* (2010). Tubular overexpression of transforming growth factor-ß1 induces autophagy and fibrosis but not mesenchymal transition of renal epithelial cells. *Am J Pathol*, 177, 632–43.

Kretzler, M., Koeppen-Hagemann, I., and Kriz, W. (1994). Podocyte damage is a critical step in the development of glomerulosclerosis in the uninephrectomized desoxycorticosterone rat. *Virchows Arch*, 425, 181–93.

Kriz, W. and Endlich, K. (2005). Hypertrophy of podocytes: a mechanism to cope with increased glomerular capillary pressures? Kidney Int, 607, 373–4.

Kriz, W., Gretz, N., and Lemley, K. (1998). Progression of glomerular diseases: is the podocyte the culprit? Kidney Int, 54, 687–97.

Kriz, W., Hähnel, B., Hosser, H., *et al.* (2003). Pathways to recovery and loss of nephrons in anti-Thy-1 nephritis. *J Am Soc Nephrol*, 14, 1904–26.

Kriz, W., Hähnel, B., Rosener, S., *et al.* (1995). Long-term treatment of rats with FGF-2 results in focal segmental glomerulosclerosis. *Kidney Int*, 48, 1435–50.

Kriz, W., Kaissling, B., and Le Hir, M. (2011). Epithelial-mesenchymal transition (EMT) in kidney fibrosis: fact or fantasy? Clin Invest, 121, 468–74.

Kriz, W. and Le Hir, M. (2005). Pathways to nephron loss starting from glomerular diseases—insights from animal models. *Kidney Int*, 67, 404–19.

Kriz, W., Shirato, I., Nagata, M., *et al.* (2013). The podocyte's response to stress: the enigma of foot process effacement. *Am J Physiol Renal Physiol*, 304(4), F333–F47.

Le Hir, M. and Besse-Eschmann, V. (2003). A novel mechanism of nephron loss in a murine model of crescentic glomerulonephritis. *Kidney Int*, 63, 591–9.

Le Hir, M., Keller, C., Eschmann, V., *et al.* (2001). Podocyte bridges between the tuft and Bowman's capsule: an early event in experimental crescentic glomerulonephritis. *J Am Soc Nephrol*, 12, 2060–71.

Lemley, K., Lafayette, R. A., Safai, M., *et al.* (2002). Podocytopenia and disease severity in IgA nephropathy. *Kidney Int*, 61, 1475–85.

Li, L., Zepeda-Orozco, D., Black, R., *et al.* (2010). Autophagy is a component of epithelial cell fate in obstructive uropathy. *Am J Pathol*, 176, 1767–78.

Lubran, M. (1995). Renal function in the elderly. *Ann Clin Lab Sci*, 25, 122–33.

Marcussen, N. (1995). Atubular glomeruli in chronic renal disease. *Curr Top Pathol*, 88, 145–74.

Nagata, M. and Kriz, W. (1992). Glomerular damage after uninephrectomy in young rats. II. Mechanical stress on podocytes as a pathway to sclerosis. *Kidney Int*, 42, 148–60.

Nakamura, H., Ushiyama, C., Suzuki, S., *et al.* (2000a). Urinary podocytes for the assessment of disease activity in lupus nephritis. *Am J Med Sci*, 320, 112–16.

Nakamura, T., Ushiyama, C., and Suzuki, S. (2000b). Effect of angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist and calcium antagonist on urinary podocytes in patients with IgA nephropathy. *Am J Nephrol*, 20, 373–9.

Nakamura, T., Ushiyama, C., Suzuki, S., *et al.* (2000c). Urinary excretion of podocytes in patients with diabetic nephropathy. *Nephrol Dial Transplant*, 15, 1379–83.

Nyengaard, J. and Bendtsen, T. (1992). Glomerular number and size in relation to age, kidney weight, and body surface in normal man. *Anat Rec*, 232, 194–201.

Pavenstadt, H., Kriz, W., and Kretzler, M. (2003). Cell biology of the glomerular podocyte. *Physiol Rev*, 83, 253–307.

Petermann, A., Pippin, J., Krofft, R., *et al.* (2004). Viable podocytes detach in experimental diabetic nephropathy: potential mechanism underlying glomerulosclerosis. *Nephron Exp Nephrol*, 98, 114–23.

Remuzzi, G. and Bertani, T. (1998). Pathophysiology of progressive nephropathies. *N Engl J Med*, 339, 1448–56.

Ridson, R., Sloper, J., and de Wardener, H. (1968). Relationship between renal function and histological changes found in renal-biopsy specimens from patients with persistent glomerular nephritis. *Lancet*, 2, 363–6.

Schordan, S., Schordan, E., Endlich, K., *et al*. (2010). AlphaV-integrins mediate the mechanoprotective action of osteopontin in podocytes. *Am J Physiol Renal Physiol*, 300, F119–32.

Smeets, B., Uhlig, S., Fuss, A., *et al.* (2009). Tracing the origin of glomerular extracapillary lesions from parietal epithelial cells. *J Am Soc Nephrol*, 20, 2604–15.

van Damme, B., Tardanico, R., Vanrenterghem, Y., *et al.* (1990). Adhesions, focal sclerosis, protein crescents, and capsular lesions in membranous nephropathy. *J Pathol*, 161, 47–56.

Vogelmann, S., Nelson, W., Myers, B., *et al*. (2003). Urinary excretion of viable podocytes in health and renal disease. *Am J Physiol Renal Physiol*, 285, F40–F48.

Weil, E., Lemley, K. V., Yee, B., *et al*. (2011). Podocyte detachment in type 2 diabetic nephropathy. *Am J Nephrol*, 33, 21–24.

Wharram, B., Goyal, M., Wiggins, J. E., *et al*. (2005). Podocyte depletion causes glomerulosclerosis: diphtheria toxin-induced podocyte depletion in rats expressing human diphtheria toxin receptor transgene. *J Am Soc Nephrol*, 16, 2941–52.

Yang, G. and Morrison, A. (1980). Three large dissectable rat glomerular models reconstructed from wide-field electron micrographs. *Anat Rec*, 196, 431–40.

Yu, D., Petermann, A., Kunter, U., *et al.* (2005). Urinary podocyte loss is a more specific marker of ongoing glomerular damage than proteinuria. *J Am Soc Nephrol*, 16, 1733–41.

CHAPTER 140

Disordered scarring and failure of repair

Jeremy S. Duffield

Introduction

A fourth potential explanation for the progression of chronic renal disease (see Chapter 136) is that scarring following renal injury, particularly but not exclusively glomerular injury, becomes self-perpetuating.

The kidney has a large functional reserve in healthy nephrons that can be called upon to compensate for loss of nephron function elsewhere in the kidney. In fact, biopsy studies indicate substantial silent disease in patients with apparently normal function and no loss of filtration barrier (Christopher-Stine et al., 2007; Rule et al., 2010). This scenario might pertain to patients with hypertension, where ischaemia of the kidney cortex and medulla may be central to the pathogenesis of hypertension (Johnson et al., 2002; Rodriguez-Iturbe and Johnson, 2010). Therefore the burden of patients with occult compromise of kidney function, and 'at risk' of developing loss of organ function is likely to be significant. The patients with occult disease and those with overt CKD share similar histological characteristics: *glomerulosclerosis, inflammation, microvascular rarefaction, interstitial fibrosis*, and *tubule atrophy* (Fig. 140.1). Although these pathological features involve distinct tissue compartments, increasing evidence suggests that these pathological manifestations are inter-related.

Although CKD can affect people of all ages it is predominantly a disease of ageing, and the fastest growing group of patients in developed nations are in the 45–64-year age range (United States Renal Data System, 2011). Animal studies and human biopsy findings support the notion that ageing per se is a cause of fibrosis and CKD (Abrass, 2000; Abrass et al., 2010; Rule et al., 2010). In addition, CKD is now recognized to be a frequent consequence of acute kidney injury (AKI), particularly in older patients, and particularly in those with repeated AKI episodes (Ishani et al., 2009). Finally, CKD is the final common pathway for many acute kidney diseases such as vasculitis and other chronic systemic disorders, including diabetes and ischaemic vascular disease (Fig. 140.2). In these settings, even though the original disease may be quiescent or 'burnt-out', the CKD process remains self-sustaining and active, and able to drive progression of CKD towards organ failure and cardiovascular disease.

In kidney allografts, a similar disease process is frequently seen from 6 months after transplantation, known as chronic allograft dysfunction (CAD), previously chronic allograft nephropathy (CAN) (Racusen and Regele, 2010). Although the mechanisms of disease may be distinct in allografts, the pattern of disease is remarkably similar to CKD, characterized by *glomerulosclerosis, inflammation, microvascular rarefaction, interstitial fibrosis*, and *tubule atrophy* (Figs 140.1 and 140.2), and it is very likely that similar pathogenic paradigms will exist.

Failure of normal repair processes may increase the consequences of an insult would otherwise be recoverable. Disordered control of scarring could increase the long term impact of a 'healed' injury.

Pathogenesis of kidney fibrosis

Normal tissue repair after injury

One approach to understanding pathogenesis in CKD is to understand how the normal adult kidney responds to injury (see also Chapter 221). In response to injury, tissues have great capacity to repair and regenerate damaged areas. Low-level damage occurs continually throughout life and is repaired. Following a single acute injury, for the most part the tissues undergo normal and near-complete repair. It is frequently in circumstances of repetitive injury or following very severe injury that the fibrogenic process occurs and fails to resolve.

What are the features of normal organ repair? (Table 140.1). Following tissue injury there is loss of cell viability, characterized by three cellular processes—necrosis, apoptosis, and autophagy—and a marked increase in local generation of an environment high in formation of radicals including oxidizing and nitrosylating molecules. These factors damage vital basement membranes and local connective tissue.

In response to this, local cells and recruited cells of the immune system acquire debriding and phagocytosing functions, and capacity to survive in a hostile environment; in doing so they lose normal functions (Lupher and Gallatin, 2006). The debriding process may contribute to sterilization of the injured tissue and presentation of antigens. The phagocytic capacity of surviving and recruited cells contributes to clearance of damaged tissues and serves as an energy supply, critical to cell survival.

A critical gene that mediates phagocytic clearance by epithelial cells of debris in tubule lumens is the scavenger receptor kidney injury molecule 1 (KIM-1) (Ichimura et al., 2008). KIM-1 is also cleaved and shed into the tubule lumen where it serves as a marker of epithelial injury (Han et al., 2008).

In kidney, the proximal tubules, especially of the outer medulla (S3 segment), and peritubular capillaries in the outer medulla are susceptible to damage and cell death following ischaemic or toxic injuries, due to a combination of high metabolic rate and relatively compromised oxygen delivery and blood flow, and lack of anaerobic respiration (Duffield and Bonventre, 2005).

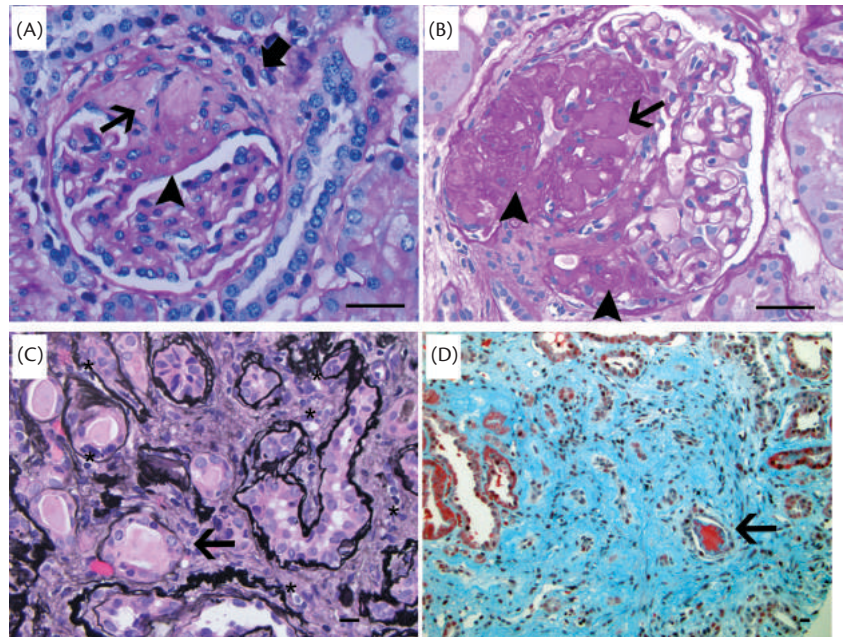

Fig. 140.1 Characteristic fibrotic changes in glomeruli and interstitium of kidney cortex.
(A) Wedge-shaped sclerotic region showing dense pink material on periodic acid–Schiff (PAS)-stained section (arrowhead) and rather acellular weaker pink-stained material more peripherally (arrow) and obliteration of capillary loops. Also note the sclerotic region is fused to Bowman's capsule where there is local destruction of the basement membrane and periglomerular fibrosis. At the lower pole note a combination of increased cellularity and fibrosis in the mesangium, and basement membrane thickening in glomerular loops. (B) Glomerulus showing typical focal segmental glomerulosclerosis (FSGS) changes with hyaline material (also referred to as fibrin cap (arrow) formed by leakage of plasma proteins into the subendothelial space of the glomerular capillaries, and areas of nodular expansion of mesangial areas with PAS pink fibrotic material. The remainder of the glomerulus is normal. (C) Silver methenamine combined with PAS-stained image of cortex from diabetic nephropathy, showing injured tubules (tubule atrophy and tubule cell vacuolization, apoptotic cells, arrow), marked reduction in capillary density (denoted by asterisk), expansion of the interstitial space with fibrotic material (fine black stain), and an increase in inflammatory cells. Note also thickening of the tubule basement membrane (black). (D) Trichrome-stained image of kidney cortex from ischaemic kidney disease showing marked expansion of interstitial fibrosis (cyan colour) which has overtaken all of the tubules. The fibrosis is cellular showing inflammatory cells and myofibroblasts. The remaining tubules all show tubular atrophy with intraluminal debris.

Following the phase of clearance of damaged structures and dead tissues, local and recruited cells activate programmes of coordinated organ regeneration. These programmes include, but are not restricted to, reactivation of cell-to-cell signalling pathways involved in organ development (nephrogenesis), by coordinately regulating cell fate, polarity, spatial orientation, migration, differentiation, and matrix deposition. These cell pathways include WNT, PDGF, FGF, HGF, IGF, TGF-β superfamily, NOTCH, HEDGEHOG, VEGF, and angiopoietins (Table 140.2) (Karihaloo et al., 2005; Kobayashi et al., 2008; Lin et al., 2010; Sirin and Susztak, 2011).

Nephron regeneration requires re-epithelialization. Injured epithelial cells acquire a flattened migratory phenotype, and are able to synthesize new tubule basement membrane and migrate to close denuded areas. In addition to migration, the cells proliferate. This process may be referred to as an epithelial to mesenchymal transition. In this state the epithelial cells are more likely to survive and activate developmental cell–cell signalling pathways that include WNT, HGF, IGF, EGF, FGF, NOTCH, and HEDGEHOG (Wang et al., 2003; Franquesa et al., 2005). These signalling pathways regulate activation of genes that control regenerative programmes.

At the same time as nephron regeneration occurs, regeneration of capillaries must occur, also requiring coordinated activation of developmental cell–cell signalling pathways. However, whereas nephrons rarely become disconnected following injury, capillaries frequently lose connections and therefore re-capillarization is a complex process requiring three cell types, endothelial cells, pericytes (mural cells), and macrophages.

Following damage, macrophages may be critical in a number of angiogenic events, including generating new tunnels in matrix for endothelial cells to grow through, in directing branching, and stimulating endothelial migration (Glod et al., 2006; Gelati et al., 2008; Stefater et al., 2011).

Pericytes are critical in coordinating angiogenesis, deposition of new basement membrane, and stabilizing endothelial cells (Armulik et al., 2005; Schrimpf and Duffield, 2011; Schrimpf et al., 2012). Endothelial cells, macrophages, and pericytes work in a coordinate manner by cell-to-cell signalling to successfully rebuild the capillary lumen and its basement membrane.

In many organs the presence of quiescent or active local tissue stem or progenitor cells contributes significantly to organ regeneration after injury, but the human kidney does not appear to have stem or progenitor cells that can rebuild the nephron (Humphreys et al., 2008, 2011). Rather, the nephron appears to be rebuilt by surviving epithelial cells. The mechanism of reconstitution of the capillaries is less well understood and it is not known whether progenitor cells contribute to vascular regeneration.

A normal component of tissue injury is the stimulation of tissue fibrosis. Within days of acute injury, such as after ischaemic injury, there is increased matrix production in the interstitial space and within the mesangium. Activated pericytes, that are no longer associated closely with endothelial cells, synthesize matrix,

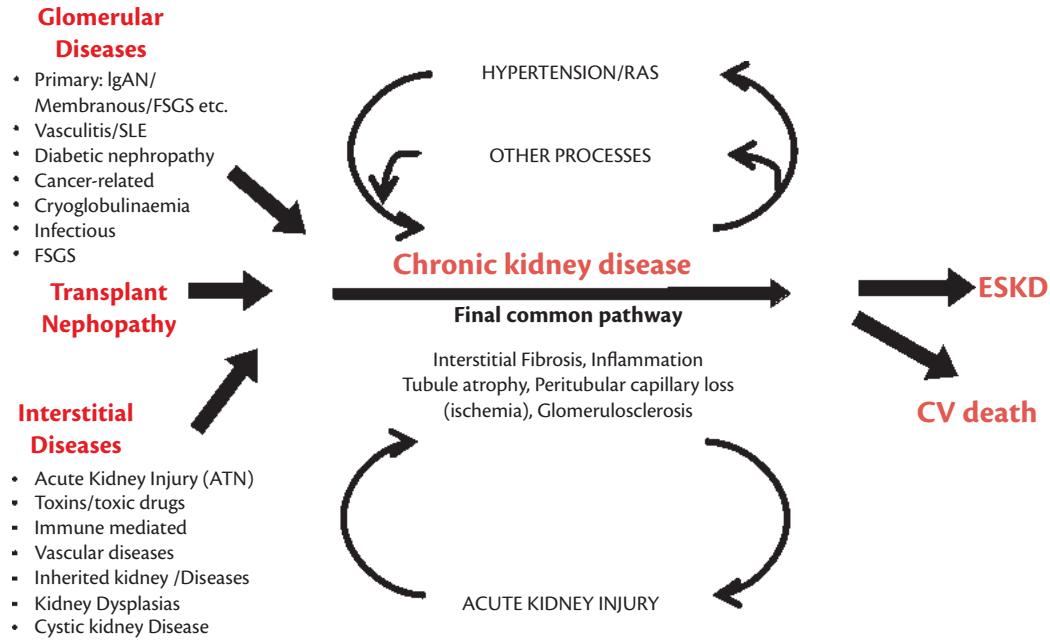

Fig. 140.2 Schema showing the multitude of kidney diseases that result in pathologically similar chronic disease processes in the kidney. CKD is characterized by glomerulosclerosis, capillary loss (glomerular and post glomerular), inflammation (leucocytes), interstitial fibrosis, and tubule injury (atrophy). These pathological features become self-perpetuating and are driven by a number of increasingly recognized cell-to-cell signalling pathways including the renin–angiotensin system acting through the angiotensin receptor 1. Episodes of AKI also accelerate the pathological processes in CKD. The outcome is disease progression which results in organ failure or cardiovascular events outside of the kidney.

presumably to stabilize the organ architecture, and maintain lumina of capillaries.

The glomerulus is essentially a modified vascular plexus and has been shown in animals to have significant regenerative capacity (Ma and Fogo, 2007). Although it was believed that the podocytes, which overlie the glomerular capillaries, are terminally differentiated and unable to proliferate, newer findings raise the possibility that some degree of replacement may be possible from parietal epithelial cells (Moeller et al., 2004; Appel et al., 2009; Shkreli et al., 2011; and see Chapter 344). A vascular progenitor cell may also exist that can replenish both of these cells in response to glomerular injury. It is already established that 'glomerular pericytes', mesangial cells, can be replenished from an extra-glomerular progenitor arising within the afferent arteriole (Pippin et al., 2013). Therefore acute injuries to the glomerulus may theoretically be able to result in capillary loop regeneration.

One of the most striking features of kidney repair after acute injury is the lack of complete nephron and microvascular regeneration (Li et al., 2010). Whereas skin wounding results in a marked angiogenesis that can last for many months before eventual regression, and appears to be very important in normal wound healing, the angiogenic response after kidney injury is attenuated, and frequently the outcome is capillary rarefaction rather than

Table 140.1 Regenerative mechanisms activated after kidney injury

Phase I	Endothelial activation and coagulation cascade activation
	Activation of acute stress and survival pathways in resident cells
	Recruitment of leucocytes
	Activation and migration of myofibroblasts
Phase II	Phagocytic clearance of dead cells, debris and damages membranes by leucocytes and surviving epithelial cell
	Deposition of pathological extracellular matrix
Phase III	Re-epithelialization[a]
	Angiogenesis[a]
	Basement membrane re-synthesis
	Resorption of matrix[a]
Phase IV	Remodelling of extracellular matrix
	Disappearance of myofibroblasts and leucocytes[a]

[a] May be incomplete in the kidney.

Table 140.2 Developmental cell-to-cell signalling pathways activated in repair and chronic kidney disease

Vascular	Epithelial
PDGF	HGF
VEGF	EGF
TGF-β	TGF-β
NOTCH	IGF
HEDGEHOG	WNT
WNT	

angiogenesis (Schrimpf et al., 2012). This occurs despite active proliferation of endothelial cells suggesting an intrinsic regenerative defect in mammalian kidneys.

The final component of the regenerative process is the resolution of inflammation. Inflammation (infiltration of leucocytes) appears to be important for normal tissue regeneration, and many cells including macrophages are critical in the early regenerative process (Lin et al., 2010; Lee et al., 2011). During the later phase of resolution, macrophages play important roles in generating anti-inflammatory cytokines, including interleukin 10, and resorbing increased matrix deposition by proteolysis and endocytosis. Although resorptive roles for macrophages have been shown in organs such as the liver, this function for macrophages in the kidney has not been clearly demonstrated, and could potentially reflect another defect in the normal repair process inherent to the kidney. The remodelling phase which includes resorption of matrix, is important in the kidney to maintain normal tissue tension and architecture. Finally the total population of normal inflammatory cells slowly resides to leave a non-inflamed tissue.

Interstitial fibrosis

Understanding of the cellular origin of interstitial fibrosis in the kidney was dramatically changed by a series of studies from 2008. In a reversal of previous focus on tubular epithelial cells, attention turned to an extensive network of discrete mesenchymal cells in adult kidneys that were previously poorly appreciated (Lin et al., 2008; Asada et al., 2011; Schrimpf and Duffield, 2011). These comprised up to 5% of all nucleated cells in the adult kidney, and are referred to as pericytes (mural cells) when seen attached to capillaries or resident fibroblasts when embedded in stroma between capillaries and tubules (Fig. 140.3). Genetic fate mapping studies in animal models of kidney disease indicate that these cells are the major precursors of myofibroblasts (Humphreys et al., 2010; Asada et al., 2011). Myofibroblasts are the cells that in the kidney interstitium synthesize and deposit fibrotic interstitial matrix. Although the fibrotic interstitial matrix comprises a multitude of proteins, glycoproteins, and proteoglycans including hyaluronan and fibronectin, the major constituents that define fibrotic matrix are collagen I and collagen III fibrils. Myofibroblasts have been shown to be the cells responsible for the production and deposition of these proteins in the kidney (Fig. 140.4). Until recently, it has been difficult to study myofibroblasts since their definition was unclear, and all cells when cultured *in vitro* on plastic can generate fibrillar collagens and other characteristics of myofibroblasts; an unfortunate artefact of cell culture, making *in vitro* study of myofibroblasts problematic.

For more than a decade it was thought that epithelial cells were myofibroblast progenitors, and many studies of fibrogenic mechanisms in the kidney have relied heavily on dissecting mechanisms on epithelial cells in culture. Now, a number of comprehensive critical genetic studies in animals have shown no evidence that epithelial cells are myofibroblast progenitors (Zeisberg and Duffield, 2010; Grgic et al., 2011).

Key features of myofibroblasts:

- myofibroblasts appear as a result of chronic or mal-adaptive activation of normal developmental pathways involved in angiogenesis.
- evidence suggests that myofibroblasts, after a protracted period of activation, lose pericyte functions and become persistently activated, developing a degree of autonomy, losing requirement of regulatory signals from other cells.
- the loss of pericyte functions results in microvascular instability that may result in capillary demise. Loss of capillaries promotes ischaemia, which will prevent normal regeneration from occurring and will stimulate further inflammation.
- myofibroblasts are inflammatory cells themselves, able to generate an array of inflammatory cytokines and chemokines that may perpetuate a disease process.
- Since myofibroblasts are therefore critical in the outcome for capillaries, inflammation, and fibrosis, they are a central cellular target in chronic disease of the kidney.

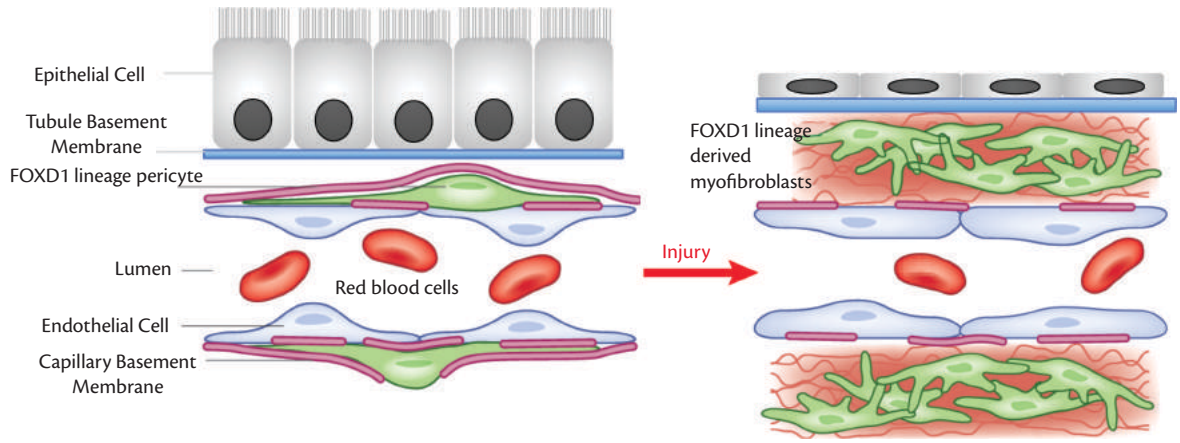

Fig. 140.3 Schema of pericyte to myofibroblast transition in kidney disease. In healthy adult kidney, pericytes are partially embedded in the capillary basement membrane of the peritubular capillaries and are closely attached to microvascular endothelial cells. In response to endothelial or epithelial injury, pericytes become activated and migratory, and enter cell cycle to proliferate. These changes constitute a transition to the myofibroblast cell type, which is the principal cell to deposit fibrillary collagens that constitute fibrosis. Whereas pericytes normally perform homeostatic roles in maintaining endothelial cell integrity, myofibroblasts lose this capacity, rendering the endothelium unstable, leaky, and liable to demise. Interstitial and capillary changes promote epithelial compromise. Activated epithelial cells contribute to tubule basement membrane thickening.

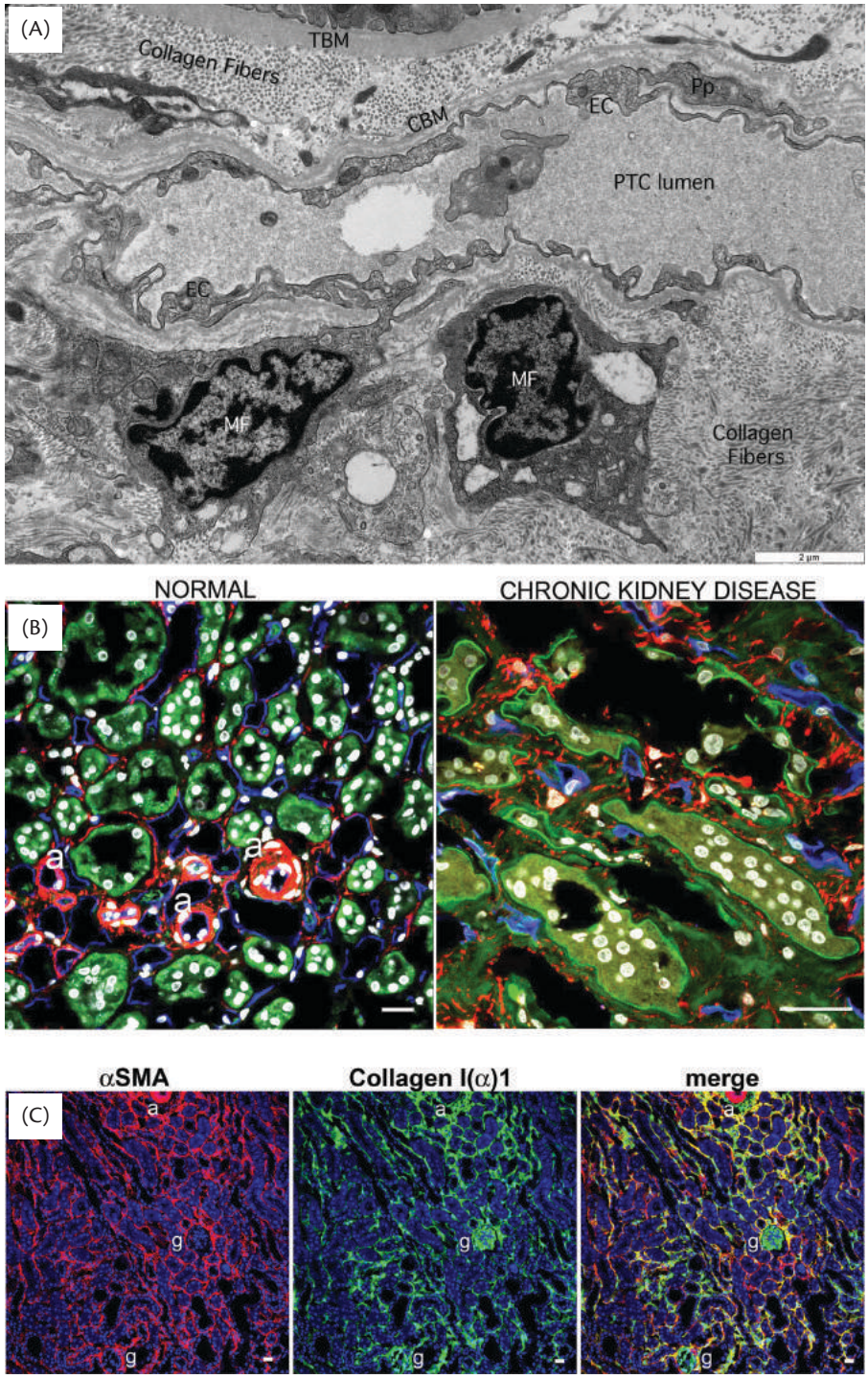

Fig. 140.4 Characterization of pericytes and myofibroblasts in human kidneys.
(A) Transmission electron micrograph of human kidney cortex from a patient with interstitial fibrosis showing a peritubular capillary with adjacent myofibroblasts (MF) embedded in fibrillary collagen matrix (fibrosis). Note capillary basement membrane (CBM), and on the presence of a pericyte process (Pp) embedded in the CBM overlying the endothelial (EC) cytoplasm. (Bar = 2 µm.) (B) Immunofluorescent staining of normal, and CKD adult kidney cortex showing pericytes and arteriolar (a) vascular smooth muscle (red). Pericytes are attached to capillaries (blue). Tubules (brown/green) and nuclei (white) and laminin (green) can also be seen. Note in CKD the capillaries are diminished in number and are reduced in size due to expanding fibrotic matrix. Note that pericytes (red) are no longer attached to capillaries, but are now abundant in the interstitial space as myofibroblasts (red). (Bar = 50 µm.) (C) Interstitial fibrosis in a mouse model of adult human interstitial kidney disease showing cells expressing the myofibroblast marker αSMA (red) and cells synthesizing collagen Iα1 protein (green). Note that all collagen Iα1 producing interstitial cells also express αSMA in disease. Also note that podocytes in unaffected glomeruli also produce collagen Iα1 protein (a = arteriole; g = glomeruli where podocytes express collagen Iα1 protein). (Bar = 50 µm.)

Although it now appears that epithelial cells are not themselves a significant source of myofibroblast progenitors, epithelial cells can serve as major stimulants of the fibrogenic process, particularly proximal tubule cells (Friedman et al., 2013). Chronic or severe injury to epithelial cells results in a number of critical changes to epithelial cell function and phenotype that contribute to the fibrogenic process mainly by cell-to-cell signalling. Epithelial cells exposed to toxins such as cisplatin, aminoglycosides, or products of pathogens; chronic ischaemia; crystal formation; or unfavourable metabolic environments, activate cell-stress responses which include stress responses in the endoplasmic reticulum, abnormalities in tertiary protein folding, and also chronic activation of the process of autophagy, an intracellular disposal system that is vital in recycling intracellular structures as a source of energy and new cellular building blocks such as amino acids (Scarlatti et al., 2009). Such stressed epithelial cells paradoxically downregulate normal metabolic pathways, generate increased oxygen radicals, and exhibit arrest of the cell cycle (Cybulsky, 2009; Yang et al., 2010; Chau et al., 2012). In addition to these processes, injured epithelial cells undergo phenotypic changes known as epithelial to mesenchymal transition, characterized by acquisition of a mesenchymal cell appearance, loss of polarity and cell junctions, and activation of mesenchymal transcription factors including SNAIL. Such epithelial cells generate pro-inflammatory and profibrotic cytokines, and evidence of a more migratory, less polarized phenotype, unable to perform normal epithelial functions. Part of this stressed epithelial response is to deposit increased tubular basement membrane (TBM), leading to TBM thickening, seen in many CKDs.

As a result of the capillary instability and loss of microvasculature, the expanding interstitial space, and the contractile forces that disrupt normal tissue architecture, and stress responses in epithelial cells, normal tubular function is compromised. The tubules normally play critical roles in reabsorption of vital small molecules that are filtered by the nephron, in addition to salts and water. These functions are compromised.

Tubules also perform critical secretory roles, particularly of organic anions, that are underappreciated, as estimates of glomerular filtration rate do not measure the capacity of tubules to secrete toxins. Tubular secretion of endogenous as well as exogenous toxins is an important component of homeostasis and failure to clear such toxins may contribute to uraemic symptoms, disease progression, and cardiovascular disease. Uraemic toxins cleared by tubular secretion include hippurate, p-cresol, and indoxyl sulphate and are generated in part by gut flora (see Chapter 254). They are protein bound, therefore not filtered but are secreted by proximal tubular organic anion transporters OAT1, OAT3, and OATP (Ohtsuki et al., 2002; Dou et al., 2004; Deguchi et al., 2005; Enomoto and Niwa, 2007).

Glomerulosclerosis

The glomerulus is a specialized vascular bed comprising endothelial cells with their respective mural cells. Whereas most capillary beds have a single population of mural cells, the glomerular capillary loops have both a mesangial cell (true pericyte) with direct communication to the glomerular endothelium and also a highly specialized podocyte (pericyte-like) that lies on the abluminal glomerular capillary basement membrane (GBM) where it performs unique functions in tightly and regulating glomerular capillary permeability and flow. The mesangial cell has long been recognized as the precursor of the scar forming myofibroblast that deposits fibrillar matrix during mesangial expansion and nodule formation (Johnson et al., 1992). This expanding fibrillar matrix can encroach on capillary loops.

The composition of glomerulosclerosis is somewhat distinct from the composition of interstitial fibrosis and frequently contains plasma proteins. This difference may be due to leakage of plasma proteins into areas of tissue injury directly underlying the fenestrated and therefore highly permeable glomerular endothelial cells. This intra- and pericapillary material is known as hyaline due to its acellular glassy appearance in stained sections, but its composition is not fully characterized. The composition of glomerulosclerosis may also differ in that there may be high levels of GBM proteins deposited aberrantly in mesangial areas or in the capillary tuft.

In addition, injury to the glomerulus is characterized by obliteration of individual capillary loops structures, and therefore other cells including podocytes, leucocytes, and possibly endothelial cells may therefore contribute to the formation of fibrotic matrix in areas of capillary loop demise by aberrant deposition of GBM components.

Formation of glomerular crescents by excessive proliferation of parietal epithelial cells and podocytes in the urinary space as well as recruitment of periglomerular fibroblasts may all contribute to the development of encasing fibrosis that develops from a fibrocellular crescent (Alpers et al., 1994).

Surprisingly podocytes, rather than mesangial cells generate large amounts of collagen Iα1 protein in heath (Fig. 140.4) (Lin et al., 2008) so may be poised to have capacity to deposit fibrillar matrix in glomerular disease states where they proliferate.

Whereas in the cortex and medulla of the kidney, chronic or iterative kidney tubular or endothelial injury are major stimulants of fibrosis, in the glomerulus, deposition of immune complexes in mesangial or endothelial areas, inappropriate activation of leucocytes in the glomerular microcirculation, direct endothelial toxicity, or toxicity to podocytes are frequent factors in glomerular fibrogenesis.

Link between glomerular disease and tubular disease and vice versa

While it is clear that injury to either the glomerular compartment or the tubulo-vascular compartment of the kidney contribute to organ fibrosis and functional compromise, glomerular disease alone has the capacity to lead to tubular disease. The peri-tubular capillaries are supplied directly from the glomerular capillaries, therefore occlusion or constriction of glomerular capillaries, or injury to the glomerulus will compromise PTC blood flow. This compromise will stimulate ischaemic responses in the tubule and PTC endothelium that is fibrogenic. In addition to this link, the tubule itself can feedback information directly to its own glomerulus, tubuloglomerular feedback (Wunderlich et al., 1980; Takabatake et al., 1983). Although incompletely understood, one mechanism involves salt delivery to the distal tubule. If delivery is increased, glomerular flow is diminished by an ATP-dependent mechanism. While this mechanism has a physiological role, in situations of chronic tubular disease, this mechanism may contribute to glomerular pathology.

Normal repair gone awry

Studies of cellular and molecular mechanisms involved in the normal repair process have demonstrated considerable overlap

between repair and chronic disease with fibrosis. In fact, increasingly repair processes are clearly identified in chronic disease with fibrosis.

One explanation is that the kidney is continually trying to repair itself in response to injury, but the repetitive injury leads to a frustrated repair response, which is ineffective (Table 140.2). It is easy to imagine how a coordinated repair response such as a wave of tubule epithelial proliferation, migration of new cells along a damaged basement membrane, and regeneration of that membrane could be easily thwarted by a new injury, which disrupts this process. Alternatively in the glomerulus, mesangial cells and podocytes actively engaged in regenerating GBM around a lumen may continue to synthesize membrane inappropriately if the capillary lumen subsequently loses flow and endothelium.

One tissue response to such scenarios may be to further upregulate the repair mechanisms that have already been instigated. However, it is likely that chronic disease is more complicated than simply overactivation of reparative and developmental cell signalling pathways, although there is ample evidence that such pathways are overactivated (Lin et al., 2011). Equally a number of other processes are in play:

- there is evidence that in chronic disease, activation of signalling pathways which recapitulate development, including TGF-β, stimulate intracellular production of oxygen radicals (oxidative stress) via activation of NADPH oxidases, in distinction to normal development (Cucoranu et al., 2005; Hecker et al., 2009; Amara et al., 2010). Oxygen radical production (see Chapter 112) may contribute to tissue injury.
- although similar receptors are activated, the ligands that activate those receptors may be different and the signalling complexes that form are different, which results in distinct intracellular signalling pathway activation (Lin et al., 2011).
- compared with regeneration, the immune cells that are recruited to the tissue injury are activated differently resulting in a distinct repertoire of cytokines produced, which serve to amplify rather than resolve the inflammatory process (Duffield, 2010).

Mechanisms that perpetuate the scarring process

Although fibrogenesis is part of the normal wounding response, there is ample evidence of mechanisms by which fibrogenesis can become self-perpetuating.

Low nephron mass

(See Chapter 138)

It is widely accepted that in response to loss of nephrons, rather than grow new nephrons the kidney 'adapts' by increasing the function of the surviving nephrons. This overwork, is initially adaptive, but with time itself causes new disease. The process is known as hyperfiltration (Hostetter et al., 1981). Overworked nephrons compensate by becoming larger. This increase in size has several consequences. It requires increased blood supply, and the shear forces within glomerular capillaries increase, resulting in rounds of endothelial cell and podocyte injury and activation, and inflammatory responses, which stimulate fibrogenesis.

Repetitive stimuli

Chronic exposure to toxins, which may include dietary intake of herbs, metals, other plant- or pathogen-derived toxins, chemotherapies, or therapeutic agents cause cell injury or cell activation in the kidney. In conditions such as diabetes, long-term exposure of matrix components to elevated glycaemia results in glycation (covalent binding of sugar residues) of a heterogeneous group of proteins and lipids, known as advanced glycation end-products (AGEs). These AGEs can stimulate activation of the innate immune system which includes activation of all cell types in the kidney, by binding to pathogen recognition receptors. In fact, AGEs form in ageing without the presence of hyperglycaemia. This formation may, of course, reflect decreased turnover of membranes.

Ischaemia

The destruction of capillaries promotes ischaemia which itself drives inflammation due to release of pro-inflammatory factors. However, there are a number of other mechanisms that result in perpetuation.

Matrix stiffness

Elegant studies in fibrogenesis in the liver show that myofibroblasts and their progenitors in liver, hepatic stellate cells (HSCs), respond to tension with phenotypic changes. The higher the surface tension, the more activated phenotype myofibroblasts display (Georges et al., 2007; Olsen et al., 2011). In fact, simply culturing HSCs on normal tension gels renders them insensitive to activation. These findings have two profound implications. Firstly, in oedema states tissue tension increases and may therefore be a pro-inflammatory, profibrotic state. Secondly, as pathological fibrillar collagen matrix is deposited, it becomes cross-linked by enzymes such as lysyl oxidases and transglutaminases. This crosslinking increases the stiffness in a fibrogenic matrix.

Myofibroblast contractility

A characteristic of myofibroblasts is their contractile function. As myofibroblasts contract, tissue stiffness will likely increase. Novel therapies that target this crosslinking process selectively in pathological states may prove attractive new therapies to counteract fibrosis. However, one potentially deleterious outcome is that normal (non-pathological) fibrillar matrix, such as found in skin, eye, or large vessels, becomes compromised.

Matrix signalling

While pericytes normally find themselves embedded in, and contribute to, a matrix environment which is an organized structure of the capillary basement membrane, when they become myofibroblasts, the matrix environment changes. Pericytes in health generate matrix rich in certain laminins (e.g. α4) and collagen IV, but pathological matrix comprises a different group of collagens and laminins. *In vitro* studies show that mesangial cells cultured on laminins found in normal basement membrane result in distinct cellular responses from those cultured on pathological laminins (Hansen and Abrass, 2003; Abrass et al., 2006). The matrix composition itself therefore dictates the phenotype and activation state of myofibroblasts.

Chronic leucocyte activation

Inflammatory leucocytes show levels of inappropriate activation in chronically inflamed tissues. This activation state can result in perpetuation of a fibrotic process by injuring or activating local cells including myofibroblasts, or by directly stimulating myofibroblasts with growth factors.

Epigenetic changes in myofibroblasts

Although this is an evolving area of research, there is early evidence that myofibroblasts undergo a number of epigenetic changes. These are modifications to the genomic DNA that render distinct chromosomal areas activated or inactivated compared with the precursor cells. Changes to the DNA can result in long-term phenotypic changes. One recent study identified a methylated part of the DNA that regulates expression of an inhibitor of the Ras signalling pathway. The Ras pathway is a signalling pathway that regulates activation and migration (Bechtel et al., 2010; Mann et al., 2010).

Cell senescence

Although cells can proliferate in response to injurious stimuli, many cells in the body have a limited capacity to proliferate, able to undergo a restricted number of cell cycles. Curtailed proliferation is known as senescence and is associated with DNA damage and accumulation of P16INK4a (Yang and Fogo, 2010). This process may be due to a shortening of the telomeres with each cell division, although alternative mechanisms involving DNA and mitochondrial damage appear to be more common. Senescence of epithelial cells, myofibroblasts and endothelial cells leads to abnormal cytokine generation and altered responses to injury that may perpetuate the fibrosing process (Yang et al., 2011).

Fibrosis, chronic kidney disease, and ageing

Population studies show that normal aged organs are fibrotic. Frequently this fibrosis is silent. The glomeruli and interstitial compartment of kidney are no exception (Rule et al., 2010). Aged animals maintained in a sterile facility also show fibrosis in the kidney with ageing. This process can be retarded by caloric restriction (Hernandez-Corbacho et al., 2011).

The fibrotic process of ageing, shows similar pathological features with CKD, in particular there is loss (rarefaction) of capillaries (Abrass et al., 2010). One component of this process is the glycation of proteoglycans or the presence of oxidized fatty acids in the circulation that stimulate cell activation. Another is the wear and tear of the vasculature that occurs with pressure changes, flow changes, changes that result in pericyte and endothelial activation leading to capillary instability. Another is the decline of silent regenerative and remodelling processes that occur including changes in the turnover of cell membranes, and another is the progression to cell senescence.

Studies in animals suggest that *ad libitum* diets promote cell stress responses that lead to greater production of oxygen radicals, and mitochondrial injury in aged cells than in younger cells. Oxygen radicals stimulate cell activation and injury. All of these features promote pericyte/myofibroblast activation and the fibrotic process (Chen et al., 2009; Mishra et al., 2009; Hasegawa et al., 2010; Romano et al., 2010).

New findings indicate that the pathological fibrotic milieu leads to chromosomal instability in epithelial cells and renders them at risk of neoplastic change, in multiple organs including lung and liver. It is likely that this is true in kidney also, and patients with kidney disease are at elevated risk of developing many cancers including renal cell carcinomas (Boland et al., 2005; Walser et al., 2008; Yan et al., 2009).

One intriguing possibility is that whereas the pericytes are essentially nurse cells for the endothelium and, when they become activated myofibroblasts, they lose those nursing functions, pericytes may also provide homeostatic signals to epithelium, maintaining them in a quiescent state. Following pericyte activation to myofibroblasts, the epithelial cells are now in a toxic inflammatory environment, but they have lost vital homeostatic signals from the pericyte population. While other possible explanations exist, one additional benefit that might result from treating fibrogenesis is a reduced risk of the development of cancer.

References

Abrass, C. K. (2000). The nature of chronic progressive nephropathy in aging rats. *Adv Ren Replace Ther*, 7(1), 4–10.

Abrass, C. K., Berfield, A. K., Ryan, M. C., *et al.* (2006). Abnormal development of glomerular endothelial and mesangial cells in mice with targeted disruption of the lama3 gene. *Kidney Int*, 70(6), 1062–71.

Abrass, C. K., Hansen, K., Popov, V., *et al.* (2010). Alterations in chromatin are associated with increases in collagen III expression in aging nephropathy. *Am J Physiol Renal Physiol*, 300(2), F531–9.

Alpers, C. E., Hudkins, K. L., Floege, J., *et al.* (1994). Human renal cortical interstitial cells with some features of smooth muscle cells participate in tubulointerstitial and crescentic glomerular injury. *J Am Soc Nephrol*, 5(2), 201–9.

Amara, N., Goven, D., Prost, F., *et al.* (2010). NOX4/NADPH oxidase expression is increased in pulmonary fibroblasts from patients with idiopathic pulmonary fibrosis and mediates TGFbeta1-induced fibroblast differentiation into myofibroblasts. *Thorax*, 65(8), 733–8.

Appel, D., Kershaw, D. B., Smeets, B., *et al.* (2009). Recruitment of podocytes from glomerular parietal epithelial cells. *J Am Soc Nephrol*, 20(2), 333–43.

Armulik, A., Abramsson, A., and Betsholtz, C. (2005). Endothelial/pericyte interactions. *Circ Res*, 97(6), 512–23.

Asada, N., Takase, M., Nakamura, J., *et al.* (2011). Dysfunction of fibroblasts of extrarenal origin underlies renal fibrosis and renal anemia in mice. *J Clin Invest*, 121(10), 3981–90.

Bechtel, W., McGoohan, S., Zeisberg, E. M., *et al.* (2010). Methylation determines fibroblast activation and fibrogenesis in the kidney. *Nat Med*, 16(5), 544–50.

Boland, C. R., Luciani, M. G., Gasche, C., *et al.* (2005). Infection, inflammation, and gastrointestinal cancer. *Gut*, 54(9), 1321–31.

Chau, B. N., Xin, C., Hartner, J., *et al.* (2012). MicroRNA-21 promotes fibrosis of the kidney by silencing metabolic pathways. *Sci Transl Med*, 4(121), 121ra18.

Chen, Y. F., Kao, C. H., Kirby, R., *et al.* (2009). Cisd2 mediates mitochondrial integrity and life span in mammals. *Autophagy*, 5(7), 1043–5.

Christopher-Stine, L., Siedner, M., Lin, J., *et al.* (2007). Renal biopsy in lupus patients with low levels of proteinuria. *J Rheumatol*, 34(2), 332–5.

Cucoranu, I., Clempus, R., Dikalova, A., *et al.* (2005). NAD(P)H oxidase 4 mediates transforming growth factor-beta1-induced differentiation of cardiac fibroblasts into myofibroblasts. *Circ Res*, 97(9), 900–7.

Cybulsky, A. V. (2009). Endoplasmic reticulum stress in proteinuric kidney disease. *Kidney Int*, 77(3), 187–93.

Deguchi, T., Takemoto, M., Uehara, N., *et al.* (2005). Renal clearance of endogenous hippurate correlates with expression levels of renal organic anion transporters in uremic rats. *J Pharmacol Exp Ther*, 314(2), 932–8.

Dou, L., Bertrand, E., Cerini, C., *et al.* (2004). The uremic solutes p-cresol and indoxyl sulfate inhibit endothelial proliferation and wound repair. *Kidney Int*, 65(2), 442–51.

Duffield, J. S. (2010). Macrophages and immunologic inflammation of the kidney. *Semin Nephrol*, 30(3), 234–54.

Duffield, J. S. and Bonventre, J. V. (2005). Acute renal failure: bench to bedside. In B. J. Pereira, M. H. Sayegh, and P. Blake (eds.) *Chronic Kidney Disease, Dialysis and Transplantation*, pp. 765–86. Philadelphia, PA: Elsevier Saunders.

Enomoto, A. and Niwa, T. (2007). Roles of organic anion transporters in the progression of chronic renal failure. *Ther Apher Dial*, 11 Suppl 1, S27–31.

Franquesa, M., Alperovich, G., Herrero-Fresneda, I., *et al.* (2005). Direct electrotransfer of hHGF gene into kidney ameliorates ischemic acute renal failure. *Gene Ther*, 12(21), 1551–8.

Friedman, S. L., Sheppard, D., Duffield, J. S., *et al.* (2013). Therapy for fibrotic diseases: nearing the start line. *Science Trans Med*, 5(167), 167sr1.

Gelati, M., Aplin, A. C., Fogel, E., *et al.* (2008). The angiogenic response of the aorta to injury and inflammatory cytokines requires macrophages. *J Immunol*, 181(8), 5711–19.

Georges, P. C., J. J. Hui, *et al.* (2007). Increased stiffness of the rat liver precedes matrix deposition: implications for fibrosis. *Am J Physiol Gastrointest Liver Physiol*, 293(6), G1147–54.

Glod, J., Kobiler, D., Noel., M, *et al.* (2006). Monocytes form a vascular barrier and participate in vessel repair after brain injury. *Blood*, 107(3), 940–6.

Grgic, I., Duffield, J. S., and Humphreys, B. D. (2011). The origin of interstitial myofibroblasts in chronic kidney disease. *Pediatr Nephrol*, 27(2), 183–93.

Han, W. K., Waikar, S. S., Johnson, A., *et al.* (2008). Urinary biomarkers in the early diagnosis of acute kidney injury. *Kidney Int*, 73(7), 863–9.

Hansen, K. and Abrass, C. K. (2003). Laminin-8/9 is synthesized by rat glomerular mesangial cells and is required for PDGF-induced mesangial cell migration. *Kidney Int*, 64(1), 110–18.

Hasegawa, K., Wakino, S., Yoshioka, K., *et al.* (2010). Kidney-specific overexpression of Sirt1 protects against acute kidney injury by retaining peroxisome function. *J Biol Chem*, 285(17), 13045–56.

Hecker, L., Vittal, R., Jones, T., *et al.* (2009). NADPH oxidase-4 mediates myofibroblast activation and fibrogenic responses to lung injury. *Nat Med*, 15(9), 1077–81.

Hernandez-Corbacho, M. J., Jenkins, R. W., Clarke, C. J., *et al.* (2011). Accumulation of long-chain glycosphingolipids during aging is prevented by caloric restriction. *PLoS One*, 6(6), e20411.

Hostetter, T. H., Olson, J. L., Rennke, H. G., *et al.* (1981). Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol*, 241(1), F85–93.

Humphreys, B. D., Czerniak, S., DiRocco, D. P., *et al.* (2011). Repair of injured proximal tubule does not involve specialized progenitors. *Proc Natl Acad Sci U S A*, 108(22), 9226–31.

Humphreys, B. D., Lin, S. L., Kobayashi, A., *et al.* (2010). Fate tracing reveals the pericyte and not epithelial origin of myofibroblasts in kidney fibrosis. *Am J Pathol*, 176(1), 85–97.

Humphreys, B. D., Valerius, M. T., Kobayashi, A., *et al.* (2008). Intrinsic epithelial cells repair the kidney after injury. *Cell Stem Cell*, 2(3), 284–91.

Ichimura, T., Asseldonk, E. J., Humphreys, B. D., *et al.* (2008). Kidney injury molecule-1 is a phosphatidylserine receptor that confers a phagocytic phenotype on epithelial cells. *J Clin Invest*, 118(5), 1657–68.

Ishani, A., Xue, J. L., Himmelfarb, J., *et al.* (2009). Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol*, 20(1), 223–8.

Johnson, R. J., Floege, J., Yoshimura, A., *et al.* (1992). The activated mesangial cell: a glomerular "myofibroblast"? *J Am Soc Nephrol*, 2(10 Suppl), S190–7.

Johnson, R. J., Herrera-Acosta, J., Schreiner, G. F., *et al.* (2002). Subtle acquired renal injury as a mechanism of salt-sensitive hypertension. *N Engl J Med*, 346(12), 913–23.

Karihaloo, A., Karumanchi, S. A., Cantley, W. L., *et al.* (2005). Vascular endothelial growth factor induces branching morphogenesis/tubulogenesis in renal epithelial cells in a neuropilin-dependent fashion. *Mol Cell Biol*, 25(17), 7441–8.

Kobayashi, T., Terada, Y., Kuwana, H., *et al.* (2008). Expression and function of the Delta-1/Notch-2/Hes-1 pathway during experimental acute kidney injury. *Kidney Int*, 73(11), 1240–50.

Lee, S., Huen, S., Nishio, H., *et al.* (2011). Distinct macrophage phenotypes contribute to kidney injury and repair. *J Am Soc Nephrol*, 22(2), 317–26.

Li, B., Cohen, A., Hudson, T. E., *et al.* (2010). Mobilized human hematopoietic stem/progenitor cells promote kidney repair after ischemia/reperfusion injury. *Circulation*, 121(20), 2211–20.

Lin, S. L., Chang, F. C., Schrimpf, C., *et al.* (2011). Targeting endothelium-pericyte cross talk by inhibiting VEGF receptor signaling attenuates kidney microvascular rarefaction and fibrosis. *Am J Pathol*, 178(2), 911–23.

Lin, S. L., Kisseleva, T., Brenner, D. A., *et al.* (2008). Pericytes and perivascular fibroblasts are the primary source of collagen-producing cells in obstructive fibrosis of the kidney. *Am J Pathol*, 173(6), 1617–27.

Lin, S. L., Li, B., Rao, S., *et al.* (2010). Macrophage Wnt7b is critical for kidney repair and regeneration. *Proc Natl Acad Sci U S A*, 107(9), 4194–9.

Lupher, M. L., Jr. and Gallatin, W. M. (2006). Regulation of fibrosis by the immune system. *Adv Immunol*, 89, 245–88.

Ma, L. J. and Fogo, A. B. (2007). Modulation of glomerulosclerosis. *Semin Immunopathol*, 29(4), 385–95.

Mann, J., Chu, D. C., Maxwell, A., *et al.* (2010). MeCP2 controls an epigenetic pathway that promotes myofibroblast transdifferentiation and fibrosis. *Gastroenterology*, 138(2), 705–14, 714 e1–4.

Mishra, P. K., Raghuram, G. V., Panwar, H., *et al.* (2009). Mitochondrial oxidative stress elicits chromosomal instability after exposure to isocyanates in human kidney epithelial cells. *Free Radic Res*, 43(8), 718–28.

Moeller, M. J., Soofi, A., Hartmann, I., *et al.* (2004). Podocytes populate cellular crescents in a murine model of inflammatory glomerulonephritis. *J Am Soc Nephrol*, 15(1), 61–7.

Ohtsuki, S., Asaba, H., Takanaga, H., *et al.* (2002). Role of blood-brain barrier organic anion transporter 3 (OAT3) in the efflux of indoxyl sulfate, a uremic toxin: its involvement in neurotransmitter metabolite clearance from the brain. *J Neurochem*, 83(1), 57–66.

Olsen, A. L., Bloomer, S. A., Chan, E. P., *et al.* (2011). Hepatic stellate cells require a stiff environment for myofibroblastic differentiation. *Am J Physiol Gastrointest Liver Physiol*, 301(1), G110–18.

Pippin, J. W., Sparks, M. A., Glenn, S. T., *et al.* (2013). Juxta-glomerular cells are progenitors of podocytes and parietal epithelial cells in experimental glomerular disease. *J Am Soc Nephrol*, 183(2), 542–57.

Racusen, L. C. and Regele, H. (2010). The pathology of chronic allograft dysfunction. *Kidney Int Suppl*, 119, S27–32.

Rodriguez-Iturbe, B. and Johnson, R. J. (2010). The role of renal microvascular disease and interstitial inflammation in salt-sensitive hypertension. *Hypertens Res*, 33(10), 975–80.

Romano, A. D., Serviddio, G., de Matthaeis, A., *et al.* (2010). Oxidative stress and aging. *J Nephrol*, 23 Suppl 15, S29–36.

Rule, A. D., Amer, H., Cornell, L. D., *et al.* (2010). The association between age and nephrosclerosis on renal biopsy among healthy adults. *Ann Intern Med*, 152(9), 561–7.

Scarlatti, F., Granata, R., Meijer, A. J., *et al.* (2009). Does autophagy have a license to kill mammalian cells? *Cell Death Differ*, 16(1), 12–20.

Schrimpf, C. and Duffield, J. S. (2011). Mechanisms of fibrosis: the role of the pericyte. *Curr Opin Nephrol Hypertens*, 20(3), 297–305.

Schrimpf, C., Xin, C., Campanholle, G., *et al.* (2012). Pericyte TIMP3 and ADAMTS1 modulate vascular stability after kidney injury. *J Am Soc Nephrol*, 23(5), 868–83.

Shkreli, M., Sarin, K. Y., Pech, M. F., *et al.* (2011). Reversible cell-cycle entry in adult kidney podocytes through regulated control of telomerase and Wnt signaling. *Nat Med*, 18(1), 111–19.

Sirin, Y. and Susztak, K. (2011). Notch in the kidney: development and disease. *J Pathol*, 226(2), 394–403.

Snyder, J. J., Foley, R. N., and Collins, A. J. (2009). Prevalence of CKD in the United States: a sensitivity analysis using the National Health and Nutrition Examination Survey (NHANES) 1999–2004. *Am J Kidney Dis*, 53(2), 218–28.

Stefater, J. A., 3rd, Lewkowich, I., Rao, S., *et al.* (2011). Regulation of angiogenesis by a non-canonical Wnt-Flt1 pathway in myeloid cells. *Nature*, 474(7352), 511–15.

Takabatake, T., Ohta, H., Hara, H., *et al.* (1983). Activation of tubuloglomerular feedback in rat nephrons by sera from rabbits with fulminant hepatic failure. *Nephron*, 35(2), 136–9.

United States Renal Data System (2011). USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. <http://www.usrds.org/atlas.aspx>

Walser, T., Cui, X., Yanagawa, J., *et al.* (2008). Smoking and lung cancer: the role of inflammation. *Proc Am Thorac Soc*, 5(8), 811–15.

Wang, Z., Chen, J. K., Wang, S. W., *et al.* (2003). Importance of functional EGF receptors in recovery from acute nephrotoxic injury. *J Am Soc Nephrol*, 14(12), 3147–54.

Wunderlich, P. F., Brunner, F. P., Davis, J. M., *et al.* (1980). Feedback activation in rat nephrons by sera from patients with acute renal failure. *Kidney Int*, 17(4), 497–506.

Yan, B., Peng, Y., and Li, C. Y. (2009). Molecular analysis of genetic instability caused by chronic inflammation. *Methods Mol Biol*, 512, 15–28.

Yang, H. and Fogo, A. B. (2010). Cell senescence in the aging kidney. *J Am Soc Nephrol*, 21(9), 1436–9.

Yang, H. C., Rossini, M., Ma, L. J., *et al.* (2011). Cells derived from young bone marrow alleviate renal aging. *J Am Soc Nephrol*, 22(11), 2028–36.

Yang, L., Besschetnova, T. Y., Brooks, C. R., *et al.* (2010). Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury. *Nat Med*, 16(5), 535–43, 1p following 143.

Zeisberg, M. and Duffield, J. S. (2010). Resolved: EMT produces fibroblasts in the kidney. *J Am Soc Nephrol*, 21(8), 1247–53.

CHAPTER 141

Modality selection for renal replacement therapy

Raj Thuraisingham and Cormac Breen

Introduction

Most patients with advanced chronic kidney disease (CKD) experience a steady and progressive loss of kidney function to the point where renal replacement therapy (RRT) is required to sustain life (Fig. 141.1). The choice of RRT modality is of great importance and in many ways defines the management of CKD. In countries with well-developed renal services, the backbone that underpins the care of such patients is the low-clearance or pre-dialysis clinic in the case of patients with known CKD. In most centres this is a multidisciplinary clinic that includes nephrologists, specialist nurses, dieticians, and often psychologists and social workers. One of the aims of the clinic should be to inform patients of the choices available to them and guide them through the complex decision-making process such that they are able to start their chosen treatment modality in a timely fashion. The methods and timing of information delivery need to be considered very carefully as they can profoundly influence the paths and outcomes patients experience. Patients who present late crucially miss out on this process and it is clear that they suffer as a result, proving the value of such schemes (Stack, 2003).

The presence of a pre-dialysis or low-clearance clinic does not, however, always ensure favourable outcomes. Numerous studies have explored methods to improve the processes in such clinics. Many have suggested that patients are not provided with sufficient information on treatment options (Mehrotra et al., 2005). Along with the quantity and quality, when the information is delivered has profound long-term implications as it is clear that the initial mode of therapy often determines patients' long-term dialysis modality (Morton et al., 2010). Detailed analysis of qualitative data has shown that there is great inertia on the part of both clinicians and patients to move from one modality to another and, as the default position in many centres is haemodialysis (HD), there often is a systematic bias away from peritoneal dialysis (PD) and other home-based treatments, especially in patients who present late (Saggi et al., 2012). Not only is the timing of information provision important, the way patients are presented with the information can have a profound influence as factors such as medical and nursing bias will often steer patients towards particular treatment modalities (Morton et al., 2010). Novel ideas such as using established patients as mentors to help ease new patients through this difficult time has been shown to be of some benefit (Morton et al., 2010).

Interventions such as creating vascular access often mean that other treatment modalities are never considered. This is especially important as many guidelines suggest that patients have their vascular access created early to avoid starting dialysis with central venous catheters (CVCs). This raises another issue. In the elderly the likelihood of a patient with stage 4 CKD dying prior to needing dialysis is far in excess of those who eventually progress to dialysis. If all the patients with stage 4 opting of HD have vascular access procedures in a timely manner, many of these will never be used (O'Hare et al., 2007).

In England alone, £1 of every £77 spent by the National Health Service (NHS) is for the care of kidney patients (NHS Kidney Care Report, 2012, It is therefore not surprising that in less affluent countries, socioeconomic factors play a vital role in the treatment of patient with stage 5 CKD with dialysis not being generally available for many patients with CKD. Transplantation however is more cost-effective and provides patients with a better quality of life and allows them to contribute economically to their families and society; however, deceased donor programmes are not fully established in the less affluent nations.

Even in developed nations, socioeconomic factors have been shown to play a role in the choice of RRT modality in that patients from more deprived backgrounds may be less likely to be referred for transplantation (Udayaraj et al., 2010, 2012). Also factors such as poor quality of housing may limit the ability of patients to undertake home-based treatment modalities such as PD and home HD.

From the clinicians' perspective, there are two key scenarios to consider for patients with CKD. First, is the patient who is referred in a timely manner to renal services prior to developing CKD stage 5 disease. Second, is the patient who presents late or 'crash-lands'. The options open to an individual patient in these two scenarios are often different and renal services need to have pathways to cope with both.

The planned care pathway

These patients tend to be managed in a multidisciplinary clinic setting which serves two purposes: the medical supervision of the patient, and the preparation for RRT. This is an important period in the overall management of the patient with CKD with the patient invited to make decisions about the type of RRT they receive.

In the ideal pathway towards RRT the rate of decline of kidney function will be slowed sufficiently to allow for unhurried decision-making. An initial role of the clinical assessment, alongside management to slow progression of CKD and manage complications, is to assess which treatment options are suitable for that patient. This allows for appropriate treatment options to be

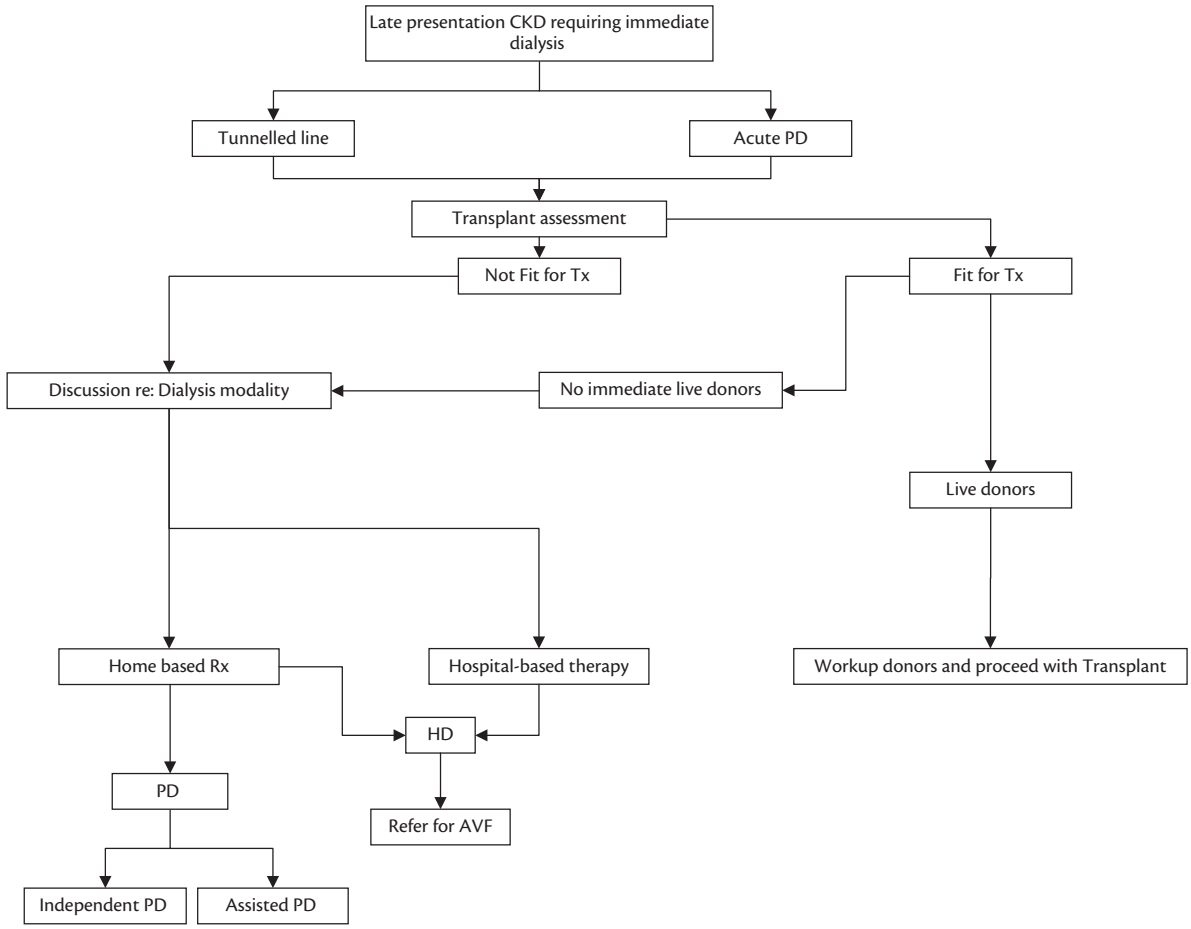

Fig. 141.1 Modality selection for late presentation CKD requiring immediate renal replacement therapy.

discussed, and for the decisions to be appropriately individualized to each patient and their circumstances. It is increasingly common for this to include an assessment of whether the patient is suitable for or wishes to undertake a RRT modality at all. Once the initial clinical assessments and patient choices have been made there will be a focus on preparing the patient for these treatments.

These discussions and the choice of treatment modality that they facilitate are best undertaken in a dedicated clinic with the involvement of the multidisciplinary kidney care team. Much of this will be shared between the nephrologist and specialist renal nurses, but access to other professionals, including psychologists and social workers, give important support to the process and help to address other aspects of the patient's situation that can impact of the choice of treatment.

Transplantation

Kidney transplantation is the gold standard treatment for patients with CKD stage 5. This was a long-held view but it was not until 1999 that Wolfe et al. demonstrated the survival benefits of transplantation conclusively (Wolfe et al., 1999). This study was based on patients on the transplant waiting list and compared those remaining on dialysis to first-time recipients of deceased donor kidneys. It showed that those transplanted enjoyed better long-term outcomes compared to those on dialysis. Subsequently others have shown similar data but again only for first-time recipients of deceased donor kidneys (Oniscu et al., 2005). Data from the UK Renal Registry and NHS Blood and Transplant provided further information and was able to look at the benefits stratified by recipient risk and this showed that low- and medium-risk subjects experienced benefit in terms of increased longevity; however, this was not clearly demonstrated in high-risk recipients. This was based on patients awaiting their first deceased donor transplant (Udarayaj *et al.*, 2010). The outcomes may be different if the transplants are performed pre-emptively and from live donors. Also there is less information available for the benefits of transplantation compared to dialysis for recipients of second and subsequent grafts.

Given the benefits of transplantation, patients deemed suitable should be assessed as early as possible for this treatment modality. Ideally this should be discussed at the same time that dialysis modalities are deliberated. If live donors are available then their work up should proceed as soon as the patient is deemed suitable for transplantation. If the donor workup suggests that a live donor transplant is a possibility then there is no need for advanced planning for dialysis as a pre-emptive transplant should be aimed for. If no live donor is available and after workup, the patient should be listed on the deceased donor list according to local/national rules. In the United Kingdom, for instance, they should be listed 6 months before their anticipated dialysis start date.

The timing of a kidney transplant does have some bearing on the long-term outcome of transplantation. There is good evidence that the earlier a transplant is carried out in a patient's time on dialysis, the better the long-term graft survival. In paired donor kidney analysis, kidneys transplanted from deceased donors into patients on dialysis for < 6 months had better long-term graft survival compared to the contralateral kidney transplanted into patients on dialysis for > 2 years (Meier-Kriesche and Kaplan, 2002). Other studies support this information with both living and deceased donor transplantation pre-emptively being associated with better outcomes for graft (25% for deceased and 27% for living) and patient survival (16% of deceased and 31% for living) compared to transplant performed after commencing dialysis (Kasiske et al., 2002).

For patients with type I diabetes, if fit enough, a pre-emptive simultaneous kidney–pancreas transplant is the treatment of choice. Allocation schemes, however, vary from country to country and in some the waiting times may be prolonged in which case a living donor kidney followed by a deceased donor pancreas may be the best treatment.

Dialysis

The education about and planning for dialysis will usually be undertaken in the majority of patients with advanced CKD, although how this is approached may vary depending on the preferred treatment option. Patients aiming for pre-emptive transplantation will need to know what type of dialysis they may fall back on if their proposed transplant fails to transpire or if they progress faster than expected. Patients choosing conservative care should in many cases know what dialysis involves as part of the process of choosing not to undertake it.

For those patients where dialysis is likely to be necessary there are number of factors that go into making the choice of dialysis modality. Clinical factors including the patient's underlying disease, the presence and severity of comorbid conditions, and the duration of which dialysis is likely to be needed will often influence the clinical recommendation of one modality over another. It is especially important to recognize clinical reasons why a patient may not be able to have PD at an early stage, including ones that should be readily apparent such as a history of major abdominal surgery.

Personal and social factors will also play an important role, particularly around the location and frequency of treatment they are able to undertake; ideally this should take into account dependents and carers of the patient. Long-term goals and aspirations of the patient are increasingly taking an important position in the decision-making process. Taking each of these factors into account allows for a holistic assessment of the patient and helps to support the patient's decisions.

Initial discussions will often focus on determining the choice of dialysis modality, this resting between PD and HD. This approach assumes that each treatment option is suited to different patient characteristics, and that clinical criteria can be used to judge patient suitability. Although this approach can confirm whether patients are potentially suitable for PD, these are a rather narrow set of criteria for judging the correct choice of modality. Identifying clinical reasons why PD may not be possible is an important part of the selection process to avoid patients unsuitable for PD being offered this as a treatment option.

It is becoming increasingly common for the discussion about the dialysis modality to initially focus on the setting of treatment that best suits the patient, particularly whether the patient wishes to or is able to undertake treatment at home. This reflects the growing recognition of the benefits and cost-effectiveness of domiciliary therapies. If home treatment is possible then the patient is able to make a direct choice between PD and HD, taking into account clinical advice and the other opportunities that each modality can offer.

Peritoneal dialysis

If the choice is made to have dialysis at home, it is necessary to choose the type of dialysis. PD is, by design, a home-based treatment so any patient choosing this treatment needs to have living accommodation that meets the requirements. These include a clean and safe environment, a suitable room to undertake treatment, and sufficient space for storing fluids and other supplies. It is also necessary to choose between the two most common types, continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). The initial choice is usually a lifestyle decision, based on convenience, work, and other social factors.

Another frequent reason for patients choosing PD is the flexibility that this modality offers for travel. This travel may include short trips, including business travel, and for longer holidays. The availability of arrangements for delivery of consumables to a variety of locations is an attractive option for a number of patients. This can help maintain the flexible approach to treatment when travelling, and avoid the need otherwise to book dialysis treatment during trips. It also minimizes the risk of acquiring blood-borne infections whilst dialysing abroad.

Most patients selecting PD will be expected to learn the technique themselves during training and be self-caring. Assessment of patients will usually take into account manual dexterity and intellectual capability amongst other factors. Some patients, including the young and elderly, will only be able to undertake some of the supervision of their treatment, and in these cases a carer who is able to undertake the treatment on their behalf will usually be identified.

For frailer patients or those requiring other care in addition to dialysis, assisted APD with dialysis procedures being undertaken by healthcare professionals may be a useful option. This helps patients who wish to undertake dialysis but are unable to manage the treatment themselves and do not have a suitable carer, avoiding the need for centre-based HD.

Home haemodialysis

Other patients choosing to dialyse at home will do this by using HD. Although home HD has had low uptake for many years it has recently become a more common choice of modality. In addition to the standard preparation for HD, patients have to undergo a period of training in the treatment technique. The patient has to be capable of undertaking the physical requirements of the treatment, including the insertion of dialysis needles into the fistula. Other requirements include a suitable home environment with sufficient space for the dialysis equipment and for storing supplies. Patients must also be able to authorize home conversion works allowing a water supply and drainage to be brought to the proposed location of the dialysis machine; this is usually possible for homeowners but

can prove more difficult for patients living in temporary or rented accommodation.

An important factor here is the presence or absence of a partner or carer, and the clinical and technical dialysis teams will usually meet them early in the selection process, either in the clinic or at a home visit. Although carers are usually not regarded as mandatory for patients starting home dialysis, and ideally, unless this is planned in advance, patients should be self-caring with their dialysis treatment in most instances, it is important that the views of other people living with the patient are taken into account at this planning and selection stage. If, as is sometimes the case, some or all of the dialysis treatment is to be delivered by a carer then they need to be assessed in a similar way to self-caring patients and able to deliver the physical requirements of the dialysis process.

If the patient is able to meet these criteria, the next decisions are to choose the treatment system and the likely dialysis schedule. Conventional HD machines, similar to those used for in-centre dialysis, have the greatest requirement for space and home adaptation, and offer the widest range of potential treatment schedules. If the home environment is suitable these machines can be placed in a location to support whichever schedule is most suitable for the individual patient. Although in the past many patients were commenced on the same thrice-weekly schedule that they would have with in-centre treatment, it is more typical for the patient to dialyse at least on alternate days, thereby avoiding the 3-day gap between treatments, and many choose schedules that are either more frequent or for longer duration.

Increasingly patients have a wider range of dialysis systems to choose from with new systems having been designed more specifically for use in the home setting. These newer systems offer variations on the standard dialysis setup and procedure which may be more appealing to some patients, with the potential of machines fitting into a smaller space, requiring less permanent home adjustments, and the potential of more portability.

Selecting the dialysis schedule is influenced by clinical and lifestyle factors. Patients new to dialysis with preserved residual renal function or who are planned to receive a kidney transplant and therefore not likely to spend a long time on dialysis will often be suitable for a shorter duration intermittent dialysis schedule. The choice of longer treatment times offers them less overt clinical benefit in the short term. It is reasonable to allow lifestyle factors to guide the choice of treatment schedule, especially where daily or nocturnal treatment might facilitate working or study. Conversely, patients who are likely to spend a prolonged time receiving dialysis, such as those in whom transplantation is not contemplated, commencing from the outset on a higher dose or more frequent treatment is clinically appropriate, particularly if this also is able to support the lifestyle and work needs of the patient.

In-centre haemodialysis

In patients choosing not to or unable to have dialysis at home, the only dialysis choice is for in-centre treatment. For many patients this will be an active choice. The convenience of a dialysis centre, particularly as these are often provided in community settings relatively close to the patient's home, will often be appealing. These centres will generally provide dialysis with full nursing care, but patients can often choose to learn self-care dialysis and gain flexibility in scheduling if they can undertake their dialysis independent of nursing care. Some dialysis centres accommodate this, such as allowing independent patients to dialyse on evening shifts, or allowing patients to agree and change their dialysis schedule by agreement with other self-caring patients. This flexibility of scheduling can be an important factor for patients with work, study, or family commitments, and may contribute to the choice of a dialysis centre.

For a small proportion of the patients commencing RRT there will be very little choice about dialysis modality. In most of these cases there will be a clear clinical reason, such as medical or psychiatric illness that affects their stability during treatment or requires additional clinical support only available in a main hospital centre. Limitations on mobility that cause difficulties in accessing a dialysis centre or needing to lie down during treatment, or the presence of an active viral illness for which isolation facilities are only available in a main centre are other reasons. The other significant group are those for whom the presence of a violent psychological or behavioural condition means that the safety of dialysis staff and other patients requires the presence of adequate security personnel.

Conservative kidney care

Although not strictly a treatment modality, the choice of patients approaching end-stage kidney disease not to receive RRT is one that is becoming more common. This reflects the increasingly large number of elderly patients with significant co-morbidity developing advanced stages of CKD, although patients choosing to have conservative care do not always have a significant burden of other disease.

The planning for conservative kidney care will usually start somewhat in advance of the patient reaching a conventional trigger to start RRT, often after they have received information and education about treatment choices. This planning should involve the patient's family from the outset to help ensure that the decision has been properly made. Once they have agreed to conservative treatment the patient continues to receive standard medical and nursing care, but in addition to that they will all often engage in a process of advanced decision-making. Dependent on local availability they may become engaged with specialist renal or general palliative care services, especially when kidney function deteriorates or they become symptomatic.

It is important for the patient selecting conservative care to know that this decision is not irrevocable. A proportion of patients change their mind as they near end-stage kidney disease, and at this stage it is important to take them again through the modality selection process, albeit at a faster pace than previously.

Timing the start of renal replacement treatment

The optimal time to start treatment varies between patients and between modalities. As indicated, the timing of transplantation from a living donor ideally should be pre-emptive (before the need for dialysis) and could arguably be undertaken before significant symptoms or complications of CKD are present. Patients suitable for transplantation but lacking a living kidney donor should be listed before they reach the need for dialysis, and in some cases may also be transplanted pre-emptively, although this is usually not

a common occurrence as in most countries there is a significant shortfall in the availability of deceased donor kidneys.

The timing of starting a dialysis modality may be due to a number of factors. Most commonly preparation for dialysis commences in advance of the predicted need for dialysis. This is most true for HD with the need for arteriovenous (AV) fistula formation in enough time to allow the blood flow and volume to develop adequately. PD catheter placement is usually deferred to nearer the anticipated start time, though some centres favour earlier placement.

Most commonly it is the increasing presence of symptoms that triggers the commencement of dialysis, and generally this will correspond to a decline in kidney function measured by glomerular filtration rate (GFR). Some patients will develop severe fluid retention unresponsive to diuretic therapy or electrolyte disturbances, particularly hyperkalaemia, that requires dialysis to start in the absence of symptoms.

The other trigger for commencing dialysis is decline in kidney function with a threshold being set for initiating treatment even in the absence of symptoms. This may not always be accepted by patients who do not feel unwell. There is no clear evidence that commencing patients at a certain level of kidney function, as compared to letting the treatment start be triggered by the development of symptoms, offers any improvement in immediate or longer-term outcome, nor indeed that being guided by symptoms leads to delays in starting dialysis for many patients. Indeed there is evolving data to suggest that patients starting dialysis with an estimated GFR of around 7 mL/min have better outcomes than those starting with higher estimated GFRs (Cooper et al., 2010).

Crash-lander pathway

Late presentation of CKD is the norm worldwide considering the burden of disease in the developing nations (Fig. 141.1). Studies from India indicate that up to 75% of patients are seen by a nephrologist for the first time within 3 months of requiring RRT (Parameswaran et al., 2011). In developed nations this figure is lower and falling; below 19% now in the United Kingdom (Gilg et al., 2014) and similar data comes from Australia and New Zealand where a direct relationship between economic status and late presentation has been demonstrated (Cass et al., 2002). The challenge with these patients is to provide them with the necessary information in order to establish them on their chosen mode of RRT in a timely fashion. In many cases this is not possible and frequently these patients are never appropriately 'educated'.

The other scenario that occurs is for patients to be known to nephrologists but nonetheless begin dialysis in an unplanned fashion. In a UK study, up to 49% of patients who were known to renal services for > 4 months still started dialysis as an emergency. Reasons for this included intercurrent illness requiring earlier than anticipated decline in function and delays in referral or timely access surgery (Buck et al., 2007).

Conservative management

Conservative management of renal failure or maximal medical therapy is still the most frequently deployed treatment modality for patients with CKD stage 5 worldwide given the costs of chronic dialysis, especially for patient who present late. Some patients in the developing world start on dialysis programmes but then withdraw for financial reasons (Parameswaran et al., 2011). In developed countries this does not generally occur, withdrawal from dialysis being largely based on non-financial factors. There is evidence that patients opting for conservative management in developed countries may have a better quality of life compared to dialysis with shorter survival however (Da Silva-Gane et al., 2012). Such data usually comes from the context of patients in a low-clearance clinic and hence is not applicable to patients presenting late. There is some evidence that patients presenting late to nephrologists have a poorer survival even in the context of conservative management (Ellam et al., 2009).

Haemodialysis

The usual modality provided for most patients who require an unplanned start to dialysis is HD. By the very nature of their presentation, vascular access is usually via a CVC, ideally tunnelled but usually untunnelled. The advantage of this method is that dialysis can be initiated in the time it takes to place a CVC. Life-threatening complications therefore can be treated rapidly and the patient's condition stabilized. The disadvantages, however, include sepsis related to the CVC (Astor et al., 2005; Patel et al., 2010) and complications of the insertion procedure, the latter can be minimized by using ultrasound-guided insertion techniques.

Once established on HD the aim should be for creation of an AV fistula as soon as possible unless the patient wishes to pursue PD or if there is the imminent prospect of a live donor transplant.

Peritoneal dialysis

In the past, 'hard catheter PD' was a commonly used modality for treating patients with late presentation of renal failure. This technique fell out of favour with better access to HD and the advent of CVCs. More recently, several publications have shown the feasibility of using PD as the initial dialysis modality in unplanned dialysis with outcomes comparable to that of HD (Koch et al., 2012). These patients who are referred late appear to do as well as patients who start PD in a planned fashioned (Fan et al., 2002).

Summary

The choice of RRT modality for those with CKD stage 5 is a complex one with many options open to patients. Guiding patients thorough these choices needs to be done sensitively and in a timely manner, taking into account the unique circumstances of the individual. The pre-dialysis multidisciplinary team needs to play a pivotal role in this process.

References

Astor, B. C., Eustace, J. A., Powe, N. R., *et al.* (2005). Type of vascular access and survival among incident hemodialysis patients: the Choice for Healthy Outcomes In Caring for ESRD (CHOICE) study. *J Am Soc Nephrol*, 16, 1449–55.

Buck, J., Baker, R., Cannaby, A. M., *et al.* (2007). Why do patients known to renal services still undergo urgent dialysis initiation? A cross-sectional survey. *Nephrol Dial Transplant*, 22(11), 3240–5.

Cass, A., Cunningham, J., Arnold, P. C., *et al.* (2002). Delayed referral to a nephrologist: outcomes among patients who survive at least one year on dialysis. *Med J Aust*, 177, 135–8.

Cooper, B. A., Branley, P., Bulfone, L., *et al.* (2010). A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med*, 363(7), 609–19.

Da Silva-Gane, M., Wellsted, D., Greenshields, H., *et al.* (2012). Quality of life and survival in patients with advanced kidney failure managed conservatively or by dialysis. *Clin J Am Soc Nephrol*, 12, 2002–9.

Ellam, T., El-Kossi, M., Prasanth, K. C., *et al.* (2009). Conservatively managed patients with stage 5 chronic kidney disease—outcomes from a single center experience. *QJM*, 102(8), 547–54.

Fan, S. L., Marsh, F. P., Raftery, M. J., *et al.* (2002). Do patients referred late for peritoneal dialysis do badly? *Perit Dial Int*, 22(5), 630–2.

Gilg, J., Pruthi, R., and Fogarty, G. (2014). UK Renal Replacement Therapy Incidence in 2013: National and Centre-Specific Analyses. *UK Renal Registry 17th Annual Report*. <https://www.renalreg.org/reports/2014-seventeenth-annual-report/>

Kasiske, B. L., Snyder, J. J., Matas, M. D., *et al.* (2002). Pre-emptive kidney transplantation: the advantage and the advantaged. *J Am Soc Nephrol*, 13, 1358–64.

Koch, M., Kohnle, M., Trapp, R., *et al.* (2012). Comparable outcome of acute unplanned peritoneal dialysis and haemodialysis. *Nephrol Dial Transplant*, 27(1), 375–80.

Mehrotra, R., Marsh, D., Vonesh, E., *et al.* (2005). Patient education and access of ESRD patients to renal replacement therapies beyond in-center hemodialysis. *Kidney Int*, 68(1), 378–90.

Meier-Kriesche, H. U. and Kaplan, B. (2002). Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: a paired donor kidney analysis. *Transplantation*, 74(10), 1377–81.

Morton, R. L., Tong, A., Howard, K., *et al.* (2010). The views of patients and carers in treatment decision making for chronic kidney disease: systematic review and thematic synthesis of qualitative studies. *BMJ*, 340, c112.

NHS Kidney Care (n.d.). Chronic Kidney Disease in England: The Human and Financial Cost. [Online] <http://webarchive.nationalarchives.gov.uk/20130504185629/http://kidneycare.nhs.uk/our_work_programmes/preventing_ill_health/chronic_kidney_disease_in_england_the_human_and_financial_cost/#>

O'Hare, A. M., Bertenthal, D., Walter, L. C., *et al.* (2007). When to refer patients with chronic kidney disease for vascular access surgery: should age be a consideration? *Kidney Int*, 71(6), 555–61.

Oniscu, G. C., Brown, H., and Forsythe, J. L. (2005). Impact of cadaveric renal transplantation on survival in patients listed for transplantation. *J Am Soc Nephrol*, 16(6), 1859–65.

Parameswaran, S., Geda, S. B., Rathi, M., *et al.* (2011). Referral pattern of end-stage renal disease patients and its impact on outcome at a public sector hospital. *Natl Med J India*, 24(4), 208–13.

Patel, P. R., Kallen, A. J., and Arduino, M. J. (2010). Epidemiology, surveillance, and prevention of bloodstream infections in hemodialysis patients. *Am J Kidney Dis*, 56, 566–77.

Saggi, S. J., Allon, M., Bernardini, J., *et al.* (2012). Considerations in the optimal preparation of patients for dialysis. *Nat Rev Nephrol*, 8(7), 381–9.

Stack, A. G. (2003). Impact of timing of nephrology referral and pre-ESRD care on mortality risk among new ESRD patients in the United States. *Am J Kidney Dis*, 41(2), 310–18.

Udayaraj, U., Ben-Shlomo, Y., Roderick, P., *et al.* (2010). Social deprivation, ethnicity, and access to the deceased donor kidney transplant waiting list in England and Wales. *Transplantation*, 90(3), 279–85.

Udayaraj, U., Ben-Shlomo, Y., Roderick, P., *et al.* (2012). Social deprivation, ethnicity, and uptake of living kidney donor transplantation in the United Kingdom. *Transplantation*, 93(6), 610–16.

Wolfe, R. A., Ashby, V. B., Milford, E. L., *et al.* (1999). Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med*, 341(23), 1725–30.

CHAPTER 142

Patient education and involvement in pre-dialysis management

Sue Cox and Nicola Thomas

Introduction

This chapter outlines the aims and potential benefits of timely education in pre-dialysis care and describes the methods and models of care that should be considered when delivering a high-quality education programme for patients and their families.

Aims

One of the aims of a pre-dialysis education programme is to provide objective information about the different treatment options, to allow individuals and their families to make decisions in partnership with clinicians on the optimal treatment for them.

Patient education

A pre-dialysis education programme has long been recognized as an integral part of care of people with established renal disease (Goovaerts et al., 2005). High-quality patient education is a fundamental part of any pre-dialysis service and is instrumental in supporting patients in understanding their kidney disease and the treatment choices available to them. The Renal National Service Framework (NSF) Part One specified that an individual should be cared for in a multidisciplinary clinic offering education and support 12 months before they reach end-stage kidney disease (ESKD) and subsequently require renal replacement therapy (RRT) (Department of Health, 2004).

Education and health promotion for people with stage 3 chronic kidney disease (CKD) should start in primary care and structured education programmes should be provided for people who have progressive stage 4 CKD and for people at stage 5 CKD. An accelerated educational package should also be provided for those starting dialysis as an emergency (Farrington and Warwick, 2010). The information provided at the pre-dialysis stage needs to be comprehensive. It should cover all aspects of care including delaying the progression of CKD, understanding CKD, and living with CKD. Information on treatment options should include benefits of living kidney donation and pre-emptive transplantation and home dialysis.

Standards one and two of the Renal NSF (Department of Health, 2004) focus on access to information that enables shared decision-making, encourages self-management, and ensures timely preparation for desired RRT minimizing complications and slowing progression. The Renal Association of the UK has produced several guidelines relevant to the pre-dialysis setting and these are outlined in Box 142.1.

Benefits of patient education

There are a number of important benefits that result from a timely, patient-centred, and well-organized pre-dialysis education programme. These benefits include better outcomes for patients, increased choice of modality, and opportunities for home therapies (Little et al., 2001; Department of Health, 2004; Marron et al., 2006; Mendelssohn et al., 2009).

It is suggested that those receiving RRT who commence treatment in a timely manner with permanent access have reduced complications, hospital admissions resulting in fewer deaths, improved quality of life (Yeoh et al., 2003; Goovaerts et al., 2005; Marron et al., 2006), and reduced healthcare costs (McLaughlin et al., 2001; Crooks, 2004). Those starting dialysis as an emergency and thus having limited access to education packages have been shown to have poorer outcomes (Ravani et al., 2003; Chan et al., 2007; Mendelssohn et al., 2009).

Starting pre-dialysis education early when the patient still feels well has many advantages and seems to be a significant factor in determining whether patients have an optimal or suboptimal dialysis start. Patients receiving education in a timely manner may be more likely to adopt behaviours that may delay the progression of their kidney disease and delay the initiation of RRT (Pagels et al., 2008; Davies, 2011). Patients are more likely to engage in behaviour to help manage cardiovascular risk and other co-morbid conditions as well as optimizing biochemistry, such as anaemia and phosphate control. Timely education has also shown a better understanding of medical conditions resulting in better health outcomes, increased adherence, and more empowered patient decision-making (Little et al., 2001; Rankin and Stallings, 2001; Goovaerts et al., 2005).

These benefits can result in patients starting on their treatment of choice including opting for non-dialytic therapy (maximum conservative management). The patient also has time to discuss treatment options with their family and friends, both of which have been shown to have a significant influence on the modality

Box 142.1 Renal Association guidelines (2010) for education during pre-dialysis care

- 'all patients with severe CKD (stage 5 and progressive stage 4) together with their families and carers, should be offered an appropriate education programme aimed at improving their knowledge and understanding of their condition, and of the options for treatment' (Guideline 4.1)
- 'all patients should be encouraged to perform home dialysis therapy where possible, as part of an integrated approach to renal replacement therapy' (Guideline 3.5)
- 'all medically suitable patients should be informed about the advantages of pre-emptive living kidney transplantation and efforts made to identify potential donor to allow pre-emptive transplantation before the need for renal replacement therapy' (Guideline 3.3)
- patients needing RRT within 3 months 'access an accelerated care pathway to deliver education, information and prepare for RRT' (Guideline 3.2) (Farrington, Mooney et al., 2014).

Box 142.2 Principles of shared decision-making

- *Support* patients to understand and articulate what they want to achieve from the RRT options available (their preferred outcome or goal).
- *Support* patients to articulate their current understanding of their condition.
- *Inform* patients about their condition, about the RRT options available and the benefits of each.
- *Support* patients to understand and articulate their own concepts of risk/harm.
- *Describe* what is known about risks or harm associated with the RRT options.
- *Ensure* that patients and clinicians arrive at a decision based on mutual understanding of this information.

Adapted from Coulter and Collins (2011, p. 12).

an individual chooses (Murray et al., 2009). These patients are likely to choose a mode of self-care dialysis, such as peritoneal dialysis, home haemodialysis, or have a pre-emptive transplant (Mendelssohn et al., 2009).

Patient involvement and shared decision-making

Shared decision-making is a process in which clinicians and patients work together to select tests, treatments, management, or support packages, based on clinical evidence and the patient's informed preferences. It involves the provision of evidence-based information about options, outcomes, and uncertainties, together with decision support counselling and a system for recording and implementing patients' informed preferences (Coulter and Collins, 2011).

The principles of a shared decision-making conversation are shown in Box 142.2

If patients are truly going to take part in the decision-making process (e.g. such as choosing the type of dialysis), it has been suggested that they need not only clear, comprehensible information about the condition and the treatment or support options, but also prompts to help them think about what the different options might mean for them and to reach an informed preference (Coulter and Collins, 2011). These prompts are called decision aids and work is ongoing to develop decision aids for people with kidney disease, including end-of-life care. (See 'Decision aids' later in this chapter.)

Models of care

Pre-dialysis information provided ideally needs to be incrementally built upon over time. The information and support provided to the patients prepares them, ensuring that they start on their treatment of choice in an ordered and timely way (NHS Institute for Innovation and Improvement, 2008).

Assessment and discussion about transplantation needs to occur in parallel with dialysis planning and, where possible, a pre-emptive live donor transplant as the goal. Discussions for transplantation need to start early to allow time for live donors to be assessed and necessary workup completed, and not all donors are suitable, extending the workup time as most units workup one donor at a time. If transplantation is not considered the best option this needs to be discussed with the individual to ensure clarity around transplant status and treatment planning (NHS Institute for Innovation and Improvement, 2008). Patients with a failing transplant graft also need to access the education and information given to those in pre-dialysis or advanced kidney care clinics (AKCCs).

It is now considered by many units as preferential to present dialysis options as home dialysis versus unit dialysis. This allows the patient to choose between hospital-based or home-based therapy rather than the specific details of haemodialysis versus peritoneal dialysis. The benefits of self-management and self-care must also be highlighted, including the clinical benefits of increased dialysis hours. Maximum conservative management should be discussed with all patients with appropriate links to palliative care or specialist renal palliative services.

The education provided needs to be multidisciplinary and multifaceted, addressing the individual needs of the diverse patient population. Access to a clinical psychologist and/or renal social workers can be invaluable at this time, providing information on living with kidney disease as well as general information on benefits and other social concerns. Patients not only face physiological changes but also psychological stress associated with chronic disease and long-term treatment (Pagels et al., 2008; Murray et al., 2009).

An overview of quality standards for the education team, processes, content/topics, media/material/funding and quality measurements for renal replacement therapy option education has been published by a group of experts (Goovaerts et al., 2014).

Assessment

In order for this high-level education to be provided at the right time, at the right level, and in the right format for the individual patient, there needs to be an efficient assessment process in place. Patients require information to be presented accurately and that is easily understood, comprehensive, and unbiased. This information then needs to be assimilated in agreement with the patient's own beliefs and values, which also must be acknowledged by the clinician (O'Connor et al., 1999; Marteau et al., 2001; Bekker et al., 2004). In order to achieve anything from the consultation it is vital that the patient's priorities are addressed initially so that the patient can then concentrate on the information being provided to them.

There are often many barriers preventing patients gaining optimal benefit from the education process. Assessment of an individual's readiness to learn before commencing education will help to ensure optimal benefit from the information given. There are many environmental, physical, and psychosocial barriers to learning (Chang and Kelly, 2007). Potential barriers that should be considered before teaching can commence include physical problems such as poor eyesight, cognitive impairment, poor literacy, and a range of psychosocial issues such as confidence in undertaking a self-care therapy.

It is difficult to assess a person's learning style in a busy clinical area, although taking the time to ask an individual about their preferred learning style could also benefit the patient, resulting in information and education being much more effective (Smith et al., 2007). Further information on differing learning styles can be found at http://en.wikipedia.org/wiki/Learning_styles

Once an individual's learning style has been assessed, a learning plan can be developed in partnership with the patient, focusing on aims of learning and how much information is wanted and when. The plan should be regularly reviewed with the patient until it is achieved.

Individualized planning

Patient-centred education is essential in order to achieve the desired outcome. There is often a mismatch between the patient's and clinician's goal of a consultation. Only 25% of patients want as much information as possible (Ormandy et al., 2007). Best practice should be to provide information that is 'relevant to the person, with the method, scale, pace and scope of the delivery being suited to the individual's learning style, capacity and preferences' (Farrington and Warwick, 2010, Guideline 4.2).

There are many factors that can affect and influence a patient's decision (Box 142.3) and family and friends play a major part in the decision process. If these influencing factors remain unresolved, these patients are more likely to delay making a decision, change their mind, or even portion blame to the healthcare providers (Murray et al., 2009).

Educational material, both in content and delivery, may sometimes need to be altered to meet the needs of a specific patient group. Two examples are the young adult (typically classified as 16–25-year-olds) and patients who present late and start RRT as an emergency or within 3 months of presenting to a renal unit for the first time (unplanned starts). The UK Renal Registry reports that 19% of all patients start RRT in an unplanned way (Gilg et al., 2010).

Box 142.3 Influencing factors on the decision-making process

- Knowledge gaps
- Lack of clarity of what matters most
- Knowing other's experience
- Self-perceived burden to family
- Uncertainty regarding outcomes—fear and disappointment
- Personal responsibility and personal risk/benefit ratios
- Preservation of current well-being and normality, quality of life
- Maintaining individuality
- Feeling pressured to make a decision
- Interpersonal relationships of both family and healthcare provider
- Provider/patient interactions
- Trust in providers
- Need for control and to manage situation (Murray et al., 2009).

These patients have little time for psychological preparation and often education is only given after the event, limiting patient choice and delaying transplant work up (NHS Institute for Innovation and Improvement, 2008). As a result, such patients require an accelerated education and preparation programme for RRT, mirroring that given to those patients in the pre-dialysis clinic/AKCC (Farrington and Warwick, 2010).

For the young adult group, the education format needs to be altered to have resonance to young adults and presented in a way that appeals to them (Korus et al., 2011), such as web-based material and use of social media. Individualized face-to-face consultations remain an effective way of providing education as some young people may not wish to participate in standard pre-dialysis education groups with older people. Establishing a separate young person's clinic may be beneficial to provide the opportunity for age-appropriate education and peer support.

Implementation

When delivering information, an individualized approach should be taken, utilizing a variety of educational tools that suit individual learning styles (NHS Institute for Innovation and Improvement, 2008; Warwick, Mooney et al., 2014). Information needs to be culturally sensitive, relevant to the local population, and may be required in different languages, large print, audio format, and Braille. The way information is provided and communicated influences choice far greater than the information itself. Those delivering the education programme need to have appropriate teaching and facilitation skills and healthcare providers may be unaware of the way in which everyday communication can bias decisions rather than facilitate patient choice (Bekker, 2010).

Ormandy et al. (2007) identified preferred ways in which pre-dialysis education could be delivered. Verbal information received face to face was the most preferred method, with 70% of patients wanting a relative or friend present. This format is best

Box 142.4 Reasons why patients might not attend group sessions

- Distance to travel to hospital
- Work commitments
- Language barriers or hearing difficulties
- Too distressing for the patient
- Not considered age appropriate
- 'Dr knows best' attitude
- Patient doesn't feel the need to consider treatment options
- Patient may feel embarrassed in larger groups
- One-to-one sessions preferred as can ask specific questions (Ormandy et al., 2007).

provided in both individual and group sessions. Visual aids, practical demonstrations, expert patients, and multidisciplinary involvement provide rich group education sessions. Patients may benefit from the discussion generated and the support networks formed during these sessions.

However, group sessions may not be suitable for all patients (see Box 142.4). Individual one-to-one sessions are then vital in overcoming some of these aspects and can be tailored to the individual's needs. These are usually provided by the pre-dialysis nurse and often at the time of existing outpatient appointments. Patients having attended the group sessions often benefit from a one-to-one session to consolidate and clarify any questions that have arisen. If appropriate, a treatment plan can be formulated with the patient at this point.

For patients that remain in pre-dialysis or AKCC and do not progress onto RRT for some time, an update or refresher session may be required due to advances in treatment or change in their own circumstances.

Take-home tools are a way of re-enforcing learning and facilitate discussion with family and friends. The following information tools can be used in both the group education sessions and individual sessions:

Written information

This can be a selection of short introductory leaflets or more comprehensive booklets, although often a selection of both is required. Many patients will want to find out more (Ollerenshaw, 2007) so signposting to further verified information is vital.

Visual tools

Pictorial tools can speak across cultural and language barriers. Examples are:

- Image library—images of local patients showing all aspects of treatment. These can be stored on computer or used as a flip chart.
- DVDs—many that are produced use a mixture of clinician explanations and patient stories covering a range of aspects for CKD stages 4–5. Examples of DVDs produced are:
  - 'Kidney Research UK'—modules one (stage 1 –3 CKD) and two (pre-dialysis) <https://www.kidneyresearchuk.org/health-information/resources/dvds>
  - 'Your Kidneys, Your Choice'—providing information on CKD and treatment choices promoting joint decision-making <http://www.mykidney.org/Videos/YourKidneys.aspx>
  - 'Living Life to the full on dialysis'—promoting dialysis self-care options <http://www.mykidney.org/Videos/LivingLife.aspx>
  - 'The Gift of Life'—providing information on living donation (Guys and St Thomas' NHS Foundation Trust, 2007)
  - Practical demonstrations—visits to dialysis units and demonstrations of both unit and home dialysis equipment.

Web-based material

Information from the Internet can provide broader information in alternative formats and in greater depths, including patient stories (e.g. <http://www.nhs.uk/Conditions/Kidney-disease-chronic/Pages/Introduction.aspx>). Support networks can also be formed online and social media is a growing form of providing information and education and also putting kidney patients in touch with each other.

Peer support

Patient-to-patient support often occurs informally in many renal units. By formalizing the process and providing specific peer support training, individuals can be put in contact with a peer supporter who has experience of a particular treatment or procedure, including kidney donation. Peer support provides the real lived experience for the patient at various stages in the pre-dialysis pathway, complementing the clinical information provided, and is reported as the most highly valued aspect of education (Colella and King, 2004; NHS Institute for Innovation and Improvement, 2008). Patients should be matched for lifestyle, age, and cultural background, which is one of the great strengths of peer support (Colella and King, 2004; Hughes et al., 2009). Patients have the option of one-to-one meetings or telephone consultations. Group peer support can be very beneficial for those who may feel uncomfortable on a one-to-one basis.

Decision aids

Patient decision aids are designed to help clinicians with shared patient-centred care and actively engaging patients in the decision-making process. Decision aids include several components with relevant information that helps patients to remember facts and make deliberate choices between two or more treatment options. It allows them to process information provided with their own thoughts and beliefs and have awareness of relevant consequences of the different options (Bekker, 2010).

Evaluation and patient involvement

Education programmes need to be responsive to the information needs of the patient group. If programmes are not formally evaluated there is a potential for a mismatch in perceptions between the clinician and the patient about the content and structure of education delivery. Consequently education programmes may not be optimizing the potential learning opportunities or providing the information and support desired. This can leave patients feeling disengaged, uncomfortable, and even alienated.

It is now widely recognized and a national recommendation that user involvement in all aspects of service development is

vital to bridge the gap between service provision and patient needs (Department of Health, 2001; NHS Institute for Innovation and Improvement, 2008). The patient's expectations must be incorporated as they often differ from the clinician's view of a patient's needs and so inclusion is a prerequisite for success (Blomqvist et al., 2010). User involvement when developing or evaluating education and information tools maximizes validity and ensures patient focus. Any new tools produced need to adhere to the local Trust policy for consent, copyright, and clinical governance.

To know that the teaching outcomes are successful, assessment of the amount of information obtained by the patient and their understanding of it is required. Evaluation of all educational tools and styles used as well as clinical outcomes resulting from teaching is also essential.

Methods of evaluation

Simple questionnaires can be used for both education groups and information tools used (NHS Institute for Innovation and Improvement, 2008). The reasons that patients opt for certain treatments should be documented and analysed through a questionnaire to determine future guidelines for education programmes (Goovaerts et al., 2005). Consultation days for patients and staff can elicit views on gaps and expectations of services provided. Both questionnaires and consultation days often do not represent the diverse patient population. In-depth patient interviews are needed to access the hard to reach patient groups providing greater feedback on all aspects of the education programme and are more likely to be representative of the patient population.

Conclusion

This chapter has outlined the aims and potential benefits of timely education in pre-dialysis care and has described the methods and models of care that should be considered when delivering a high-quality education programme for patients and their families. Pre-dialysis education delivered in an individualized, timely way has many benefits, including better clinical outcomes for patients and most importantly, increased opportunities for home therapies.

References

Bekker, H. L. (2010). The loss of reason in patient decision aid research: Do checklists damage the quality of informed choice interventions? *Patient Educ Couns*, 78(3), 357–64.

Bekker, H. L., Hewison, J., and Thonrton, J. G. (2004). Applying decision analysis to facilitate informed decision making about prenatal diagnosis for Down syndrome: a randomised controlled trial. *Prenat Diagn*, 24(4), 265–75.

Blomqvist, K., Theander, E., Mowide, I., *et al.* (2010). What happens when you involve patients as experts? A participatory action research project at a renal failure unit. *Nurs Inq*, 17(4), 317–23.

Chan, M. R., Dall, A. T., Fletcher, K. E., *et al.* (2007). Outcomes in patients with chronic kidney disease referred late to nephrologists: a meta-analysis. *Am J Med*, 120(12), 1063–70.

Chang, M. and Kelly, A. E. (2007). Patient education: addressing cultural diversity and health literacy issues. *Urol Nurs*, 27 (5), 411–17.

Colella, T. and King, K. (2004). Peer support. An under-recognized resource in cardiac recovery. *Eur J Cardiovasc Nurs*, 3, 211–17

Crooks, P. (2004). International care models for chronic kidney disease: methods and economics—United States. *Blood Purif*, 22, 13–20.

Coulter, A. and Collins, A. (2011). Making Shared Decision-Making a Reality; No Decision About Me, Without Me. London: Kings Fund.

Davies, N. (2011). Healthier lifestyles: behaviour change. *Nurs Times*, 107(23), 20–3.

Department of Health (2001). Health and Social Care Act 2001 Section 11 Public Involvement and Consultation. London: Department of Health.

Department of Health (2004). National Service Framework for Renal Services: Part One—Dialysis and Transplantation. London: Department of Health.

Warwick, G., Mooney, A., Russon, L., and Hardy, R. (2014). Planning, Initiating and Withdrawal of Renal Replacement Therapy. [Renal Association Guidelines] [Online] <http://www.renal.org/clinical/GuidelinesSection/RenalReplacementTherapy.aspx>

Gilg, J., Castledine, C., Fogarty, D., *et al.* (2010). The Thirteenth Annual Report. *Chapter 1: UK RRT Incidence in 2009: National and Centre-Specific Analyses*. The Renal Association UK Renal Registry. <http://www.renalreg.com/Report-Area/Report%202010/Chap01_Renal10_web.pdf>

Goovaerts, T., Jadoul, M., and Goffin, E. (2005). Influence of a pre-dialysis education programme (PDEP) on the mode of renal replacement therapy. *Nephrol Dial Transplant*, 20, 1842–7.

Goovaerts, T., Isnard Bagnis C., Crepaldi C., *et al.* (2014). Continuing education: preparing patients to choose a renal replacement therapy. *J Renal Care*, 41(1), 62–75.

Guy's and St Thomas' NHS Foundation Trust (2007). Making the Gift of Life. [DVD] London: Guy's and St Thomas' Charity.

Hughes, J., Wood, E., and Smith, G. (2009). Exploring kidney patients' experience of receiving individual peer support. *Health Expect*, 12(4), 396–406.

Korus, M., Stinson, J. N., Pool, R., *et al.* (2011). Exploring the information needs of adolescents and their parents throughout the kidney transplant continuum. *Prog Transplant*, 21(1), 53–60.

Little, J., Irwin, A., Marshall, T., *et al.* (2001). Predicting a patient's choice of dialysis modality: experience in a United Kingdom renal department. *Am J Kidney Dis*, 37, 981–6.

Marron, B., Oritz, A., de Sequera, P., *et al.* (2006). Impact of end-stage renal disease care in planned dialysis start and type of renal replacement therapy a Spanish multicentre experience. *Nephrol Dial Transplant*, 21 Suppl 2, 51–5.

Marteau, T. M., Dormandy, E., and Michie, S. (2001). A measure of informed choice. *Health Expect*, 4, 99–108.

McLaughlin, K., Manns, B., Culleton, B., *et al.* (2001). An economic evaluation of early versus late referral of patients with progressive renal insufficiency. *Am J Kidney Dis*, 38(5), 1122–18.

Mendelssohn, D. C., Malmberg, C., and Hamandi, B. (2009). An integrated review of 'unplanned' dialysis initiation: reframing the terminology to 'suboptimal' initiation. *BCM Nephrol*, 10, 22.

Murray, M. A., Brunier, G., Chung, J. O., *et al.* (2009). A systematic review of factors influencing decision-making in adults living with chronic kidney disease. *Patient Educ Couns*, 76, 149–58.

NHS Institute for Innovations and Improvement (2008). Focus on: Preparing for End Stage Renal Disease. [Online] <http://www.institute.nhs.uk>

O'Connor, A. M., Rostom, A., Fiset, V., *et al.* (1999). Decision aides for patients facing treatment or screening decisions: systematic review. *BMJ*, 319, 731–4.

Ollerenshaw, H. (2007). Patient information services: a strategic partnership approach. *Health Expect*, 10, 92–100.

Ormandy, P., Hulme, C., Caress, A. -L., *et al.* (2007). Identifying CKD Patients' Priorities and Preference for Information Topics. *Executive Summary*. Salford: Institute for Health and Social Care Research, University of Salford. <http://usir.salford.ac.uk/13966/1/Executive_Summary_CKD_Inf~Ormandy_P_et_al_2007.pdf>

Pagels, A., Wång, M., and Wengström, Y. (2008). The impact of a nurse-led clinic on self-care ability, disease-specific knowledge, and home dialysis modality. *Nephrol Nurs J*, 35(3), 242–8.

Rankin, S. H. and Stallings, K. D. (2001). Patient Education: Principles and Practice. (4th ed.). Philadelphia, PA: Lippincott.

Ravani, P., Marinangeli, G., Stacchiotti, L., *et al.* (2003). Structured pre-dialysis programs: more than just timely referral? *J Nephrol*, 16(6), 785–6.

Smith, S., Mitchell, C., and Bowler, S. (2007). Patient-centred education: applying learner-centred concepts to asthma education. *J Asthma*, 44(10), 799–804.

Warwick, G., Mooney, A., Russon, L., *et al.* (2014). Planning, Initiating and Withdrawal of Renal Replacement Therapy. [Renal Association Guidelines] [Online] <http://www.renal.org/clinical/GuidelinesSection/ RenalReplacementTherapy. *J Asthma*, 44(10), 799–804.

Yeoh, H., Tiquia, H., Abcar, A., *et al.* (2003). Impact of predialysis care on clinical outcomes. *Haemodial Int*, 7(4), 338–41.

CHAPTER 143

Preparation for renal replacement therapy

Muh Geot Wong, Bruce A. Cooper, and Carol A. Pollock

Introduction

Although the primary aim of management in chronic kidney disease (CKD) is to prevent progression to stage 5 CKD, for many patients renal replacement therapy (RRT) is inevitable.

Planning for the initiation of dialysis is aimed at ensuring that it takes place in a supported environment in which adverse events will be minimized, that the modality chosen is appropriate for the individual circumstances, and the patient has full knowledge of what RRT entails. Beginning dialysis inevitably involves medical, psychological, family, and social issues, and preparation for RRT is optimally managed by a team with appropriate expertise in these areas. Multidisciplinary education programmes that inform patients and their families about their disease and the treatment options are likely to result in patients starting dialysis in a planned and elective manner (Levin et al., 1997).

Individual and family expectations concerning what RRT will *not* deliver also need to be managed so that realistic goals of RRT can be set from the outset. For some, RRT will be a bridge to transplantation, for others it will be an ongoing part of life. This chapter will focus primarily on planning for dialysis: planning for transplantation, although considered by many patients preparing for RRT, is covered elsewhere. Discussions concerning RRT should generally include options for conservative approaches to ongoing care, as well as advanced care planning. Although these issues are a very important component of planning for RRT, they will only be briefly addressed here.

Predialysis care: timing of referral to a nephrologist.

The transition from CKD to RRT is a stressful and emotional event in a patient's life. This period, immediately prior to RRT and the subsequent months, is dominated by health challenges, the recognition of a high mortality risk, and disproportionately high personal healthcare costs. Most observational studies have demonstrated that early referral of patients with CKD to nephrological care is associated with slower rates of kidney functional decline and decreased patient morbidity and mortality, decreased hospitalization rates, increased likelihood of either the creation of permanent dialysis access prior to its initiation, or of kidney transplantation, and reduced initial costs of care following the commencement of dialysis (Cass et al., 2003; Curtis et al., 2005; Jungers et al., 2006; Chan et al., 2007; Smart and Titus, 2011). Dialysis, Outcomes and Practice Patterns observational data in 8500 incident haemodialysis patients suggest that the adjusted hazard ratio (HR) of death falls progressively with up to five nephrological consultations prior to the start of dialysis (Hasegawa et al., 2009). Furthermore, there is a graded benefit in referral, > 3 months versus 3–12 months versus > 12 months prior to the start of dialysis, independent of the presence of diabetes and the age of the patient (de Jager et al., 2011).

In general terms, the potential benefits associated with timely, appropriate nephrologist referral include:

- optimized patient planning and preparation for dialysis or kidney transplantation (including establishment of permanent dialysis access, which is discussed elsewhere—see Chapter 256)
- improved diagnosis and management of treatable kidney disease requiring specialist medical investigation and/or therapy
- retarded CKD progression through improved control of CKD risk factors
- enhanced management of CKD-related complications, such as significant renal anaemia, CKD mineral and bone disorder (CKD-MBD) and refractory hypertension.

Potential disadvantages of nephrologist referral include:

- saturation of limited nephrology manpower and resources, thereby limiting the access of high-risk CKD patients most likely to benefit from specialist renal services
- inefficient healthcare utilization
- heightened anxiety for the patient, and possibly unnecessary and costly investigation of patients with less serious CKD that is eminently manageable in primary healthcare.

Most countries report that some one-third of the patients commenced on dialysis are referred 'late' (i.e. within 3 months of needing to commence kidney replacement therapy) to the care of a nephrologist (Kinchen et al., 2002; Marron et al., 2006; Luxton, 2010; Hommel et al., 2012; Yamagata et al., 2012). A recent online survey of 479 internal medicine residents in the United States to determine their perceptions of indications for nephrology referral in CKD management showed widely divergent results for proteinuria (45%), uncontrolled hypertension (64%), hyperkalaemia (26%),

anaemia (28%), CKD bone disorder (45%), glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 (90%), and rapid decline in GFR (79%) (Agrawal et al., 2009). Lee and Forbes (2009), examined the impact of unsolicited nephrologist referrals for CKD patients from generalists in Kaiser Permanente Hawaii (214,000 members) based on (a) GFR < 20 mL/min/1.73 m^2; (b) GFR 20–40 mL/min/1.73 m^2, plus urinary protein:creatinine ratio > 2 g/mmol; or (3) urinary protein:creatinine ratio > 4 g/mmol, regardless of GFR. Between 2004 and 2008, the proportion of late nephrologist referrals (within 4 months of onset of RRT) decreased from 32% to 12% (P = 0.001), whilst the proportion of patients who started haemodialysis as outpatients increased from 35% to 53% (P = 0.003), and the proportion who started with permanent dialysis access increased from 18% to 36% (P = 0.003).

In a small, non-randomized controlled trial of 52 CKD patients with diabetes mellitus, Martinez-Ramirez et al. (2006) demonstrated that patients who were subsequently referred to a nephrologist exhibited better preservation of renal function, delayed progression of albuminuria, and better blood pressure control than those who remained treated only by their family doctors. Nephrologists were more likely to use angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins, and to discontinue non-steroidal anti-inflammatory drugs, than were family doctors. However, the decision to refer was not randomized and there remains insufficient evidence to indicate whether or not the outcomes of patients with both diabetes mellitus and CKD are improved by nephrologist referral.

Black et al. (2010) conducted a systematic review of the evidence of the clinical effectiveness and cost-effectiveness, and an economic analysis, of early referral strategies for the management of people with markers of renal disease. Five retrospective studies examining patients who had commenced RRT found that early referral (> 12 months prior to RRT) was associated with reduced odds of mortality for up to 5 years after commencement of RRT, which is further supported by the Danish cohort study (Hommel et al., 2012). Both studies involving predialysis CKD patients showed slowing in CKD progression in patients referred early to a nephrology service. In one study (Black et al., 2010), all early referral strategies produced more quality-adjusted life years (QALYs) than referral upon transit to stage 5 CKD (estimated GFR (eGFR) 15 mL/min/1.73 m^2). Referral for patients with an eGFR < 60 mL/min/1.73 m^2 generated the most QALYs and had an incremental cost-effectiveness ratio (ICER) of approximately £3806 per QALY compared with referral of patients with an eGFR < 30 mL/min/1.73 m^2. However, the workforce implications of referral of all patients with eGFR < 60 mL/min/1.73 m^2 suggest such an approach would be untenable.

In a large (N = 162,113) community-based study of the comorbidity and medical management of a cohort of patients treated in primary care in the United Kingdom (New Opportunities for Early Renal Impairment Intervention by Computerised Assessment (NEORICA)) (Klebe et al., 2007), a 12-month cost analysis was performed on all those patients with recorded serum creatinine results who were categorized as requiring additional tests and nephrologist referral according to the new UK CKD guidelines. In the first year, implementation of CKD guidelines resulted in a significant increase in nephrology referral (147.5 patients/10,000 over and above those already known) with projected additional costs in the first year of €17,133 (increasing to €29,790 after the effect of creatinine calibration was taken into account). Formal cost-effectiveness studies were not performed, although the authors contended that the additional costs of implementing the UK CKD guidelines could be offset by delaying dialysis requirement by 1 year in 1 individual per 10,000 patients. Since criteria for nephrologist referral have substantial implications for healthcare utilization, health costs, clinical outcomes, and patient quality of life, it is important that guidelines maximize anticipated health outcomes in the face of constrained manpower and limited resources. Patients who have a functioning arteriovenous fistula, haemoglobin > 11 g/dL, and normal serum albumin at the time of dialysis initiation, reflecting both optimal predialysis care and lack of comorbidity, have been determined in retrospective analyses to have a lower risk of death in the first year on dialysis.

Early referral is likely to be associated with increased uptake of peritoneal dialysis (Cooper et al., 2010) and lower rates of treatment failure requiring a switch to in-centre haemodialysis (Winkelmayer et al., 2001; Stack, 2002). However, it has been suggested that the improvement in early outcomes in patients treated with peritoneal dialysis may be due to the lead time bias demonstrated in early referral (Chan et al., 2011). Increased access to kidney transplantation is also seen in patients referred for early nephrological care (Cass et al., 2003; Winkelmayer et al., 2007).

There is strong evidence that eGFR and albuminuria provide additional and complementary information for effective risk stratification of patients with CKD at all ages. Clinical parameters (such as diabetes, age, gender, etc.) and laboratory parameters (such as haematuria) do not significantly add to predictive information. There is limited evidence to suggest that specialist referral based on risk stratification using both GFR and albuminuria/proteinuria leads to improved patient outcomes in terms of timely referral, timely dialysis access creation, and reduced hospitalization.

In the HUNT 2 study involving 65,589 adults residing in Nord-Trondelag county in Norway (Hallan et al., 2009), if all high-risk patients (diabetes, hypertension, or age > 55 years) in the general population were screened by eGFR and albuminuria assessments and all patients with an eGFR < 60 mL/min/1.73 m^2 and/or urinary albumin:creatinine ratio (ACR) > 3 mg/mmol were referred to nephrologists, 63.5% of all patients in the general population who would progress to end-stage kidney disease (ESKD) over 10 years (1.4% of the population overall) would be placed under specialist care. However, 11.4 patients who would not progress would be referred and followed by a nephrologist for every case of ESKD (i.e. number needed to follow (NNTF) = 11.4). If more stringent referral criteria of eGFR < 30 mL/min/1.73 m^2 plus ACR > 3 mg/mmol or eGFR < 44 mL/min/1.73 m^2 plus ACR > 30 mg/mmol were applied, the proportion of patients progressing to ESKD over 10 years placed under specialist care would fall to 31.5% (0.2% of the overall population), although the NNTF would be only 2.6.

A particularly contentious issue is how referral guidelines should apply to older adults who have a much higher prevalence of CKD (Campbell et al., 2008). Importantly, the level of eGFR below which the risk of ESKD exceeded the risk of death varied by age, ranging from 45 mL/min/1.73 m^2 for 18- to 44-year-old patients to 15 mL/min/1.73 m^2 for 65- to 84-year-old patients (overall, the average cross-over point at which the risk of ESKD exceeds death is approximately 30 mL/min/1.73 m^2 (O'Hare et al., 2007)). Whilst advanced age (and its attendant associations with cognitive impairment, functional loss, and competing medical comorbidity and mortality

risks) clearly should have some bearing on the decision to refer a patient with CKD for specialist renal care, there are currently no evidence-based, rational, or consistent means of determining when referrals should be made for elderly patients.

The impact of anaemia and CKD-MBD on the progression of CKD is discussed in other chapters (see Chapters 115 and 123). There is no evidence to suggest that early nephrological intervention will affect patient-level outcomes. Similarly, UK NICE guidelines (Crowe et al., 2008) recommend referral to a nephrologist for CKD patients with suspected renal artery stenosis. The evidence supporting this is tenuous, as the limited randomized controlled trial evidence to date does not demonstrate any significant difference in outcomes for treatment with medical treatment versus angioplasty versus angioplasty with stenting versus surgery. There is no evidence that referral of CKD patients with other specific conditions to specialist renal services leads to improved patient outcomes compared with continued management in primary care.

A renewed focus on clinical practice guidelines to general physicians that recommend earlier referral to a nephrologist has not been received without criticism (Burden and Tomson, 2005; Crowe et al., 2008; Levin et al., 2008). To date, there are no randomized controlled trials of outcomes following the application of nephrologist referral criteria to the population in a primary or institutional healthcare setting. Hence, although the evidence base for many nephrology guidelines is not based on level 1 evidence, primary care physicians are less likely to be aware of existing guidelines (Boulware et al., 2006; Montgomery et al., 2006), and therefore to adhere to them. There have been no assessments of the health-related economic impact of implementing such guidelines, and no account has been taken of the complexities of the decision-making processes for referral of CKD patients, such as the poor predictability of CKD progression, the presence of multiple comorbid medical problems in a predominantly aged population, the role of functional loss, and cognitive impairment in the decision-making process (Campbell et al., 2008), and the presence of competing mortality risks, with CKD patients more likely to die as a consequence of cardiovascular disease rather than progressing to ESKD requiring RRT. In addition, there is variable appreciation of the views and factors influencing the decision-making of patients and carers (Morton et al., 2010) and randomized studies of specific interventions in patients with CKD are limited. Indeed, the SHARP study in patients with stage 3–4 CKD demonstrated a mortality benefit in patients treated with a relatively low-dose statin and ezetimibe (Baigent et al., 2011). Conversely, a relatively small, although randomized, study of multifaceted pharmacological intervention to optimize cardiovascular outcomes was unsuccessful in reducing the high rates of major atherosclerotic cardiovascular events in this population (Rakhit et al., 2006).

The impact of early nephrological care on patient survival has more recently been questioned. Recent data analysing the large United States Renal Data System (USRDS) showed a dramatic increase in predialysis nephrological care over the period from 1996 to 2006. Patients commencing dialysis were less anaemic, had greater use of erythropoietic-stimulating agents, and higher serum albumin. Patient survival remained unchanged over the 11 years of the study, but if adjusted for eight comorbid conditions in addition to age, race, region, and being a beneficiary of Medicaid, then a slight improvement in mortality of 0.9% per annum was observed. Although late referral was associated with a hazard ratio for mortality of 1.36, this effect was attenuated when added to the other variables. The modest improvement in outcome could be almost entirely attributed to the patients having starting dialysis with more preserved renal function, in effect reflecting a lead time bias. Importantly, over the period of study comorbid conditions were more closely coded, and this may suggest an overestimation of comorbidity over time compared with 1996 (Winkelmayer et al., 2011). This observational study also reported that increasing age and female gender were associated with delayed nephrological care, which has been observed in other studies. However, prospective analyses of patients from the Australian and New Zealand Dialysis and Transplant Registry confirm that commencing dialysis at age > 75 years is associated with a burden of greater comorbidity and a worse prognosis (Foote et al., 2012). Although the benefit of dialysis treatment in this age group needs to be considered in concert with the considerable treatment and social burdens that accompany dialysis, effective predialysis care has a positive effect on outcomes.

Multidisciplinary care

Ideally, multidisciplinary CKD care involves nephrologists and nurses with experience in all aspects of RRT, the social worker, the renal dietician and renal pharmacist, dialysis and transplant access co-ordinator, access to psychological/psychiatric expertise, a surgeon as required and, ideally, to experienced patient support groups. Observational studies of the use of multidisciplinary care programmes in planning for RRT have shown improved patient survival. One such large observational study of 6978 patients found that a multidisciplinary care clinic that included physicians, nurse clinicians, dieticians and social workers reduced the risk of death by 50% compared with non-multidisciplinary care (HR 0.50; 95% confidence interval (CI) 0.35–0.71), although there was no reduction in all-cause or cardiac-specific hospitalization between the two groups (Hemmelgarn et al., 2007). However, a randomized controlled trial of 437 patients with CKD over 5 years did not find any improvement in kidney function, health service utilization, or mortality (Harris et al., 1998).

There is evidence to support the use of multidisciplinary CKD care in increasing the uptake of home dialysis therapies (McLaughlin et al., 2003, 2008; Manns et al., 2005). These studies show that if patients received specifically targeted education they were more likely to choose a home-based dialysis therapy.

The specific aspects of multidisciplinary care that may have a positive impact on patient outcomes are difficult to ascertain. Predialysis dietary advice delivered by a dietician is recognized in observational studies as an important component of care. Slinin et al. (2011) reported that in a large (N = 156,440) retrospective cohort analysis the majority of patients (88%) were not reviewed by a dietician before the initiation of dialysis; 9% of patients received ≤ 12 months dietician support and only 3% received >12 months of predialysis dietician care. They found, using a multivariate Cox model, a significant association between subsequent survival on dialysis and predialysis care by a dietician for both 0–12 months (HR 0.95; 95% CI 0.91–0.99) and > 12 months (HR 0.85; 95% CI 0.79–0.91) compared with no such care. Predialysis dietician care was also associated with higher albumin and lower cholesterol levels at the commencement of dialysis therapy.

The setting of key performance indicators (KPIs) is helpful in identifying potential problem areas in the pathway from stage 4 CKD to dialysis, although these indicators themselves do not

necessarily indicate why poor performances are occurring. One system that has been successfully used to identify problem areas and implement improvement in predialysis clinical care is clinical audit and redesign. Owen et al. (2006) found that by implementing a system of registering patients with an eGFR < 30 mL/min/1.73 m^2 with the dialysis service, providing timely education with a series of seminars and reviews, and early referral (eGFR < 25 mL/min/1.73 m^2) for vascular access resulted in significant improvements in several KPIs. Over a 3.5-year time period, late notifications of patients to the dialysis unit fell from 29% to 6% ($P < 0.01$), the median time between registration of patients for dialysis and its commencement increased from < 1 month to 14 months ($P < 0.01$), patients not registered with the service fell from 57% to 0% ($P < 0.001$), and the number of patients starting haemodialysis with permanent access, facilitated by a dedicated access coordinator as part of the multidisciplinary team, increased from 24% to 83% ($P < 0.001$).

Role of patient education prior to renal replacement therapy

Patient education in CKD is covered in detail elsewhere (see Chapter 142). Observational studies suggest that patients attending predialysis education programmes during preparation for RRT are more likely to select peritoneal dialysis as their modality of choice (adjusted odds ratio (OR) 5.13; 95% CI 3.58–7.35), and those who select in-centre haemodialysis are significantly more likely to start dialysis with a fistula or graft (adjusted OR 2.06; 95% CI 1.88–2.26) (Lacson et al., 2011).

Not unexpectedly, in observational studies, pre-RRT education in observational studies has shown a positive influence on patient outcomes. However, the characteristics of patients attending such programmes would suggest that they are more likely to be young, white, and have a slightly higher body mass index, all characteristics that portend an improved longevity (Mason et al., 2008). A large systematic review has been performed of randomized controlled trials studying structured educational interventions compared with usual care (Mason et al., 2008). This review identified 22 studies involving a wide range of multicomponent interventions with variable aims and outcomes. The majority of studies were aimed at improving adherence to recommendations regarding diet and/or fluid intake in patients with all stages of CKD, as well as in the dialysis population. Mortality and cardiovascular endpoints were not assessed. Due to the heterogeneity of the studies a meta-analysis was not possible, although 18 of the studies reported significant results for at least one of the outcome measures.

Important factors that influence a patient's decision to choose peritoneal dialysis rather than haemodialysis included the provision of written information ($P = 0.048$), lifestyle issues ($P = 0.025$), employment ($P = 0.03$), and attendance at the formal education session ($P = 0.011$). Demographic factors that appeared to be important in determining the patient's decision to choose peritoneal dialysis over the other alternatives included being married ($P < 0.001$), being employed ($P = 0.015$), and not living alone ($P = 0.003$). Internet access, religious beliefs, and the views of friends and family did not influence choice of RRT modality (Chanouzas et al., 2012).

Despite nephrologists indicating that up to 80% of patients with ESKD are potential candidates for home dialysis (Mendelssohn et al., 2009) this does not translate into actual patient numbers. Indeed, the prevalence of home-based dialysis in the United States and Europe is very low (peritoneal dialysis 7.5–15% and home haemodialysis 0.6–2%) (MacGregor et al., 2006; Qamar et al., 2009). In Australia and New Zealand, the proportion of patients on home-based RRT is up to 35% (McDonald et al., 2009). However, these rates may increase with targeted CKD education (Morton et al., 2012b). In this study, given various clinical scenarios, patients chose home dialysis, in-centre dialysis, and conservative care in 65%, 35% and 10% respectively. Their carers also recorded similar rates. Conversely, a national survey of US nephrologists indicated that only 6% would choose in-centre dialysis, 45% peritoneal dialysis, 25% home haemodialysis, and 3% nocturnal in-centre haemodialysis (Merighi et al., 2012).

The characteristics of patients who initiate RRT with peritoneal dialysis or home haemodialysis differ, as was shown in an observational cohort study over a 5-year period in a Canadian University Health Network (Rioux et al., 2010). Home haemodialysis was significantly more likely to be started in younger, male, non-diabetic patients without vascular comorbidity.

The patient's decision-making process needs to involve education on all the options available, although this does not always occur. Morton et al. performed a prospective, multinational, multicentre study of information given to patients in Australian renal units (Morton et al., 2011). Of the 721 patients surveyed they found that 84% received information about their options prior to commencing treatment. Seventy-five per cent were presented with the option of home dialysis, 32% with pre-emptive transplantation, and 65% were informed about conservative care. Patients known to a nephrologist for > 3 months or who were being treated in a small unit (< 100 dialysis patients) were more likely to receive information prior to commencing treatment (OR 7.29; 95% CI 3.86–13.79 and OR 2.4; 95% CI 1.26–4.60 respectively). The mean GFR at the time of education was 13.3 mL/min/1.73 m^2 (95% CI 12.7–13.8).

There will always be some patients who require emergency unplanned dialysis, and who as a result almost always commence treatment with haemodialysis. However, even in this group, in-hospital education can still result in a proportion of patients taking up a home-based dialysis therapy. Rioux et al. found that 71 out of 132 consecutive patients educated in hospital by an advanced nurse practitioner subsequently transferred to peritoneal dialysis or home haemodialysis (Rioux et al., 2011).

Supported care pathways

For an increasing proportion of patients a non-RRT pathway is chosen, that is, a management plan that does not include preparation for dialysis and transplantation. Supportive care pathways aim to manage patients' needs and uraemic symptoms using diet changes, medication, psychosocial support, and, ultimately, palliative care. Clinical practice guidelines recommend that all CKD patients approaching dialysis be informed about their treatment options including that of conservative care (Department of Health National Service Framework Renal Team, 2005; Hemodialysis Adequacy 2006 Work Group, 2006; Peritoneal Dialysis Adequacy Work Group, 2006; Kainer and Fetherstonhaugh, 2010). An Australian and New Zealand unit-based study (N = 721) of patient education and choice found that only 15% of dialysis units had a formal conservative-care pathway for patients with CKD (Rioux et al., 2011). Of the patients surveyed, 470 (65%) were presented with conservative care as a treatment option. Increasing age ≥ 65 years of age was associated with a higher likelihood of being presented with conservative care (65–74 years (OR 3.45), 75–84 years (OR 5.84), and 85 years and

older (OR 11.52)). In addition, patients referred early (> 3 months prior to estimated start of dialysis), were much more likely to receive conservative care information (3–12 months (OR 6.47), 1–2 years (OR 5.68), and > 2 years (OR 3.14)). Women were more likely to choose conservative care (OR 2.23) and patients with private health insurance were less likely to choose this option (OR 0.40). Importantly, a non-English speaking background had no significant impact on decisions regarding RRT or a supported care approach.

The patient's perspective of dialysis and conservative care choices has been reported by Morton et al. (2012a) using a discrete choice experiment to identify factors that influence patient treatment preferences and trade-offs. One hundred and five patients with stage 3–5 CKD from eight Australian renal units were surveyed. Factors found to significantly influence patients to decide on dialysis therapy were increasing life expectancy (OR 1.84; 95% CI 1.57–2.15), the option of daytime or evening dialysis rather than just daytime (OR 8.95; 95% CI 4.46–17.97), and the availability of subsidized transport services (OR 1.55; 95% CI 1.24–1.95). Significantly important factors that were associated with a conservative pathway choice included increasing number of hospital visits per week (OR 0.70; 95% CI 0.56–0.88) and increasing travel restrictions (OR 0.47; 95% CI 0.36–0.61). A benefit-to-harm trade-off analysis also found that patients were willing to forgo 7 months (95% CI 4–10) of life expectancy to reduce the number of visits per week by 1 day and 15 months (95% CI 11–22) of life expectancy to reduce their travel restrictions.

A recent single-centre, questionnaire-based study (Chanouzas et al., 2012) identified several factors that were important in influencing patients to decide in favour of conservative management. Predialysis patients with an eGFR of ≤ 25 mL/min were offered an education programme. The 10% of patients who chose conservative management were significantly older (mean age 84 years), than those choosing haemodialysis (68 years) and peritoneal dialysis (55 years; $P < 0.001$), and were more likely to have a higher comorbidity score.

Specific factors to consider in the preparation for renal replacement therapy

With the exception of lipid-lowering therapy in patients with stage 3 and 4 CKD (Baigent et al., 2011), the evidence base to support the majority of interventions demonstrated to confer cardiovascular benefit in the general population and in those with type 2 diabetes mellitus does not exist. Despite this, guidelines for lifestyle modification, including smoking cessation, cardiovascular risk factor management, prevention and treatment of metabolic bone disease, and anaemia exist and are covered in other chapters in Section 5. Formal and regular review of drugs and drug doses is imperative, ideally with pharmacy input, for patients with declining kidney function, to ensure that both safety and efficacy are taken into consideration. In particular nephrotoxicity, systemic toxicity due to drug accumulation, and electrolyte and acid–base abnormalities need to be pre-emptively considered. The use of contrast agents requires an individual assessment of the risk/benefit profile.

Vaccination

As patients with renal disease have a higher risk of developing infections, through reduced immunity, increased rates of blood transfusion, repeated exposure to body fluids during haemodialysis, and direct transmission at the time of organ donation, vaccination should be strongly considered where possible. Inevitably the prevalence of specific infections in every community will influence decisions regarding vaccination. For certain vaccinations, in particular hepatitis B, optimal seroconversion rates are achieved with administration early in the course of the CKD pathway (Fraser et al., 1994).

Hepatitis B is highly infectious with a high worldwide prevalence and vaccination is low risk and highly effective (see Chapter 129). Hence universal immunization is recommended. Antibody levels > 10 IU/L are considered protective. Factors associated with significantly lower seroconversion rates include diabetes (Fabrizi et al., 2011) and age > 40 years (Fabrizi et al., 2004). To maximize seroconversion rates it is recommended that a high strength (40 micrograms) four-dose (0, 1, 2, and 6 months) regimen be used (Centers for Disease Control and Prevention, 2001). Intramuscular and intradermal routes of administration have been evaluated (Fabrizi et al., 2001), with intradermal administration achieving an initially higher antibody level, although the difference did not persist. There is evidence to support revaccination in non-responders with a repeat full course given via either route of administration (Fabrizi et al., 1997; Micozkadioglu et al., 2007; Chaves et al., 2011). Different vaccine adjuvants to improve vaccine responsiveness have been studied with mixed results and no definitive conclusion can be drawn from these studies.

It is recommended that patients with renal disease universally receive pneumococcal, tetanus, varicella zoster, and influenza vaccinations, despite the subsequent antibody levels and duration of response being somewhat inferior to the 'normal' population (Linnemann et al., 1981; Guerin et al., 1992; Marin et al., 2007; Scharpé et al., 2009). Due to concerns regarding immunocompetence in patients with CKD, live-virus polio vaccine should be given as an enhanced-potency inactivated vaccine, which has been documented to achieve a good response in patients with CKD (Sipilä et al., 1990).

When to commence dialysis?

Over the past 15–20 years, there has been an increasing trend for commencing dialysis at a higher level of renal function, mainly driven by small observational studies demonstrating improved morbidity and mortality with starting dialysis early (Jungers et al., 2006). This led to progressive change in clinical practice where dialysis was instigated prior to the development of uraemic signs and symptoms (Golper, 1999). The National Kidney Foundation Dialysis Outcome Quality Initiative (NKF-DOQI) guidelines were updated in 2006 to indicate that dialysis commencement should be considered when eGFR by the Modification of Diet in Renal Disease (MDRD) equation fell < 15 mL/min/1.73 m^2 and that it may be appropriate to commence dialysis with eGFR levels > 15 mL/min/1.73 m^2 in patients with significant comorbidities or uraemic symptoms (Hemodialysis Adequacy 2006 Work Group, 2006; Peritoneal Dialysis Adequacy Work Group, 2006.). Other guideline groups contemporaneously recommended that dialysis commencement should be based on eGFR, at levels ranging from 8 to 12 mL/min/1.73 m^2 (Churchill et al., 1999; European Best Practice Guidelines Expert Group on Hemodialysis, 2002; Kelly et al., 2005). Consequently, dialysis registries in North America, Europe, and Australia and New Zealand have reported dialysis commencement at increasingly higher levels of eGFR over the last 10–15 years (Rosansky et al., 2011).

The IDEAL (Initiating Dialysis Early and Late) study (Cooper et al., 2010) was a landmark randomized controlled trial to examine the effect of initiating dialysis early and late on mortality in patients with stage 5 CKD. The key issues of relevance were that the patients were all randomized when their eGFRs, estimated by the Cockcroft and Gault formula, were between 10–15 ml/min/1.73 m^2 to start dialysis at a GFR of either 10–14 or 5–7 mL/min/1.73 m^2, with stratification for dialysis modality (haemodialysis or peritoneal dialysis), study centre, and the presence or absence of diabetes mellitus. A pragmatic approach to the study design was taken in that the study protocol permitted patients allocated to the late start arm to commence dialysis with an eGFR > 7 mL/min/1.73 m^2, based on the recommendation of the treating physician. The major results of the IDEAL trial were reported in 2010 (Cooper et al., 2010) and the economic analysis in 2011 (Harris et al., 2011). In summary, there was no advantage in the early commencement of dialysis on the primary end point of all-cause mortality or the secondary endpoints of cardiovascular events, infectious complications, structural cardiac disease, or nutritional parameters (Fig. 143.1). Importantly, no subgroup, including those considered previously to have perhaps benefited from the earlier start of dialysis, such as the diabetic or the elderly, demonstrated any advantage in early versus late dialysis. In patients randomized to commence dialysis late, there was paradoxically an increased use of temporary dialysis catheters, suggesting an inappropriate complacency regarding vascular access when dialysis is electively deferred. The economic analyses not unexpectedly demonstrated an increase in dialysis costs when dialysis was commenced early, and an increase in transport costs. Although the overall costs were greater in the early dialysis group, this was not statistically significant due to the large confidence intervals. Surprisingly, quality of life was not different in patients who started dialysis early versus late. Clearly, the results did not demonstrate any significant clinical or economic benefit in commencing dialysis at higher levels of endogenous renal function. Hence dialysis should be commenced based on clinical considerations as detailed in Box 143.1.

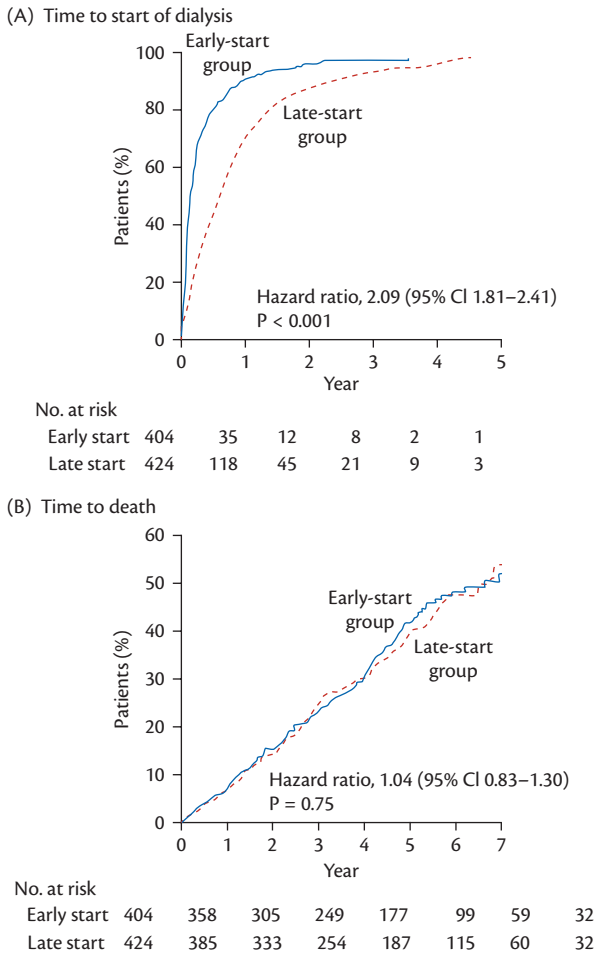

Fig. 143.1 Kaplan–Meier curves for time to the initiation of dialysis and for time to death in the IDEAL trial (Cooper et al., 2010). The data for time to the initiation of dialysis (A) were censored at the time of death, transplantation, or withdrawal of consent or at the time a patient transferred to a nonparticipating hospital, emigrated, or could not be contacted. The curves for time to death (B) are truncated at 7 years of follow-up and a cumulative hazard of 60%.

Box 143.1 Clinical indications to initiate dialysis

- Uraemia-related pericarditis or pleuritis
- Progressive encephalopathy or neuropathy with increasing confusion, asterixis, or seizure
- Uraemia-related coagulopathy
- Persistent uraemia-related gastroenteropathy (nausea with or without vomiting)
- Anorexia and unexplained weight loss
- Volume overload refractory to diuretic therapy
- Severe metabolic acidosis
- Resistant hyperkalaemia.

Conversely, multiple retrospective analyses from multiple cohorts, including the IDEAL study, demonstrate that patients who start dialysis at lower eGFRs have better survival, compared to those who start with higher levels of residual renal function (Sawhney et al., 2009; Wright et al., 2010; Clark et al., 2011; Yamagata et al., 2012). Although not tested in controlled studies, secondary analyses suggest that patients with high comorbidities including diabetes mellitus, cardiovascular disease, and advanced age are more likely to start dialysis earlier, which independently increases mortality risk.

Summary

There is minimal high-quality evidence on which to base recommendations in regard to the transition of patients from CKD to RRT (Box 143.2). The weight of anecdotal evidence, including assessments of patient satisfaction, suggests that the process of transition from CKD to RRT is optimally managed by a multidisciplinary team easily accessible to the patient. Such a team should have expertise in the utilization of drugs, judicious use of agents that may be nephrotoxic, provision of dietary advice, and be in a position to provide access to social, psychological, and peer group support as required. Patients and their families should be provided with sufficient information regarding RRT options, including supportive care, on which to base decisions. Continued attention by the nephrologist to risk factor management should

Box 143.2 Summary of preparation for renal replacement therapy

Where is the evidence?

- Early nephrological referral
- Hepatitis B immunization
- Access creation? < 6 months before initiation of dialysis
- Initiation of dialysis—a clinical judgement
- No survival benefit on early start dialysis
- Early start is associated with increased cost.

What is still unclear?

- Role of eGFR in initiation of dialysis
- Timing of early nephrological referral
- Renal trajectory decline versus residual renal function
- Timing and initiation of dialysis in elderly (> 75 years old)
- The relevance of defined conservative pathway
- The impact of patient and carer perspective and satisfaction in outcomes.

occur in the transition phase, and attention to timely access placement, advanced care directives, and vaccination protocols should reduce the physical, psychological, and social morbidity associated with RRT.

References

Agrawal, V., Ghosh, A. K., Barnes, M. A., *et al.* (2009). Perception of indications for nephrology referral among internal medicine residents: a national online survey. *Clin J Am Soc Nephrol*, 4, 323–8.

Baigent, C., Landray, M. J., Reith, C., *et al.* (2011). The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*, 377, 2181–92.

Black, C., Sharma, P., Scotland, G., *et al.* (2010). Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis. *Health Technol Assess*, 14, 1–184.

Bonomini, V., Baldrati, L., and Stefoni, S. (1983). Comparative cost/benefit analysis in early and late dialysis. *Nephron*, 33, 1–4.

Boulware, L. E., Troll, M. U., Jaar, B. G., *et al.* (2006). Identification and referral of patients with progressive CKD: a national study. *Am J Kidney Dis*, 48, 192–204.

Burden, R. and Tomson, C. (2005). Identification, management and referral of adults with chronic kidney disease: concise guidelines. *Clin Med*, 5, 635–42.

Campbell, K. H., Dale, W., Stankus, N., *et al.* (2008). Older adults and chronic kidney disease decision making by primary care physicians: a scholarly review and research agenda. *J Gen Intern Med*, 23, 329–36.

Cass, A., Cunningham, J., Snelling, P., *et al.* (2003). Late referral to a nephrologist reduces access to renal transplantation. *Am J Kidney Dis*, 42, 1043–9.

Centers for Disease Control and Prevention (2001). Recommendations for preventing transmission of infections among chronic hemodialysis patients. *MMWR Recomm Rep*, 50(RR-5), 1–43.

Chan, K. E., Maddux, F. W., Tolkoff-Rubin, N., *et al.* (2011). Early outcomes among those initiating chronic dialysis in the United States. *Clin J Am Soc Nephrol*, 6, 2642–2.

Chan, M. R., Dall, A. T., Fletcher, K. E., *et al.* (2007). Outcomes in patients with chronic kidney disease referred late to nephrologists: a meta-analysis. *Am J Med*, 120, 1063–70.

Chanouzas, D., Ng, K. P., Fallouh, B., *et al.* (2012). What influences patient choice of treatment modality at the pre-dialysis stage? *Nephrol Dial Transplant*, 27, 1542–7.

Chaves, S. S., Daniels, D., Cooper, B. W., *et al.* (2011). Immunogenicity of hepatitis B vaccine among haemodialysis patients: effect of revaccination of non-responders and duration of protections. *Vaccine*, 29, 9618–23.

Churchill, D. N., Blake, P. G., Jindal, K. K., *et al.* (1999). Clinical practice guidelines for initiation of dialysis. Canadian Society of Nephrology. *J Am Soc Nephrol*, 10 Suppl 13, S289–91.

Clark, W. F., Na, Y., Rosansky, S. J., *et al.* (2011). Association between estimated glomerular filtration rate at initiation of dialysis and mortality. *CMAJ*, 183, 47–53.

Cooper, B. A., Branley, P., Bulfone, L., *et al.* (2010). A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med*, 363, 609–19.

Crowe, E., Halpin, D., and Stevens, P. (2008). Early identification and management of chronic kidney disease: summary of NICE guidance. *BMJ*, 337, a1530.

Curtis, B. M., Ravani, P., Malberti, F., *et al.* (2005). The short- and long-term impact of multi-disciplinary clinics in addition to standard nephrology care on patient outcomes. *Nephrol Dial Transplant*, 20, 147–54.

De Jager, D. J., Voormolen, N., Krediet, R. T., *et al.* (2011). Association between time of referral and survival in the first year of dialysis in diabetics and the elderly. *Nephrol Dial Transplant*, 26, 652–8.

Department of Health National Service Framework Renal Team (2005). The National Service Framework for Renal Services. *Part Two: Chronic Kidney Disease, Acute Renal Failure and End of Life Care*. London: Department of Health.

European Best Practice Guidelines Expert Group on Hemodialysis, European Renal Association (2002). Measurement of renal function, when to refer and when to start dialysis. *Nephrol Dial Transplant*, 17 Suppl 7, 7–15.

Fabrizi, F., Andrulli, S., Bacchini, G., *et al.* (1997). Intradermal versus intramuscular hepatitis B re-vaccination in non-responsive chronic dialysis patients: a prospective randomized study with cost-effectiveness evaluation. *Nephrol Dial Transplant*, 12, 1204–11.

Fabrizi, F., Dixit, P., Martin, P., *et al.* (2011). Meta-analysis: the impact of diabetes mellitus on the immunological response to hepatitis B virus vaccine in dialysis patients. *Aliment Pharmacol Ther*, 33, 815–21.

Fabrizi, F., Fixit, V., Messa, P., *et al.* (2001). Intradermal vs intramuscular vaccine against hepatitis B infection in dialysis patients: a meta-analysis of randomized trials. *J Viral Hepat*, 18, 730–7.

Fabrizi, F., Martin, P., Dixit, V., *et al.* (2004). Meta-analysis: the effect of age on immunological response to hepatitis B vaccine in end-stage renal disease. *Aliment Pharmacol Ther*, 20, 1053–106.

Foote, C., Ninomiya, T., Gallagher, M., *et al.* (2012). Survival of elderly dialysis patient is predicted by both patient and practice characteristics. *Nephrol Dial Transplant*, 27, 3581–7.

Fraser, G. M., Ochana, N., Fenyves, D., *et al.* (1994). Increasing serum creatinine and age reduce the response to hepatitis B vaccine in renal failure patients. *J Hepatol*, 21, 450–4.

Golper, T. A. (1999). The rationale for Healthy Start dialysis. *Blood Purif*, 17, 1–9.

Guerin, A., Buisson, Y., Nutini, M. T., *et al.* (1992). Response to vaccination against tetanus in chronic haemodialysed patients. *Nephrol Dial Transplant*, 7, 323–6.

Hallan, S. I., Ritz, E., Lydersen, S., *et al.* (2009). Combining GFR and albuminuria to classify CKD improves prediction of ESRD. *J Am Soc Nephrol*, 20, 1069–77.

Harris, A., Cooper, B. A., Li, J. J., *et al.* (2011). Cost-effectiveness of initiating dialysis early: a randomized controlled trial. *Am J Kidney Dis*, 57, 707–15.

Harris, L. E., Luft, F. C., Rudy, D. W., *et al.* (1998). Effects of multidisciplinary case management in patients with chronic renal insufficiency. *Am J Med*, 105, 464–71.

Hasegawa, T., Bragg-Gresham, J. L., Yamazaki, S., *et al.* (2009). Greater first-year survival on hemodialysis in facilities in which patients are provided earlier and more frequent pre-nephrology visits. *Clin J Am Soc Nephrol*, 4, 595–602.

Hemmelgarn, B. R., Manns, B. J., Zhang, J., *et al.* (2007). Association between multidisciplinary care and survival for elderly patients with chronic kidney disease. *J Am Soc Nephrol*, 18, 993–9.

Hemodialysis Adequacy 2006 Work Group (2006). Clinical practice guidelines for hemodialysis adequacy, update 2006. *Am J Kidney Dis*, 48 Suppl 1, S2–90.

Hommel, K., Madsen, M., and Kamper, A. L. (2012). The importance of early referral for the treatment of chronic kidney disease: a Danish nationwide cohort study. *BMC Nephrol*, 13, 108.

Jungers, P., Joly, D., Nguyen-Khoa, T., *et al.* (2006). Continued late referral of patients with chronic kidney disease. Causes, consequences, and approaches to improvement. *Presse Med*, 35, 17–22.

Jungers, P., Zingraff, J., Albouze, G., *et al.* (1993). Late referral to maintenance dialysis: detrimental consequences. *Nephrol Dial Transplant*, 8, 1089–93.

Kainer, G. and Fetherstonhaugh, D. (2010). The CARI guidelines. Ethical considerations. *Nephrology*, 15 Suppl 1, S12–14.

Kelly, J., Stanley, M., and Harris, D. (2005). The CARI guidelines. Acceptance into dialysis guidelines. *Nephrology*, 10 Suppl 4, S46–60.

Kinchen, K. S., Sadler, J., Fink, N., *et al.* (2002). The timing of specialist evaluation in chronic kidney disease and mortality. *Ann Intern Med*, 137, 479–86.

Klebe, B., Irving, J., Stevens, P. E., *et al.* (2007). The cost of implementing UK guidelines for the management of chronic kidney disease. *Nephrol Dial Transplant*, 22, 2504–12.

Lacson, E., Wang, W., DeVries, C., *et al.* (2011). Effects of a nationwide predialysis education program on modality choice, vascular access, and patient outcomes. *Am J Kidney Dis*, 58, 235–42.

Lee, B. J. and Forbes, K. (2009). The role of specialists in managing the health of populations with chronic illness: the example of chronic kidney disease. *BMJ*, 339, b2395.

Levin, A., Hemmelgarn, B., Culleton, B., *et al.* (2008). Guidelines for the management of chronic kidney disease. *CMAJ*, 179, 1154–62.

Levin, A., Lewis, M., Mortiboy, P., *et al.* (1997). Multidisciplinary predialysis programs: Quantification and limitations of their impact on patient outcomes in two Canadian settings, *Am J Kidney Dis*, 29, 533–40.

Linnemann, C. C., Jr., First, M. R., and Schiffman, G. (1981). Response to pneumococcal vaccine in renal transplant and hemodialysis patients. *Arch Intern Med*, 141, 1637–40.

Luxton, G. (2010). The CARI guidelines. Timing of referral of chronic kidney disease patients to nephrology services (adult). *Nephrology*, 15 Suppl 1, S2–11.

MacGregor, M. S., Agar, J. W., and Blagg, C. R. (2006). Home haemodialysis—international trends and variation. *Nephrol Dial Transplant*, 21, 1934–45.

Manns, B. J., Taub, K., Vanderstraaten, C., *et al.* (2005). The impact of education on chronic kidney disease patients' plans to initiate dialysis with self-care dialysis: a randomized trial. *Kidney Int*, 68, 1777–83.

Marin, M., Güris, D., and Chaves, S. S. (2007). Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*, 56(RR-4) 1–40.

Marron, B., Ortiz, A., de Sequera, P., *et al.* (2006). Impact of end-stage renal disease care in planned dialysis start and type of renal replacement therapy—a Spanish multicentre experience. *Nephrol Dial Transplant*, 21 Suppl 2, ii51–5.

Martinez-Ramirez, H. R., Jalomo-Martinez, B., Cortes-Sanabria, L., *et al.* (2006). Renal function preservation in type 2 diabetes mellitus patients with early nephropathy: a comparative prospective cohort study between primary health care doctors and a nephrologist. *Am J Kidney Dis*, 47, 78–87.

Mason, J., Khunti, K., Stone, M., *et al.* (2008). Educational interventions in kidney disease care: a systematic review of randomized trials. *Am J Kidney Dis*, 51, 933–51.

McDonald, S., Excell, L., and Livingston, B. (eds.) (2009). ANZDATA Registry Report 2009, 32nd Report: Adelaide: ANZ Dialysis and Transplant Registry.

McLaughlin, K., Jones, H., VanderStraeten, C., *et al.* (2008). Why do patients choose self-care dialysis? Nephrol Dial Transplant, 23, 3972–6.

McLaughlin, K., Manns, B., Mortis, G., *et al.* (2003). Why patients with ESRD do not select self-care dialysis as a treatment option. *Am J Kidney Dis*, 41, 380–5.

Mendelssohn, D. C., Mujais, S. K., Soroka, S. D., *et al.* (2009). A prospective evaluation of renal replacement therapy modality eligibility. *Nephrol Dial Transplant*, 24, 555–61.

Merighi, J. R., Schatell, D. R., Bragg-Greshan, J. L., *et al.* (2012). Insights into nephrologist training, clinical practice, and dialysis choice. *Hemodial Int*, 16, 242–51.

Micozkadioglu, H., Zumrutal, A., Torun, D., *et al.* (2007). Low dose intradermal vaccination is superior to high dose intramuscular vaccination for hepatitis B in unresponsive haemodialysis patients. *Ren Fail*, 29, 285–8.

Montgomery, A. J., McGee, H. M., Shannon, W., *et al.* (2006). Factors influencing general practitioner referral of patients developing end-stage renal failure: a standardised case-analysis study. *BMC Health Serv Res*, 6, 114.

Morton, R., Snelling, P., Webster, A. C., *et al.* (2012a). Factors influencing patient choice of dialysis versus conservative care to treat end-stage kidney disease. *CMAJ*, 184, E277–83.

Morton, R. L., Howard, K., Webster, A. C., *et al.* (2011). Patient INformation about Options for Treatment (PINOT): a prospective national study of information given to incident CKD Stage 5 patients. *Nephrol Dial Transplant*, 26, 1266–75.

Morton, R. L., Snelling, P., Webster, A. C., *et al.* (2012b). Dialysis modality preference of patients with CKD and family caregivers: a discrete-choice study. *Am J Kidney Dis*, 60, 102–11.

Morton, R. L., Tong, A., Howard, K., *et al.* (2010). The views of patients and carers in treatment decision making for chronic kidney disease: systematic review and thematic synthesis of qualitative studies. *BMJ*, 340, c112.

O'Hare, A. M., Choi, A. I., Bertenthal, D., *et al.* (2007). Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol*, 18, 2758–65.

Owen, J. E., Walker, R. J., Edgell, L., *et al.* (2006). Implementation of a pre-dialysis clinical pathway for patients with chronic kidney disease. *Int J Qual Health Care*, 18, 145–51.

Peritoneal Dialysis Adequacy Work Group (2006). Clinical practice guidelines for peritoneal dialysis adequacy. *Am J Kidney Dis*, 48 Suppl 1, S98–129.

Qamar, M., Bender, F., Rault, R., *et al.* (2009). The United States' perspectives on home dialysis. *Adv Chronic Kidney Dis*, 16, 189–97.

Rakhit, D. J., Marwick, T. H., Armstrong, K. A., *et al.* (2006). Effect of aggressive risk factor modification on cardiac events and myocardial ischaemia in patients with chronic kidney disease. *Heart*, 92, 1402–8.

Rioux, J. -P., Bargman, J. M., and Chan, C. T. (2010). Systematic differences among patients initiated on home haemodialysis and peritoneal dialysis: the fallacy of potential competition. *Nephrol Dial Transplant*, 25, 2364–7.

Rioux, J. -P., Cheema, H., Bargman, J. M., *et al.* (2011). Effect of an in-hospital chronic kidney disease education program among patients with unplanned urgent-start dialysis. *Clin J Am Soc Nephrol*, 6, 799–804.

Rosansky, S., Glassock, R. J., and Clark, W. F. (2011). Early start of dialysis: a critical review. *Clin J Am Soc Nephrol*, 6, 1222–8.

Sawhney, S., Djurdjev, O., Simpson, K., *et al.* (2009). Survival and dialysis initiation: comparing British Columbia and Scotland registries. *Nephrol Dial Transplant*, 24, 3186–92.

Scharpé, J., Peetermans, W. E., Vanwalleghem, J., *et al.* (2009). Immunogenicity of a standard trivalent influenza vaccine in patients on long-term haemodialysis: an open-label trial. *Am J Kidney Dis*, 54, 77–85.

Sipilä, R., Hortling, L., and Hovi, T. (1990). Good seroresponse to enhanced-potency inactivated poliovirus vaccine in patients on chronic dialysis. *Nephrol Dial Transplant*, 5, 352–5.

Slinin, Y., Haifeng, G., Gilbertson, D. T., *et al*. (2011). Prehaemodialysis care by dietitians and first-year mortality after initiation of hemodialysis. *Am J Kidney Dis*, 58, 583–90.

Smart, N. A. and Titus, T. T. (2011). Outcomes of early versus late nephrology referral in chronic kidney disease: a systematic review. *Am J Med*, 124, 1073–80.

Stack, A. G. (2002). Determinants of modality selection among incident US dialysis patients: results from a national study. *J Am Soc Nephrol*, 13, 1279–87.

Winkelmayer, W. C., Glynn, R. J., Levin, R., *et al*. (2001). Later referral and modality choice in end-stage renal disease. *Kidney Int*, 60, 1–1554.

Winkelmayer, W. C., Liu, J., Chertow, G. M., *et al*. (2011). Predialysis nephrology care of older patients approaching end-stage renal disease. *Arch Intern Med*, 171, 1371–8.

Winkelmayer, W. C., Mehta, J., Chandraker, A., *et al*. (2007). Predialysis nephrologist care and access to kidney transplantation in the United States. *Am J Transplant*, 7, 872–9.

Wright, S., Klausner, D., Baird, B., *et al*. (2010). Timing of dialysis initiation and survival in ESRD. *Clin J Am Soc Nephrol*, 5, 1828–35.

Yamagata, K., Nakai, S., Masakane, I., *et al*. (2012). Ideal timing and predialysis nephrology care duration for dialysis initiation: from analysis of Japanese dialysis initiation survey. *Ther Apher Dial*, 16, 54–62.

CHAPTER 144

Choices and considerations for in-centre versus home-based renal replacement therapy

Karthik K. Tennankore and Christopher T. Chan

Introduction

Globally, the number of dialysis patients has been increasing. The 2011 United States Renal Data System (USRDS) report (USRDS, 2011) identified a 20% increase in the number of adjusted, prevalent end-stage renal disease (ESRD) patients from 2000 to 2009. Similar growth has been demonstrated in Europe and Canada (European Renal Association-European Dialysis and Transplant Association, 2009; Canadian Organ Replacement Register, 2011). Some of the increase in prevalent ESRD may be due to higher numbers of elderly dialysis patients. To accommodate this increase, in addition to transplantation, emphasis needs to be placed on selecting the appropriate balance of in-centre haemodialysis (HD) and home dialysis therapy. This balance is influenced by patient preference, patient characteristics, treatment cost, and facility infrastructure. As the perceived importance of each factor is different between dialysis centres, there is marked variation in modality distribution between countries (Fig. 144.1). Only 7% of all incident USRDS dialysis patients were on peritoneal dialysis (PD) in 2009. The 2010 UK Renal Registry reported a wide variation between in-centre HD (78%) and PD (19%) (UK Renal Registry, 2010). Contrarily, dialysis programmes in Hong Kong and Mexico have > 50% of their patients on PD (USRDS, 2011). The prevalence of home haemodialysis (HHD) is much lower, ranging between 0% and 3% in most countries. Higher numbers have been achieved in Australia and New Zealand (Australia and New Zealand Dialysis and Transplant Registry, 2010). Thus far, no study has determined the optimal balance of home versus in-centre therapy. In this chapter, we will review the important considerations surrounding optimal modality distribution, with an emphasis on patient, physician, and facility considerations.

Patient considerations

Should clinical outcome influence modality selection?

A robust review of the clinical advantages of home dialysis or in-centre HD is not the focus of this chapter, and will be presented in greater detail in other chapters of this book. To summarize:

1. Mortality comparisons between PD and in-centre HD have demonstrated different survival results depending on the population studied, time period of follow-up, relevant confounders, and study design (Perl et al., 2011; Quinn et al., 2011). PD patients may have an improved therapy satisfaction compared to in-centre HD (Rubin et al., 2004; Juergensen et al., 2006).
2. There are many potential clinical benefits to both nocturnal haemodialysis (NHD) and short daily haemodialysis (SDHD) (Perl and Chan 2009). Registry data has demonstrated a survival advantage to all forms of HHD over in-centre HD (Marshall et al., 2011).
3. Patient survival may also be influenced by treatment characteristics as opposed to location. For example, patients on extended hours in-centre HD may have a survival advantage over patients on shorter duration in-centre HD (Charra et al., 2004).

Overall, while the findings of observational studies need to be interpreted with caution, on the basis of most clinical outcomes, both home PD and HHD appear to be equivalent or superior to in-centre HD.

Does education impact patient choice?

Most patients prefer to make their own modality 'choice' (Korevaar et al., 2003). However, while informed choice is emphasized, pre-dialysis information may be lacking. Historically, as high as 66% and 88% of patients in the United States were not exposed to PD or HHD as treatment options prior to dialysis initiation (Mehrotra et al., 2005). Inadequate modality exposure leads to selection of in-centre HD (Stack 2002). This is evident in patients who are referred late (Lameire and Van Biesen, 1999). In addition, simply exposing an individual to home dialysis may not be sufficient. The quality of education, degree of patient involvement, level of patient understanding, and duration of time spent discussing treatment options are important considerations (Stack, 2002; McLaughlin et al., 2003; Mehrotra et al., 2005; McLaughlin et al., 2008). However, even with adequate exposure, not all patients select home dialysis (Kutner et al., 2011). Notwithstanding, improved education quality through standardized programmes has been successful at increasing the use of home therapies (Manns et al., 2005; Lacson et al., 2011). Even unplanned, urgent dialysis starts can be educated and immediately transitioned to home dialysis (Rioux et al., 2011). In summary, education has a major influence on modality selection. When patients are given effective pre-dialysis education, a considerable portion will chose HHD and close to 50% will chose PD over in-centre HD (Korevaar et al., 2003).

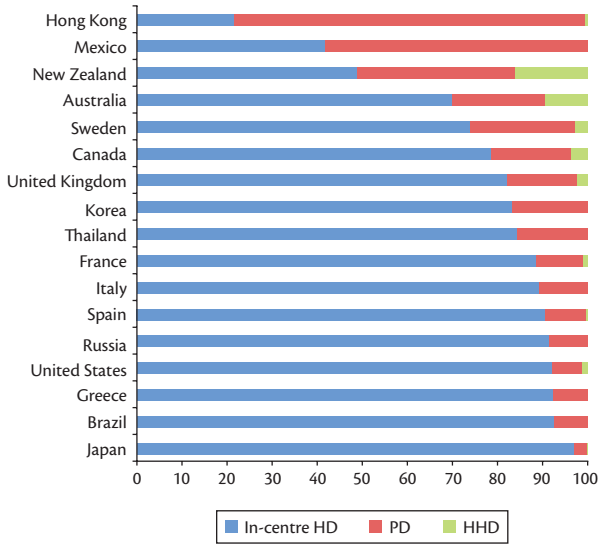

Fig. 144.1 International distribution of prevalent dialysis modalities (per cent). Adapted from the Australia and New Zealand Dialysis and Transplant Registry, Canadian Organ Replacement Register, European Renal Association-European Dialysis and Transplant Association, USRDS, and UK Renal Registry.

Do patients have self-perceived barriers to home dialysis?

Many patients have self-identified psychological obstacles to home dialysis including a lack of interest, fear of changing modality, perceived lack of self-efficacy, fear of substandard care, and belief that patients should not be involved in self-care (McLaughlin et al., 2003; Cafazzo et al., 2009; Zhang et al., 2010) (Table 144.1). Presumably, unpaid caregivers can address some of these fears by supporting patients at home. However, the transition to home can be associated with a significant burden on unpaid caregivers (Belasco et al., 2006), which is recognized by patients (Suri et al., 2011). In turn, patient perceived caregiver burden is a barrier to home dialysis (Cafazzo et al., 2009). While barriers are common, there are also patient-perceived advantages to home dialysis. These include a sense of freedom, improved lifestyle, and a greater sense of control. Education increases the number of patients who appreciate these advantages (McLaughlin et al., 2008). In addition to psychological limitations, there are treatment-specific barriers to home dialysis. For example, fear of self-cannulation, a needle disconnect, or a catastrophic event, limit patient selection of HHD (Cafazzo et al., 2009). With the use of nurse-directed cannulation training and home monitoring, these fears can be overcome (Cafazzo et al., 2010; Pipkin et al., 2010).

Table 144.1 Patient perspectives on home dialysis

	General attitude	Treatment-specific attitude
Favours selection of home dialysis	Greater freedom	Freedom of time and diet
	Better lifestyle	Accommodates desire to work
	More control	Reduced travel to dialysis unit
	Increased involvement in care	Cheaper modality
	Reduced dependence	
Favours selection of in-centre HD	Lack of self-efficacy	Therapy will interfere with home life
	Fear of substandard care and lack of supervision	Fear of machine
	Fear of social isolation	Fear of a catastrophic event
	Lack of motivation	Fear of self-cannulation (NHD)
	Fear of change	Fear of needle disconnect (NHD)
	Belief that patient should not be involved in care	Intradialytic symptoms during HD
	Family or patient disinterest	Therapy is time-consuming
	Fear of burdening caregivers	Negative impact of therapy on sleep
	Lack of social support	Unable to manage at home because of physical limitations
		Perceived lack of home space

HD = haemodialysis; NHD = nocturnal haemodialysis.

Adapted from McLaughlin et al. (2003, 2008), Cafazzo et al. (2009), and Zhang et al. (2010).

Physician considerations

Is advanced age a contraindication to dialysing patients at home?

Most national registries demonstrate an age-related decline in the use of home dialysis. Even in countries with high numbers of home dialysis patients, older age is associated with a greater use of in-centre HD (Fig. 144.2). Some of the age-related ineligibility for home dialysis may be related to concurrent medical comorbidity, cognitive impairment, poor coordination, decreased vision, and limited motor strength (Jung et al., 1999; Mendelssohn et al., 2001; Jassal et al., 2002). In addition to registry data, a prospective evaluation of modality selection identified that older patients are often deemed ineligible for PD (Mendelssohn et al., 2009). HHD patients are typically even younger than those on PD or in-centre HD (Zhang et al., 2010). However, while age may be a barrier in most countries, a registry study from France identified that in some centres, older patients were more likely to be on PD (Couchoud et al., 2008). This may reflect the use of nurse- and family-assisted PD (Lobbedez et al., 2006). Providing family assistance improves PD utilization (Oliver et al., 2010), and patients receiving assisted PD have comparable outcomes to those on autonomous PD (Verger et al., 2007). This suggests that advanced age is not a contraindication to home dialysis.

What additional patient characteristics influence modality distribution?

Medical comorbidity may limit the number of patients on home therapy (Miskulin et al., 2002). However, even if medical comorbidity limits the use of home dialysis, it may not reduce the probability of it being offered to patients (Mehrotra et al., 2005). Overall, < 20% of patients have medical contraindications to PD in studies conducted in Canada, the United Kingdom, and the Netherlands (Prichard, 1996; Little et al., 2001; Jager et al., 2004; Oliver et al., 2010). Patients with medical barriers tend to be older (Jager et al., 2004). While medical barriers exist for in-centre HD, the prevalence is low. Only 2–3% of chronic kidney disease (CKD) patients had a medical contraindication to in-centre HD in two prospective studies (Jager et al., 2004; Mendelssohn et al., 2009). In addition to medical barriers, 5% and 17% of CKD patients have been identified to be psychosocially ineligible for in-centre HD and PD, respectively (Mendelssohn et al., 2009). Barriers to all dialysis modalities are noted in Table 144.2. Once again, some barriers can be overcome. For example, providing nurse or family assistance for patients on PD has been shown to increase eligibility in those with medical or psychosocial barriers (Oliver et al., 2007, 2010).

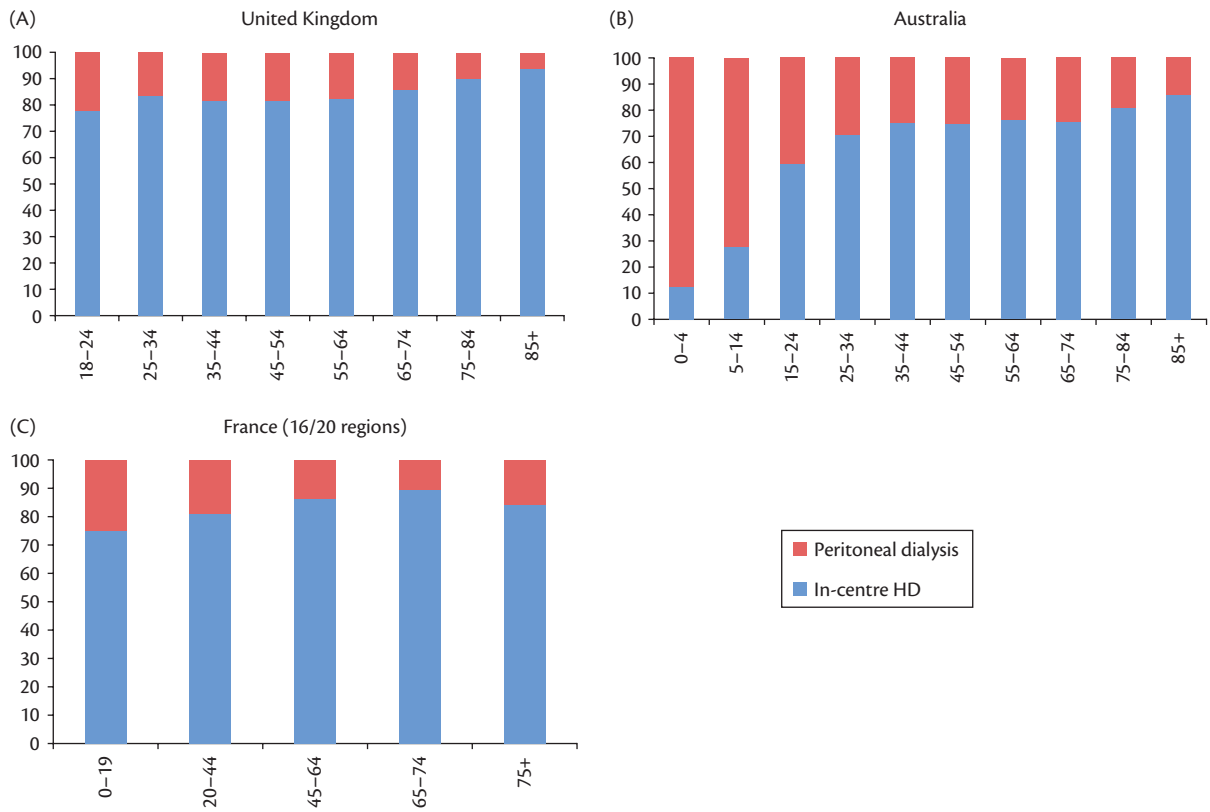

Fig. 144.2 Percentage of patients on PD and in-centre HD at different age cut-offs. (A) The United Kingdom. (B) Australia. (C) France.

Adapted from the Australia and New Zealand Dialysis and Transplant Registry, European Renal Association-European Dialysis and Transplant Association, and UK Renal Registry.

Table 144.2 Medical, cognitive, psychosocial, and treatment barriers to dialysis

	Medical	Cognitive/psychosocial	Physical/therapy
Any dialysis	Terminal illness		
In-centre HD	Poor cardiac function	Non-compliance[b]	Distance from in-centre facility
		Severe psychiatric illness[b]	Absence of suitable vascular access
		Severe dementia[b]	
Home dialysis	*PD:*	*PD and HHD:*	*PD and HHD:*
	Gastrointestinal disease[a]	Language	Lack of residence/space
	Massive polycystic kidneys	Poor memory	Poor vision[c]
	Severe lung disease	Severe dementia	Manual dexterity[c]
	Morbid obesity	Non-compliance	Limited motor strength[c]
	HHD:	Severe psychiatric illness	Living alone and requiring assistance
	Absence of suitable vascular access	Frailty and disability	
	Contraindication to use of dialysis anticoagulation		

[a] Includes both abdominal and gastrointestinal disease: severe abdominal scarring, multiple prior surgeries, acute diverticulitis or colitis, refractory hernia, ileostomy/colostomy, active bowel cancer, gastric tube, ileal conduit, ischaemic gut, intra-abdominal foreign body.

[b] Barrier to in-centre HD if the conditions lead to actions that put the staff or patient at risk.

[c] Provided no caregiver available.

HD = haemodialysis; HHD = home haemodialysis; PD = peritoneal dialysis.

Adapted from Prichard (1996), Little et al. (2001), Jager et al. (2004), Mendelssohn et al. (2009), Oliver et al. (2010), and Rioux et al. (2010b).

What non-patient factors influence physicians?

Training

The level of fellowship training may influence modality distribution. A recent survey of American Society of Nephrology fellows identified that only 16% and 56% felt well trained/competent in HHD and PD, respectively (Berns, 2010). Limited training is a barrier to the use of PD (Bouvier et al., 2009) and a lack of expertise limits HHD growth (Ludlow et al., 2011).

Reimbursement

Surveys of nephrologists suggest that physician remuneration has a minimal influence on modality selection (Jung et al., 1999; Mendelssohn et al., 2001). However, poor reimbursement relative to in-centre HD has been identified as a significant barrier to the adoption of PD in the French private sector (Bouvier et al., 2009). Contrarily, some Australian nephrologists receive government reimbursement for extra work associated with home dialysis. Not unexpectedly, only 15% support the view that they are financially disadvantaged by starting patients on home dialysis (Ludlow et al., 2011). In the United States (a country with very a low proportion of patients on home therapy), physician reimbursement is modality independent (Blake and Finkelstein 2001). While this may appear to be a strong incentive to home dialysis use, there are sources of profit that are external to capitation fees. These include additional funds for injectable medications and inpatient tests, both of which are easily provided to in-centre HD patients. In a similar capitation system in the province of Ontario, Canada, additional funds external to capitation are not provided. Ontario had seen a relative increase in the proportion of patients on home dialysis relative to the rest of Canada several years after the capitation system was instituted (Mendelssohn et al., 2004). Whether the proportion of patients on home dialysis in the United States will increase after introduction of the bundling system (which may reduce income from external sources) remains to be seen (Blagg, 2011).

Nephrologists consistently identify that patient preference is the most important consideration when determining optimal modality distribution. Most nephrologists feel that home dialysis should be > 40% of a given centre's practice (Jung et al., 1999; Mendelssohn et al., 2001; Jassal et al., 2002). Contrarily, even within single regions of a country, the number of patients on home dialysis versus in-centre HD can vary considerably from centre to centre (Ontario Renal Network, 2011). Addressing training gaps and considering financial incentives may increase the use of home therapies.

Facility considerations

Should therapy cost impact modality distribution?

Many comparative cost analyses between in-centre HD and home dialysis have been performed. Several important limitations need to be considered (Klarenbach and Manns, 2009; McFarlane and Komenda, 2011):

1. Randomized controlled trials have not demonstrated a survival benefit to home dialysis versus in-centre HD. A survival advantage of one modality over another would increase total cost; however, it would also improve cost-effectiveness.
2. Most analyses do not consider the societal or opportunity costs of dialysis. Higher employment rates (Helanterä et al.,

Table 144.3 Modality cost comparisons for selected studies

Study	Groups compared	Monetary unit	Comparison factor	Comparison result
McFarlane and Komenda, 2011	In-centre HD vs home/self-care	2011 Canadian $	Total annual cost	93,976 vs 54,936
	In-centre HD vs home NHD vs home SDHD		Total annual cost	89,154 vs 91,218 vs 82,522
	In-centre HD vs home NHD		Total annual cost	87,172 vs 71,313
	In-centre HD vs home NHD		Cost/QALY	148,722/QALY vs 84,430/QALY
Lee et al., 2002	In-centre HD vs PD	2011 Canadian $	Total annual cost	93,222 vs 49,036
Baboolal et al., 2008	In-centre HD vs PD vs HHD	2006 British £	Total annual cost	33,846 vs 18,613 vs 20,764
Agar et al., 2005	Satellite HD vs home NHD	2003-2004 Australian $	Annualized programme cost	36,284 vs 32,392
Shih et al., 2005	In-centre HD vs PD	2004 US $	Adjusted annual Medicare expenditure	68,253 vs 56,807

HD = haemodialysis; HHD = home haemodialysis; NHD = nocturnal haemodialysis; PD = peritoneal dialysis; QALY = quality-adjusted life year; SDHD = short daily haemodialysis.
Updated using Canadian consumer price index, November 2011.

2012) and a decreased need for transport favour the use of home dialysis. Contrarily, increased HHD utility costs benefit use of in-centre HD.

3. Cost utility analyses use estimates of quality of life, which may be inaccurate.
4. The fixed capital costs of establishing a home dialysis programme are not always considered in cost analyses, or compared to in-centre HD fixed costs.
5. Only a limited number of studies have used matched cohorts.
6. Studies of in-centre HD costs have not selectively considered intensive HD regimens.

A summary of select economic studies is noted in Table 144.3.

Peritoneal dialysis

Both autonomous and nurse-assisted PD are cheaper compared to in-centre HD in most developed countries (Just et al., 2008). Contrarily, PD is often more expensive in developing countries. This may be due to the cost of importing solutions (Just et al., 2008) and limited government reimbursement. Countries with a low per-capita gross national income have lower proportions of patients on PD (Li and Chow 2001).

Home haemodialysis

McFarlane and Komenda (2011) summarized four Canadian cost studies and made several important conclusions. HHD is cheaper than in-centre HD, although the magnitude of cost savings differ between studies. Most of the savings are due to decreased nursing costs, which offset the greater cost of dialysis materials (Fig. 144.3). Specific to NHD, the total cost over the lifetime of a patient remains cheaper compared to in-centre HD (McFarlane et al., 2006).

To conclude, even after considering the limitations of economic evaluations, both peritoneal and home haemodialysis should be encouraged if an emphasis is placed on total cost and cost utility.

What facility factors influence modality selection?

In addition to cost, there are other facility level considerations that impact modality distribution. Larger centres and non-chain facilities tend to have more patients on home dialysis (Walker et al., 2010). PD or HHD can be successfully performed in rural locations despite a low availability of home dialysis training (O'Hare et al., 2006). In the United States, the proportion of patients on PD is lower in most large dialysis organization (LDO) run units and for-profit dialysis units regardless of LDO status (Mehrotra et al., 2009). This suggests that facility level profit may promote the use of in-centre HD.

Infrastructure

Intuitively, establishing a new in-centre HD facility requires tremendous upfront physical resources including the dialysis machines, storage space, central nursing station, and water treatment facility. Personnel, including nurses, technicians, physicians, dieticians, pharmacists, and social workers, are also required. Providing dedicated nurses for patient training, retraining, monitoring, and home visits is an important component of home dialysis infrastructure (Bernardini et al., 2006; Rioux et al., 2010b). In addition, a successful PD programme benefits from an

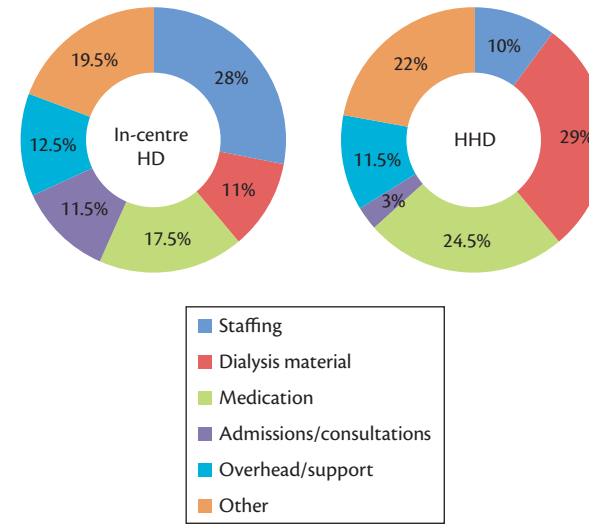

Fig. 144.3 Percentage distribution of cost categories for in-centre versus home HD.
Adapted from McFarlane et al. (2002) and Kroecker et al. (2003) (averaged data).

access nurse and dedicated surgical team for catheter implantation (Figueiredo et al., 2010). Training nephrologists to place PD catheters may be an alternative to a surgical team and has been met with success (Gadallah et al., 2001; Asif et al., 2003). Finally, while central venous catheter (CVC) HD access should not be a barrier to home dialysis (Perl et al., 2006), a dedicated HD access coordinator is an additional important resource for HHD. While infrastructure is critical for both in-centre HD and home dialysis, most institutions have established in-centre HD units. Therefore, the seamless transition of a CKD patient to in-centre HD is much easier than creating infrastructure for a new PD or HHD facility. As expected, physicians have identified that a lack of infrastructure is an important barrier to home dialysis (Ludlow et al., 2011). Centralization of training may be effective at overcoming this barrier (Honkanen and Rauta, 2008); improving an existing training facility is expected to be less resource intensive than creating a new one.

Competing therapies

Expanding satellite dialysis facilities and increasing HD capacity may limit the number of patients on home dialysis (Mendelssohn et al., 2004). Contrarily, while PD and HHD are both home dialysis therapies, they may not 'compete' for the same patients. Characteristics of patients on PD and HHD appear to be different (Rioux et al., 2010a). Only a small proportion of HHD patients come from PD technique failure (Copland et al., 2009). Finally, the expansion of a large HHD programme in Canada, did not affect the growth of PD (Copland et al., 2009). In fact, individual growth of the two therapies may work synergistically, by promoting a general shift of resources towards home dialysis.

Conclusions

In this chapter, we have highlighted some of the major considerations surrounding selection of in-centre versus home-based renal replacement therapy:

1. On the basis of clinical outcome and cost (in the developed world) a greater proportion of patients should be on home therapies.
2. There are differences between patient and physician opinion(s) and practice patterns with respect to dialysis modality. When given effective modality education and choice, more patients will select home dialysis.
3. There are surmountable demographic, medical, and psychosocial barriers to home therapies.
4. Finally, at the physician and facility level, an emphasis on training, infrastructure, incentives, and reimbursement will likely increase the use of home dialysis.

To summarize, the evidence would suggest that expansion of home dialysis should be a common initiative for physicians, multidisciplinary support staff, administrators, and policymakers. At the centre level, physicians and facility administrators need to identify and address home dialysis barriers. At the national level, home dialysis expansion needs to be an important focus of policymakers. Finally, at the international level, an emphasis needs to be placed on making home dialysis more accessible and cost-effective for developing countries. However, in-centre HD will always remain an important treatment option for the large number of dialysis patients who cannot manage at home. Furthermore, as a home dialysis programme expands, there will be continued need for a supportive in-centre HD programme to accommodate those patients who can no longer maintain at home.

Overall, recognizing that the factors that influence modality selection will differ between centres, regions, and countries, there is no standard, optimal, modality distribution. Rather, engaging stakeholders to maximize the number of patients on home dialysis therapies is an achievable, practical goal.

References

Agar, J. W., Knight, R. J., Simmonds, R. E., *et al.* (2005). Nocturnal haemodialysis: an Australian cost comparison with conventional satellite haemodialysis. *Nephrology*, 10, 557–70.

Asif, A., Byers, P., Gadalean, F., *et al.* (2003). Peritoneal dialysis underutilization: the impact of an interventional nephrology peritoneal dialysis access program. *Semin Dial*, 16, 266–71.

Australia and New Zealand Dialysis and Transplant Registry (2010). 33rd Annual Report 2010. Adelaide: Australia and New Zealand Dialysis and Transplant Registry.

Baboolal, K., McEwan, P., Sondhi, S., *et al.* (2008). The cost of renal dialysis in a UK setting—a multicentre study. *Nephrol Dial Transplant*, 23, 1982–9.

Belasco, A., Barbosa, D., Bettencourt, A. R., *et al.* (2006). Quality of life of family caregivers of elderly patients on hemodialysis and peritoneal dialysis. *Am J Kidney Dis*, 48, 955–63.

Bernardini, J., Price, V., and Figueiredo, A. (2006). Peritoneal dialysis patient training, 2006. *Perit Dial Int*, 26, 625–32.

Berns, J. S. (2010). A survey-based evaluation of self-perceived competency after nephrology fellowship training. *Clin J Am Soc Nephrol*, 5, 490–6.

Blagg, C. R. (2011). Dialysis composite rate bundling: potential effects on the utilization of home hemodialysis, daily and nocturnal hemodialysis, and peritoneal dialysis. *Semin Dial*, 6, 674–7.

Blake, P. G. and Finkelstein, F. O. (2001). Why is the proportion of patients doing peritoneal dialysis declining in North America? *Perit Dial Int*, 21, 107–14.

Bouvier, N., Durand, P. Y., Testa, A., *et al.* (2009). Regional discrepancies in peritoneal dialysis utilization in France: the role of the nephrologist's opinion about peritoneal dialysis. *Nephrol Dial Transplant*, 24, 1293–7.

Cafazzo, J. A., Leonard, K., Easty, A. C., *et al.* (2009). Patient-perceived barriers to the adoption of nocturnal home hemodialysis. *Clin J Am Soc Nephrol*, 4, 784–9.

Cafazzo, J. A., Leonard, K., Easty, A. C., *et al.* (2010). Patient perceptions of remote monitoring for nocturnal home hemodialysis. *Hemodial Int*, 14, 471–7.

Charra, B., Terrat, J. C., Vanel, T. *et al.* (2004). Long thrice weekly hemodialysis: the Tassin experience. *Int J Artif Organs*, 27, 265–83.

Copland, M., Murphy-Burke, D., Levin, A., *et al.* (2009). Implementing a home haemodialysis programme without adversely affecting a peritoneal dialysis programme. *Nephrol Dial Transplant*, 24, 2546–50.

Canadian Organ Replacement Register (2011). CORR Report 2011: Treatment of End-Stage Organ Failure in Canada 2000–2009. Ottawa: Canadian Institute for Health Information, Canadian Organ Replacement Register.

Couchoud, C., Savoye, E., Frimat, L., *et al.* (2008). Variability in case mix and peritoneal dialysis selection in fifty-nine French districts. *Perit Dial Int*, 28, 509–17.

European Renal Association-European Dialysis and Transplant Association (2009). Annual Report 2009. Amsterdam: Registry of the European Renal Association-European Dialysis and Transplant Association.

Figueiredo, A., Goh, B. L., Jenkins, S., *et al.* (2010). Clinical practice guidelines for peritoneal access. *Perit Dial Int*, 30, 424–9.

Gadallah, M. F., Ramdeen, G., Torres-Rivera, C., *et al.* (2001). Changing the trend: a prospective study on factors contributing to the growth rate of peritoneal dialysis programs. *Adv Perit Dial*, 17, 122–6.

Helanterä, I., Haapio, M., Koskinen, P., *et al.* (2012). Employment of patients receiving maintenance dialysis and after kidney transplant: a cross-sectional study from Finland. *Am J Kidney Dis*, 59(5), 700–6.

Honkanen, E. O. and Rauta, V. M. (2008). What happened in Finland to increase home hemodialysis? *Hemodial Int*, 12 Suppl 1, S11–15.

Jager, K. J., Korevaar, J. C., Dekker, F. W., *et al.* (2004). The effect of contraindications and patient preference on dialysis modality selection in ESRD patients in the Netherlands. *Am J Kidney Dis*, 43, 891–9.

Jassal, S. V., Krishna, G., Mallick, N. P., *et al.* (2002). Attitudes of British Isles nephrologists towards dialysis modality selection: a questionnaire study. *Nephrol Dial Transplant*, 17, 474–7.

Juergensen, E., Wuerth, D., Finkelstein, S. H., *et al.* (2006). Hemodialysis and peritoneal dialysis: patients' assessment of their satisfaction with therapy and the impact of the therapy on their lives. *Clin J Am Soc Nephrol*, 1, 1191–6.

Jung, B., Blake, P. G., Mehta, R. L., *et al.* (1999). Attitudes of Canadian nephrologists toward dialysis modality selection. *Perit Dial Int*, 19, 263–8.

Just, P. M., Riella, M. C., Tschosik, E. A., *et al.* (2008). Economic evaluations of dialysis treatment modalities. *Health Policy*, 86, 163–80.

Klarenbach, S. and Manns, B. (2009). Economic evaluation of dialysis therapies. *Semin Nephrol*, 29, 524–32.

Korevaar, J. C., Feith, G. W., Dekker, F. W., *et al.* (2003). Effect of starting with hemodialysis compared with peritoneal dialysis in patients new on dialysis treatment: a randomized controlled trial. *Kidney Int*, 64, 2222–8.

Kutner, N. G., Zhang, R., Huang, Y., *et al.* (2011). Patient awareness and initiation of peritoneal dialysis. *Arch Int Med*, 171, 119–24.

Lacson, E., Jr., Wang, W., Devries, C., *et al.* (2011). Effects of a nationwide predialysis educational program on modality choice, vascular access, and patient outcomes. *Am J Kidney Dis*, 58, 235–42.

Lameire, N. and Van Biesen, W. (1999). The pattern of referral of patients with end-stage renal disease to the nephrologist—a European survey. *Nephrol Dial Transplant*, 14 Suppl 6, 16–23.

Lee, H., Manns, B., Taub, K., *et al.* (2002). Cost analysis of ongoing care of patients with end-stage renal disease: the impact of dialysis modality and dialysis access. *Am J Kidney Dis*, 40, 611–22.

Li, P. K. and Chow, K. M. (2001). The cost barrier to peritoneal dialysis in the developing world—an Asian perspective. *Perit Dial Int*, 21 Suppl 3, S307–13.

Little, J., Irwin, A., Marshall, T., *et al.* (2001). Predicting a patient's choice of dialysis modality: experience in a United Kingdom renal department. *Am J Kidney Dis*, 37, 981–6.

Lobbedez, T., Moldovan, R., Lecame, M., *et al.* (2006). Assisted peritoneal dialysis. Experience in a French renal department. *Perit Dial Int*, 26, 671–6.

Ludlow, M. J., George, C. R., Hawley, C. M., *et al.* (2011). How Australian nephrologists view home dialysis: results of a national survey. *Nephrology*, 16, 446–52.

Manns, B. J., Taub, K., Vanderstraeten, C., *et al.* (2005). The impact of education on chronic kidney disease patients' plans to initiate dialysis with self-care dialysis: a randomized trial. *Kidney Int*, 68, 1777–83.

Marshall, M. R., Hawley, C. M., Kerr, P. G., *et al.* (2011). Home hemodialysis and mortality risk in Australian and New Zealand populations. *Am J Kidney Dis*, 58, 782–93.

McFarlane, P. and Komenda, P. (2011). Economic considerations in frequent home hemodialysis. *Semin Dial*, 6, 678–83.

McFarlane, P. A., Bayoumi, A. M., Pierratos, A., *et al.* (2006). The impact of home nocturnal hemodialysis on end-stage renal disease therapies: a decision analysis. *Kidney Int*, 69, 798–805.

McLaughlin, K., Jones, H., Vanderstraeten, C., *et al.* (2008). Why do patients choose self-care dialysis? *Nephrol Dial Transplant*, 23, 3972–6.

McLaughlin, K., Manns, B., Mortis, G., *et al.* (2003). Why patients with ESRD do not select self-care dialysis as a treatment option. *Am J Kidney Dis*, 41, 380–5.

Mehrotra, R., Khawar, O., Duong, U., *et al.* (2009). Ownership patterns of dialysis units and peritoneal dialysis in the United States: utilization and outcomes. *Am J Kidney Dis*, 54, 289–98.

Mehrotra, R., Marsh, D., Vonesh, E., *et al.* (2005). Patient education and access of ESRD patients to renal replacement therapies beyond in-center hemodialysis. *Kidney Int*, 68, 378–90.

Mendelssohn, D. C., Langlois, N., and Blake, P. G. (2004). Peritoneal dialysis in Ontario: a natural experiment in physician reimbursement methodology. *Perit Dial Int*, 24, 531–7.

Mendelssohn, D. C., Mujais, S. K., Soroka, S. D., *et al.* (2009). A prospective evaluation of renal replacement therapy modality eligibility. *Nephrol Dial Transplant*, 24, 555–61.

Mendelssohn, D. C., Mullaney, S. R., Jung, B., *et al.* (2001). What do American nephrologists think about dialysis modality selection? *Am J Kidney Dis*, 37, 22–9.

Miskulin, D. C., Meyer, K. B., Athienites, N. V., *et al.* (2002). Comorbidity and other factors associated with modality selection in incident dialysis patients: the Choice Study. Choices for healthy outcomes in caring for end-stage renal disease. *Am J Kidney Dis*, 39, 324–36.

O'Hare, A. M., Johansen, K. L., and Rodriguez, R. A. (2006). Dialysis and kidney transplantation among patients living in rural areas of the United States. *Kidney Int*, 69, 343–9.

Oliver, M. J., Garg, A. X., Blake, P. G., *et al.* (2010). Impact of contraindications, barriers to self-care and support on incident peritoneal dialysis utilization. *Nephrol Dial Transplant*, 25, 2737–44.

Oliver, M. J., Quinn, R. R., Richardson, E. P., *et al.* (2007). Home care assistance and the utilization of peritoneal dialysis. *Kidney Int*, 71, 673–8.

Ontario Renal Network (2011). CKD System Atlas 2011. Toronto: Ontario Renal Network. <http://www.renalnetwork.on.ca/cms/One.aspx?portalId=98038&pageId=105060>

Perl, J. and Chan, C. T. (2009). Home hemodialysis, daily hemodialysis, and nocturnal hemodialysis: core curriculum 2009. *Am J Kidney Dis*, 54, 1171–84.

Perl, J., Lok, C. E., and Chan, C. T (2006). Central venous catheter outcomes in nocturnal hemodialysis. *Kidney Int*, 70, 1348–54.

Perl, J., Wald, R., Mcfarlane, P., *et al.* (2011). Hemodialysis vascular access modifies the association between dialysis modality and survival. *J Am Soc Nephrol*, 22, 1113–21.

Pipkin, M., Eggers, P. W., Larive, B., *et al.* (2010). Recruitment and training for home hemodialysis: experience and lessons from the Nocturnal Dialysis Trial. *Clinical J Am Soc Nephrol*, 5, 1614–20.

Prichard, S. S. (1996). Treatment modality selection in 150 consecutive patients starting ESRD therapy. *Perit Dial Int*, 16, 69–72.

Quinn, R. R., Hux, J. E., Oliver, M. J., *et al.* (2011). Selection bias explains apparent differential mortality between dialysis modalities. *J Am Soc Nephrol*, 22, 1534–42.

Rioux, J. P., Bargman, J. M., and Chan, C. T. (2010a). Systematic differences among patients initiated on home haemodialysis and peritoneal dialysis: the fallacy of potential competition. *Nephrol Dial Transplant*, 25, 2364–7.

Rioux, J. P., Cheema, H., Bargman, J. M., *et al.* (2011). Effect of an in-hospital chronic kidney disease education program among patients with unplanned urgent-start dialysis. *Clin J Am Soc Nephrol*, 6, 799–804.

Rioux, J. P., Faratro, R., and Chan, C. T. (2010b). Nocturnal home hemodialysis: implementation, quality assurance and future challenges. *Minerva Urol Nefrol*, 62, 103–10.

Rubin, H. R., Fink, N. E., Plantinga, L. C., *et al.* (2004). Patient ratings of dialysis care with peritoneal dialysis vs hemodialysis. *JAMA*, 291, 697–703.

Shih, Y. C., Guo, A., Just, P. M., *et al.* (2005). Impact of initial dialysis modality and modality switches on Medicare expenditures of end-stage renal disease patients. *Kidney Int*, 68, 319–29.

Stack, A. G. (2002). Determinants of modality selection among incident us dialysis patients: results from a national study. *J Am Soc Nephrol*, 13, 1279–87.

Suri, R. S., Larive, B., Garg, A. X., *et al.* (2011). Burden on caregivers as perceived by hemodialysis patients in the Frequent Hemodialysis Network (FHN) trials. *Nephrol Dial Transplant*, 26, 2316–22.

UK Renal Registry (2010). 2010 Report. Bristol: UK Renal Registry.

United States Renal Data System (2011). USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in The United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Verger, C., Duman, M., Durand, P. Y., *et al.* (2007). Influence of autonomy and type of home assistance on the prevention of peritonitis in assisted automated peritoneal dialysis patients. An analysis of data from the French language peritoneal dialysis registry. *Nephrol Dial Transplant*, 22, 1218–23.

Walker, D. R., Inglese, G. W., Sloand, J. A., *et al.* (2010). Dialysis facility and patient characteristics associated with utilization of home dialysis. *Clinical J Am Soc Nephrol*, 5, 1649–54.

Zhang, A. H., Bargman, J. M., Lok, C. E., *et al.* (2010). Dialysis modality choices among chronic kidney disease patients: identifying the gaps to support patients on home-based therapies. *Int Urol Nephrol*, 42, 759–64.

CHAPTER 145

Conservative care in advanced chronic kidney disease

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Introduction

With increased longevity, advanced stage 5 chronic kidney disease (CKD) (estimated glomerular filtration rate (eGFR) < 15 mL/min) has become an increasingly common problem, particularly extending to those patients with multiple co-morbidities. Individuals in high-income countries are often faced with difficult treatment choices about whether to proceed with dialysis or not, while the resources for dialysis are often not widely available in low- and middle-income countries. In this chapter, we describe the development, emerging evidence, and implications for best care of those patients with stage 5 CKD who are managed conservatively, without dialysis.

Terminology

Among older people with multiple co-morbidities, kidney transplantation is rarely an option because of unacceptable risk. The pragmatic choices therefore are between various forms of dialysis, and non-dialytic or conservative therapies. There is no consensus regarding terminology for these latter conservative approaches. Box 145.1 provides a full though not exhaustive list of the commonly used terms. For the purposes of this chapter we have adopted the term conservative management (CM) to avoid confusion.

The varied terminology also reflects varying approaches to care for patients who either do not wish to receive dialysis or are not deemed suitable and therefore are not offered renal replacement therapy. Treatment pathways vary from intensive patient education, shared decision-making and follow-up by renal services with anaemia management, symptom control, treatment of intercurrent illnesses, and a package of social and supportive services that can be escalated as the patient's condition deteriorates, and discharge back into the community. Some programmes also offer patients the opportunity to create advance directives or assistance with end-of-life planning designed to meet their preferred priorities of care. This includes preferences about interventional treatments, which may be for minimal or no intervention. Increasingly, general practitioners in the United Kingdom use palliative and supportive care registers to identify patients within the last months or year of life so that they can be offered appropriate and coordinated care. CM renal patients often find their way on to these registers.

Furthermore, the existing terminology does not define whether the plan for CM was instigated by the patient alone, with their families, or on the recommendation of a nephrologist or other health professional. The grounds for the decision is also rarely recorded in a standard or systematic way, including what efforts had been made to inform the individual patient about what other options were available or what the likely outcomes of this treatment decision are.

Historical perspective

Since the introduction of chronic dialysis in the 1960s, there has been increasing demand fuelled by technical success, medical advances, and increased patient and public expectation. In the early years of chronic dialysis, provision of treatment was unashamedly rationed and only provided to young otherwise healthy candidates, or those with dependent families, as the lucky few! Throughout the 1980s, and to some extent the 1990s, increasingly older patients were commenced on dialysis—many of whom suffered much additional co-morbidity. Crude survival amongst these patients was shockingly poor: as bad or worse than many advanced cancers. Furthermore, these patients were found to suffer a considerable burden of symptoms. A landmark paper by Chandra and colleagues in 1999 (Chandna et al., 1999) questioned the wisdom of offering dialysis to all comers and suggested, for the first time, that a conservative approach might be a more humane way to deal with advanced CKD in older patients, particularly in those with poor functional status and multiple other co-morbidities. Since then, there has been growing interest both in palliative and geriatric care communities, as well as amongst nephrologists, in this conservative approach. Conservative and end-of-life care, together with symptom management, are now included on the curriculum for nephrology trainees on both sides of the Atlantic. Today most renal units in Europe and the United States aspire to improve survival but also to deliver symptom driven multidisciplinary care to their older patients. There is an increasing realization that the removal of waste solute and water alone is not the answer. In recent years, take-on rates for dialysis programmes have reached a plateau in many European countries—what part the emergence of conservative care has played in this change is unknown.

The majority of dialysed patients are still maintained on haemodialysis (HD), but peritoneal dialysis (PD) offers an appropriate and acceptable alternative for many. Renal transplantation too is a success story that began around the same time as chronic dialysis. Although growing numbers of older people are offered the option of transplantation with increasing success, the majority are considered unsuitable because of coexisting conditions and to some extent appropriate use of organs. Assisted PD, where a patient is required

Box 145.1 Terms used for non-dialytic conservative therapies

- Conservative management
- Maximum conservative management
- Renal palliative care
- Renal supportive care
- Residual renal support
- Palliative renal care
- Conservative kidney care
- The non-dialysis option.

to take no or only a very small part in their own treatment, and which is conducted in their usual place of residence with minimal need to attend hospital or outpatient departments, may be more acceptable to frail elderly patients whose motivation for choosing CM may be to avoid hospital visits. This treatment choice has been introduced in the United Kingdom and other European countries and is likely to shift the dynamic of treatment choices as it becomes more widely available (Dimkovic and Oreopoulos et al., 2008).

The ageing kidney

In high-income countries, most of those following a CM pathway will be over 75 years. It is imperative, therefore, that dialysis decisions, whether for dialysis or for CM, should be informed by a good understanding of the ageing kidney (see also Chapter 300).

The ageing process results in marked alterations within the kidneys, which impair their ability to maintain homeostasis, adapt to changing local environments, and recover from injury. These changes are both anatomical and functional, and are considered the reason for the increased propensity of older people to develop acute or chronic renal failure. This process may be accelerated and/or accentuated by diseases such as diabetes mellitus and hypertension. The majority of the early studies on ageing kidneys enrolled institutionalized older patients with co-morbidities such as hypertension and heart disease that could of themselves induce renal alterations. Recently, the selection of subjects without background renal disease or processes known to affect renal function has demonstrated that, in healthy ageing subjects, ageing changes are less pronounced than was previously thought.

Morphological studies have demonstrated decreasing renal size with age. Histological exploration of renal senescence reveals decreasing cortical mass with increased glomerular sclerosis, interstitial fibrosis, and tubular atrophy. The reported functional abnormalities include increased renal vascular resistance, decreased and aberrant renal blood flow, reduced glomerular filtration rate, altered renal tubular function, including impaired handling of water, sodium, acid, and glucose. Similarly, changes in the renin–angiotensin system, vitamin D metabolism, and antidiuretic hormone responsiveness have all been reported. Impaired angiogenesis, associated with progressive loss of the renal microvasculature, is thought to be a further cause of age-related nephropathy. Ageing-related sclerosis in the kidney varies markedly among ethnic groups, with more injury seen in white compared with Japanese individuals, and even higher rates of sclerosis in ageing black individuals. Although some studies demonstrated mean loss of GFR at 0.75 mL/min per year in ageing people, 33–66% of the elderly maintain perfectly normal GFRs with only minimal histological changes (Fogo, 2011).

These ageing-related renal changes, which are believed to accelerate after age 50–60, conspire to render the aged kidney more susceptible to injury but have additional important implications with regards to drug toxicity, and less obviously renal transplantation (Esposito and Dal Canton et al., 2010).

An understanding of renal ageing and its distinction from renal insufficiency secondary to diseases is clearly important (Zhou et al., 2008). In this context, differentiation of 'ageing' effects from nephrotoxic effects resulting from disease processes is difficult. It has been argued that hypertension is an important factor in the development and progression of renal insufficiency among older people. The relationship between hypertension, glomerular hyperfiltration, atherosclerosis, and progressive renal dysfunction needs further study but CKD in older patients is increasingly recognized as part of a multisystem process involving atherosclerosis, coronary disease, and cerebrovascular disease. Furthermore, calculating exact renal function is difficult particularly in the elderly as many of the formula-based equations are likely to be inaccurate in this group, either over- or underestimating GFR. This is less of a problem in advanced CKD although once again the severity of CKD can be underestimated because of low muscle mass in the aged (Eriksen and Ingebretsen, 2006; Delanaye and Cohen, 2008).

Another distinct aspect of ageing is the important concept of frailty (frail aged patients as distinct from frail aged kidneys!). Older people constitute an increasingly greater proportion of patients with advanced CKD, including those patients undergoing maintenance dialysis treatment. Frailty is a biologic syndrome of decreased reserve and resistance to stressors that results from cumulative declines across multiple physiologic systems and causes vulnerability to adverse outcomes (Meyer, 1989). Frailty is common in elderly CKD patients, and it may be associated with protein-energy wasting (PEW), sarcopenia, dynapenia, and other complications of CKD (Kim et al., 2012). Kim et al. classify the causes of frailty with or without PEW in the elderly with CKD into three categories: causes primarily due to ageing per se, advanced CKD per se, or a combination of both. Frailty and PEW in older CKD patients are associated with impaired physical performance, disability, poorer quality of life, and reduced survival. Prevention and treatment of these conditions requires a multifaceted approach and as such presents further challenges.

Yang and Fogo summarize the age-old renal problem as follows: 'Old kidneys are functional but fragile. Decreasing renal function with aging is usual but not inevitable' (Yang and Fogo, 2010). With more detailed knowledge relating to renal function with advancing age it has become clear that age-related changes in renal function are less severe than previously thought. However, these changes are significantly aggravated by classical cardiovascular risk factors such as hypertension, diabetes, and smoking. Fliser argues that:

> As a consequence, in the elderly with such co-morbidity the appearance of a primary kidney disease or acute renal failure may cause a serious deterioration of renal function. In addition, impaired homeostasis with respect to salt (and fluid) balance has important consequences for the management of the elderly who is exposed to the twin risks of dehydration and fluid overload. Finally, the kidney is the

main route of excretion for many drugs and their active metabolites. Diminution of renal function with age underlies, at least in part, the known predisposition of the elderly to side effects of their medication such as non-steroidal anti-inflammatory drugs. (Fliser, 2008, p. 1835)

The management choices

Regarding dialysis treatments, the choices include conventional HD performed for the most part in the same manner as for younger patients and involving connection to the dialysis machine for 4 hours three times a week, PD which can be performed four times daily by the patient or a family member at home (usually taking 20–30 minutes for each 2 L fluid exchange), or alternatively using an overnight or automated peritoneal dialysis (APD) system. More recently, in the United Kingdom, patients have been offered 'assisted PD' where overnight APD is prepared by a trained healthcare or lay assistant and the patient or their family member has only to 'connect or disconnect' the patient at before and after bedtime.

Weighing up these choices, and in particular, weighing them in relation to CM, is a detailed and complex decision. In relation to dialysis, considerations of vascular or peritoneal access, and potential complications of these, need to be considered carefully. Vascular access for HD can be either via a surgically created arteriovenous fistula or via a tunnelled plastic tubing or dialysis catheter. There are many varieties of both fistulae and dialysis catheters and much literature on the advantages and disadvantages of attempting to create fistulae in frail elderly people. Taking all ages into account, studies consistently demonstrate a lower adjusted mortality among those using a fistula compared with a catheter. Yet catheter use in the elderly is increasing in most countries (with the exception of Japan) mainly because of perceived or actual difficulties with creating and optimizing fistulae in this group. Nadeau-Fredette and colleagues have recently reported that compared with younger patients in their unit, patients over 80 years have significantly higher primary fistula failure rates (40% vs 17%, P = 0.04) and shortened fistula lifespans (Nadeau-Fredette et al., 2013). In a recent Canadian study, Moist et al. point out that the elderly, at 1 and 2 years, have primary fistula patency rates ranging from 43% to 74% and from 29% to 67%, respectively and that secondary patency (survival rate of initially functioning fistulae) rates at 1 and 2 years ranged from 56% to 82% and 44% to 67%, respectively. They examined the trade-offs involved in managing elderly patients with multiple chronic conditions and limited life expectancy. They proposed a framework for choice of vascular access based on: (1) likelihood of disease progression before death, (2) patient life expectancy, (3) risks and benefits by vascular access type, and (4) patient preference (Moist et al., 2012).

Most centres also report a range of possible debilitating complications such as ischaemia of the hand distal to the fistula, secondary to steal phenomena, heart failure from the added circulatory stress, and pain secondary to cutaneous nerve damage. These complications are very likely to occur more frequently in the elderly. Where fistulae prove difficult, or in some countries as a *de novo* procedure, synthetic grafts may be inserted to provide vascular access but primary success rates are equally disappointing. Clearly, future studies evaluating the timing and type of vascular access with careful assessments of complications, functionality, cost–benefit, and patients' preference will provide relevant information to individualize and optimize care to improve morbidity, mortality, and quality of life in the elderly patient. A realistic understanding of the problems associated with vascular access should inform treatment choices especially when survival benefits are marginal and complication rates high.

PD is achieved using a surgically placed PD catheter inserted into the peritoneal cavity and tunnelled under the skin to exit under the umbilicus. The latter can be put in place in advance of needing it in a totally subcutaneous or embedded fashion and later externalized easily when required.

Considering prognosis

In determining the best pathway decision for each individual patient, and whether CM should be considered, prognosis is a major consideration. Conventional dialysis has been a major medical advance and there is no doubt that it extends a good quality of that life, for many patients. However, for some, particularly those who are older and frail, dialysis places a significant burden on the patient, their families, and the health service, yet offers limited benefits. There is evidence that older patients experience an increased rate of deterioration in functional status and mental capacity on HD, and have a symptom burden and quality of life comparable to patients with advanced cancer (Saini et al., 2006; Solano et al., 2006; Murtagh et al., 2007a). By contrast, many patients who choose a palliative approach appear to have a relatively flat functional trajectory until about 10 days before death (Williams et al., 2002; Murtagh et al., 2011a). Symptom burden in both groups has been shown to be high and may not differ significantly between patients on CM or HD pathways (Murtagh et al., 2007b). However, many authors have documented on impressive survivals in cohorts of patients who commenced dialysis over the age of 80 years (Isaacs et al., 2012a, 2012b). There are no controlled trials of CM versus dialysis yet several authors have attempted to determine whether dialysis significantly prolongs life in the old and frail. The evidence would appear to suggest so (Smith et al., 2003; Murtagh et al., 2007d; Chandna et al., 2011), although the number of out of hospital days survived may not differ much between the two groups and CM patients are more likely to die at home or in a hospice rather than in an acute hospital setting (Carson et al., 2009). Similarly, it is not clear whether dialysis improves symptoms or quality of life or merely exchanges one set of symptoms for another in the frail and elderly.

The modality choice dilemma is further complicated by the observation that patients on CM programmes show a startling variation in physical symptoms (both between individuals and in the same person from day to day) (Dinneen et al., 2011). Furthermore, diminished cognition particularly in the lesser explored executive functioning dimensions in many elderly patients and in those with dementia makes comprehension of the choices available and weighing of the risks even more difficult.

There are no randomized trials to determine whether elderly patients who choose dialytic therapy versus CM survive longer, nor are any such studies likely to be undertaken for ethical reasons. However, there are several studies which catalogue the outcome of elderly and very elderly patients on dialysis and several attempt to compare survival (Carson et al., 2009) (see Fig. 145.1). Relatively few studies assess survival specifically in CM patients, but it is worth noting that survival on dialysis among older people can be surprisingly good. For example, Issacs et al. claim impressive

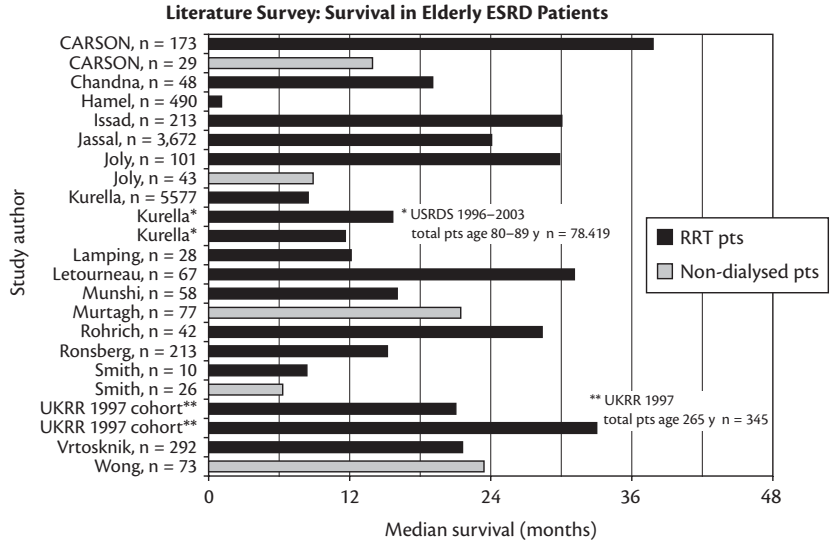

Fig. 145.1 Survival in elderly end-stage renal disease patients.
From Carson et al. (2009).

survival, even for those who initiate dialysis in their eight decade (median 46.5 months (range 0–107 months), with 1- and 5-year survival of 78.5 and 38.3% respectively) (Isaacs et al., 2012a).

Fig. 145.1 illustrates these studies but all are flawed by likely selection bias of healthier patients for dialysis interventions. Registry data suggests that older people particularly those with poor functional status and multiple co-morbidities fare very poorly with many surviving < 6 months on dialytic therapies. Chandra et al. in a landmark paper were the first to publically question the survival benefits of dialysis in patients whose physicians felt would not do well with dialysis interventions (Chandna et al., 1999). Carson et al. examined survival and hospitalization retrospectively in a single unit's population of over 75-year-olds, and found an increased survival in those dialysed but reported that almost every day of life extension was at the expense of a day spent in a hospital environment either on dialysis or as an inpatient. They also reported increased likelihood of dying at home or in a hospice in the CM patients (Carson et al., 2009). Murtagh et al. compared survival of elderly patients with CKD stage 5, managed either with dialysis or conservatively (without dialysis), after the management decision had been made, and explored which of several key variables were independently associated with survival. One- and 2-year survival rates were 84% and 76% in the dialysis group (N = 52) and 68% and 47% in the conservative group (N = 77), respectively, with significantly different cumulative survival (log rank 13.6, P < 0.001) (Murtagh et al., 2007d). However, this survival advantage was lost in those patients with high co-morbidity scores, especially when the co-morbidity included ischaemic heart disease. More recently, Da Silva-Gane and colleagues performed quality of life assessments (Short-Form 36, Hospital Anxiety and Depression Scale, and Satisfaction with Life Scale) every 3 months for up to 3 years in patients with advanced, progressive CKD (late stage 4 and stage 5) (Da Silva-Gane et al., 2012). After 3 years, 80 and 44 of 170 patients had started or were planned for HD or PD, respectively; 30 were undergoing CM; and 16 remained undecided. CM patients were older, more dependent, and more highly co-morbid; had poorer physical health; and had higher anxiety levels than the dialysis patients. Mental health, depression, and life satisfaction scores were similar in the two groups. Multilevel growth models demonstrated that quality of life measures, except life satisfaction, decreased significantly after dialysis initiation and remained stable in CM. However in their model (which controlled for co-morbidity, Karnofsky performance scale, age, physical health score, and propensity score) median survival from recruitment was 1317 days in HD patients (mean of 326 dialysis sessions) compared with 913 days in CM patients. On average, patients receiving CM did not live as long as their equivalent dialysed patients but maintained a better quality of life. Adjusted median survival from recruitment was 13 months shorter for CM patients than HD patients. Whether individuals are willing to accept shorter survival with better quality is very much an individual decision, although work by Morton and colleagues indicates that patients may be willing to forgo a surprising amount of life expectancy to improve quality (Morton et al., 2012). The case for dialysis in this group of patient therefore is not simply one of chronological survival. Carson succinctly summarizes the issues in the pithy title of her editorial: 'Deny Dialysis or "D-NI" Dialysis? The Case for "Do Not Initiate; Do Not Ignore" Orders' (Carson et al., 2012).

Considering trajectory of illness

Given the uncertain survival benefits of dialysis in the older patients with multiple co-morbidities, it is important to try and understand not only prognosis, but also the nature and trajectory of illness that will subsequently occur. Distinct trajectories of illness over time and towards death are well described in other diseases (Lunney et al., 2002, 2003; Murtagh et al., 2004). Murtagh et al., 2007b, 2011a; Understanding these trajectories can facilitate best care and inform optimal timing of discussions about goals of care, symptom management, and advance care planning, and addressing these symptoms and concerns effectively is important to achieve best possible quality of life in the last months of life. Different functional trajectories over the last year of life have been described in both cancer and non-cancer conditions (Gill et al.,

2010), Murtagh et al., 2007b, 2011a; but only recently in CM renal patients (Murtagh et al., 2011b). For CM patients and their families, and for the professionals planning and delivering their care, an understanding of what trajectory of illness to expect can inform best timing and configuration of care. Improved evidence about what patterns of illness might be expected over time with CM can also help inform dialysis decisions.

On average, CM patients tend to report low to moderate levels of physical and psychological symptom distress through the course of their illness, but also increasing concerns about information needs, practical matters, and about their family as the duration of illness extends. CM patients also tend to experience a marked increase in symptoms (Murtagh et al., 2011b) and quite sudden decline in functional status (Murtagh et al., 2011a) especially in the last 1 or 2 months of life, and sometimes only in the last 1 or 2 weeks. Worsening symptoms may be a much better prognostic indicator than biochemical or other disease markers, and services need to be responsive to sudden changes in order to best meet the needs of patients and families.

However, the 'average' trajectories, which are helpful for service development and planning, do not always reflect the patterns for individual patients. Among CM patients, three discrete symptom trajectories have emerged: (1) relatively stable, (2) steadily increasing, and (3) markedly fluctuant (Murtagh et al., 2011b), with the fluctuant pattern occurring more often in those with concurrent cardiac and/or respiratory disease. This fluctuant and rather unpredictable pattern is associated with much higher psychological distress among patients and families, and additional supportive care is often needed to help patients and families deal with the unpredictable symptoms, the associated social and practical limitations, and coping with recurrent acute crises with uncertain outcome.

Further research and a better understanding of illness trajectories in CM end-stage kidney disease are important. There are implications in terms of timing and delivery of care to improve symptoms and address concerns for these patients; care should address the moderate symptoms and concerns in last year of life, but especially focus on anticipating the increased levels towards death. Understanding the 'tipping points' (times of change or transition when care can be maximized to improve outcomes most effectively) can only be uncovered by study of trajectories. The increase in symptoms and concerns which CM patients experience a week or two before death may be just such a 'tipping point' or transition, where interventions to address symptoms and other concerns can be targeted to provide most benefit, and warning of ensuing decline needs to be acted upon by health professionals.

Decision-making

Conventional dialysis has been a major medical advance and there is no doubt that it extends a good quality of that life, for many patients. However, for some, particularly those who are older and frail, dialysis and dialysis-related procedures (including complications) clearly place a significant burden on the patient, their families, and the health service, yet offer limited benefits. There is evidence that older patients experience an increased rate of deterioration in functional status and mental capacity on HD, and have a symptom burden and quality of life comparable to patients with advanced cancer (Saini et al., 2006; Solano et al., 2006; Murtagh et al., 2007a). By contrast, many patients who choose a palliative approach appear to have a relatively flat functional trajectory until about 10 days before death (Williams et al., 2002; Murtagh et al., 2011a). Symptom burden in both groups has been shown to be high and may not differ significantly between patients on CM or HD pathways (Murtagh et al., 2007b). However, many authors have documented impressive survivals in cohorts of patients who commenced dialysis over the age of 80 years (Isaacs et al., 2012a, 2012b). As already discussed, there are no controlled trials of CM versus dialysis yet evidence shows that dialysis may significantly prolong life, even in the old and frail (Smith et al., 2003; Murtagh et al., 2007d; Chandna et al., 2011), although the number of out of hospital days survived may not differ much between the two groups and CM patients are more likely to die at home or in a hospice rather than in an acute hospital setting (Carson et al., 2009). Similarly, it is not clear whether dialysis improves symptoms or quality of life or merely exchanges one set of symptoms for another in the older and frail patient.

The modality choice dilemma is further complicated by the observation that patients on CM programmes show a startling variation in physical symptoms (both between individuals and in the same person from day to day) (Dinneen et al., 2011). Furthermore, diminished cognition particularly in executive functioning dimensions in many older patients makes comprehension of the choices available and weighing of the risks even more difficult.

So decision-making about dialysis is often challenging for patients, their families, and professionals, yet there is limited evidence to inform practice. There is particularly little evidence directly from the patient perspective, despite the major impact decisions may have for those with advanced disease.

One of the difficulties is that patients tend to focus much more on living rather than dying, becoming accustomed to living with their chronic condition, and sometimes reluctant to consider the implications of future deterioration. Calvin explored decisions among HD patients and their end-of-life treatment decisions and developed a theory of 'personal preservation' with three distinct components: knowing the odds for survival, beating the odds, and being responsible/making judgements (Calvin, 2003).

Other work (Holley et al., 1989; Main, 2000; Tonkin-Crine et al., 2015) examines the decision-making experiences of CM patients or withdrawing from dialysis, taking into account the social and personal impact of this decision. Important considerations for patients include avoiding poor quality of life, minimizing pain and suffering, and a desire not to be a burden, while for professionals prognostic uncertainty predominates. A proactive and open approach towards decisions in recommended, but is hard to achieve.

Studies by Fujimaki et al. (2003) and Chan et al. (2007) have retrospectively reviewed patients who had declined dialysis; the majority do not regret their decision. Reasons for refusal included not wishing to attend the hospital frequently, feeling 'too old' for dialysis, and that it would be more 'natural' to die without dialysis. Work by Morton and colleagues suggests that travel restrictions are an important consideration, and patients were willing to forgo a number of months of life expectancy (23 months; 95% confidence interval 19–27) in order to decrease the travel restrictions that dialysis imposes (Morton et al., 2012). But in general, the processes and determinants of decisions for or against the conservative (non-dialytic) pathway are poorly understood.

The conservative management pathway: communication and advance care planning

Delivery of optimal palliative and supportive care for patients receiving CM starts with honest prognostic information, tailored to the patient's information preferences. However, this is not always achieved (Weiner, 2010). Many factors militate against good communication, including the inherent uncertainty of prognostication, the uncertainty of an individual trajectory of illness, the imbalance of knowledge between patients and professionals, and the perceived and actual time limitations in busy healthcare settings. The annual mortality rate of dialysis patients is higher than that of prostate, breast, or colorectal cancer, but many renal patients and their families are not aware of this and in general consider renal failure as 'curable with transplantation' or 'treatable with dialysis'. Open prognostic information to counter this should be offered even before treatment pathways are considered (Davison and Torgunrud, 2007), but this infrequently occurs.

Good quality, individually tailored, and sensitive communication is paramount at every stage: before the CM decision is made, once the CM pathway has been commenced, and as conservatively managed end-stage kidney disease advances towards death. Patients with advanced CKD may have been receiving nephrology care for some months or years prior to decisions about CM care, and often become accustomed to living with their renal disease. It can therefore be difficult for healthcare professionals to introduce conversations about decline in health and limited survival. One way to overcome this is the regular introduction of the CM pathway option into early discussions and into patient education events. Another is to routinely assess symptoms and quality of life of all patients (alongside routine biochemical tests, for instance) and to then use increased symptom burden or declining quality of life as a trigger for detailed conversations about progress and an opportunity to plan ahead. This approach has been pioneered in England with considerable success (NHS Kidney Care, 2012).

Advance care planning is a dynamic process which does not occur at one point in time. A good relationship with the patient, and an understanding of their perspectives, is important before having discussions about future priorities and preferences for care. Palliative and supportive care emphasizes improving quality of life as end of life approaches, and this can only be achieved if there is genuine communication as a foundation for planning, considering outstanding issues, and addressing family relationships and conflict (Hines et al., 2001). However, these are all priorities which patients themselves rate very highly (Singer et al., 1998), and are therefore important to prioritize. Davison and Torgunrud, when studying advanced care planning among renal patients, showed that patients wanted more information and in non-medical language on prognosis, disease process, and the impact of treatment on daily life (Davison and Torgunrud, 2007) although renal teams may find this difficult, particularly when discussing end-of-life issues, which are less often part of their routine practice (Rodin et al., 1981; Cohen et al., 2003). But when sensitive, open exploration of concerns for the future is achieved, the opportunity for discussion is often appreciated by patients (NHS Kidney Care, 2012).

The conservative management pathway: managing kidney disease and minimizing complications

Once a patient has chosen to follow a CM pathway the emphasis of care shifts from preparation for renal replacement therapy to symptom control, maintenance of residual renal function, and minimizing complications related to CKD. Nephrologists now recognize the prevalence and variety of patient-reported symptoms. In untreated or newly referred patients, many symptoms relate to anaemia and most units are adept at improving and maintaining haemoglobin using both iron and subcutaneously administered erythroid-stimulating agents (usually erythropoietin, though newer molecules are on the horizon). Protocols vary from unit to unit but in general the advent of erythropoietin and the availability of safe intravenous iron preparations has meant that haemoglobin can easily be maintained at target levels in this patient group. Target levels are set by various good practice guidelines and vary from 10.5 to 11.5 g/dL (Fliser et al., 2012). Maintaining haemoglobin has the added advantage of mitigating some of the distress caused by angina and congestive cardiac failure and can improve physical functioning and reduce fatigue. Higher than target haemoglobin carries an increased risk of stroke (Jing et al., 2012). Newer longer-acting erythroid-stimulating agents are now widely available and are particularly useful in this group of patients especially if community nurses are administering the injection. Home delivery services are often provided, minimizing patient inconvenience and invasiveness. Whether optimizing haemoglobin prolongs residual renal function is unknown.

In terms of supporting residual renal function, clinicians should have three main objectives: (1) to minimize proteinuria, (2) to optimize blood pressure control, and (3) to pre-empt and avoid intercurrent illnesses which can precipitate acute kidney injury in addition to the CKD. In men, care should be taken to consider and treat new or worsening bladder outflow obstruction which might be silently accelerating the decline in renal function. Likewise, optimizing glycaemic control in diabetics is desirable but is unlikely to markedly slow progression of renal decline in this group. Use of renin–angiotensin system inhibitors to both control blood pressure and reduce proteinuria is desirable but usually results in an initial decline in renal function even in patients without renal artery stenosis and may aggravate hyperkalaemia. In practice, as renal function declines or if potassium control is difficult in a CM patient it is often useful to discontinue the renin–angiotensin system inhibitors to 'buy back' some extra clearance. This strategy has been examined by Gonçalves and colleagues who concluded that there was a significant increase in eGFR after stopping renin–angiotensin system inhibitors, making long-term survival without renal replacement therapy more likely. This evidence 'questions the universal pre-emptive indication of RAS [renin–angiotensin system] inhibitors in advanced CKD and suggests that they can be safely stopped, at least in some patients' (Gonçalves et al., 2011).

In the days before chronic dialysis was widely available, clinicians advised draconian dietary restrictions to control intake of protein, potassium, and phosphate in CKD patients and no doubt these measures extended survival. However, the cost to the patient was often severe malnutrition and associated loss of flesh weight. By contrast, most CM programmes now emphasize maintenance

of a low-salt, normal-protein diet, encouraging patients to eat and enjoy the foods they like to maintain flesh weight and enhance quality of life. Where hyperkalaemia or hyperphosphataemia are problematic, limited dietary restrictions may be suggested but it is important to remain mindful that the ethos behind CM is maintaining quality of life and clearly food is a very important contributor to this. In reality, older and frail CKD patients may lose their enjoyment of food as CKD progresses and so dieticians need to pay more attention to augmenting diets rather than restricting them in this group. Food supplements can be used to good effect in some patients. Finally, many patients believe that they need to increase their fluid intake in order to 'help' their kidneys to work and others have particular difficulty excreting salt and water, either because of concurrent diabetic nephropathy or heart failure. Advice about fluid intake therefore needs to be individualized depending on the particular individual circumstances.

Many if not most patients with advanced CKD require diuretics, with loop diuretics most commonly prescribed. They can, however, cause concurrent acute kidney injury, and exacerbate urinary frequency, nocturia, and gout. Consequently their dose and timing needs to be considered carefully on an individual basis. Controlling phosphate by dietary or pharmacological means may help reduce the distressing symptoms of itch. Some authors suggest that optimal calcium and phosphate control slows progression of CKD, but once again a balance needs to be established between the potential benefits of phosphate control and the negative effects of dietary restriction and increasing the pill burden in CM. Avoiding or treating hyperparathyroidism is only relevant in this group if a patient is symptomatic with bone pain or fractures or as part of efforts to alleviate itch. There is some work to suggest treating hyperparathyroidism itself impacts overall survival in CKD patients (Molony and Stephens, 2011) but once again the clinician has to judge the relevance of treating each individual. Similarly, many clinicians actively seek to identify and treat reduced vitamin D levels; despite a number of recent publications, it remains unclear whether this is a worthwhile strategy. Treating hypertension is also clearly desirable in this as in any other CKD patient. However, slavish attempts to reach target blood pressures may increase the risk of falls in these vulnerable patients, so caution is advised.

Finally, all of the above assumes that reversible causes of CKD have been considered and treated where possible and that due attention is given to minimizing pill burden. A clinician may also wish to clarify in advance whether a CM patient wishes to receive dialysis for a limited time to overcome a temporary reduction in renal function which might, for example, result from an intercurrent respiratory tract infection. It is often invaluable to put in place well-discussed and documented ceilings of care in accordance with a patient's wishes prior to any acute crises or events. Such ceilings might extend from not actively treating any intercurrent illnesses to short periods of dialysis to overcome reversible acute kidney injury on a background of CKD.

The conservative management pathway: symptom assessment

Symptom management in CM patients can be challenging, partly because symptoms may go unrecognized (Weisbord et al., 2007), partly because renal impairment constrains management with drugs, and partly because of the complex co-morbidities which may coexist. It is not always clear whether uraemia, dialysis, or co-morbid conditions are the main cause of each symptom, and for many patients a combination of factors contributes to their overall symptom burden. Co-morbid conditions play a major part in causing symptoms, particularly for the older patient, who may have vascular disease, cardiac problems, diabetes mellitus, or other co-morbidities. Some of the commoner co-morbid conditions which contribute to symptom burden include diabetic gastroparesis, other diabetic neuropathies, other diabetic complications, cardiovascular disease, and peripheral vascular disease. Diabetic patients with end-stage kidney disease have often had their diabetes for many years, and may have other complications in addition to their renal impairment. Diabetic gastroparesis due to autonomic nerve damage is common in long-standing diabetes, and is characterized by anorexia, early satiety (feeling full), nausea, and sometimes vomiting. Advanced uraemia itself also leads to delayed gastric emptying, which can contribute to this problem. Delayed gastric emptying may itself cause gastric reflux and dyspepsia. Diabetic patients also suffer from other neuropathies, such as autonomic neuropathies affecting the mid and lower gut, and characterized by alternating diarrhoea and constipation. Non-autonomic diabetic neuropathies that affect the peripheral nerves may occur. The neuropathic pain associated with diabetic neuropathies can be severe, persistent, and difficult to control. Skin and soft tissue problems are also common in the diabetic patient; decubitus ulcers or diabetic foot may occur and amputation may sometimes be required. The severity of these skin and soft tissue problems may be such that these pains are sometimes difficult to control.

Several global symptom measures have been used to evaluate the whole range of symptoms in renal disease. These include instruments used in other advanced diseases, such as the Edmonton Symptom Assessment System (Davison et al., 2006a, 2006b), and the Memorial Symptom Assessment Scale short form (Weisbord et al., 2003; Murtagh et al., 2007a). Other measures have been validated specifically for use in those with renal disease. These include the Dialysis Symptom Index, developed from the Memorial Symptom Assessment Scale by Weisbord et al. (2004), and the renal version of the Patient Outcome Scale (symptom module) (Murphy et al., 2009), derived from the generic version of the Patient (or Palliative) Outcome Scale which is used across a wide number of conditions and countries.

Although the whole range of symptoms which patients experience needs to be assessed, there is a wider range of instruments which have been used to assess individual symptoms, such as pain, pruritus, or depression. Various measures are available for measurement of, for example, pain (Melzack, 1975; Daut et al., 1983), depression (Beck and Steer, 1984; Kutner et al., 1985; Martin and Thompson, 2000), pruritus (Majeski et al., 2007), or restless legs syndrome (RLS) (Allen et al., 2009). A range of other measures for individual symptoms exist, and are useful for research purposes, but fairly brief validated measures which capture the whole range of symptoms may be most useful in the clinical setting.

The conservative management pathway: symptom management

Once symptoms have been identified and assessed, they need to be actively managed. Evidence shows that management of symptoms is often suboptimal for renal patients (Davison, 2003; Bailie et al.,

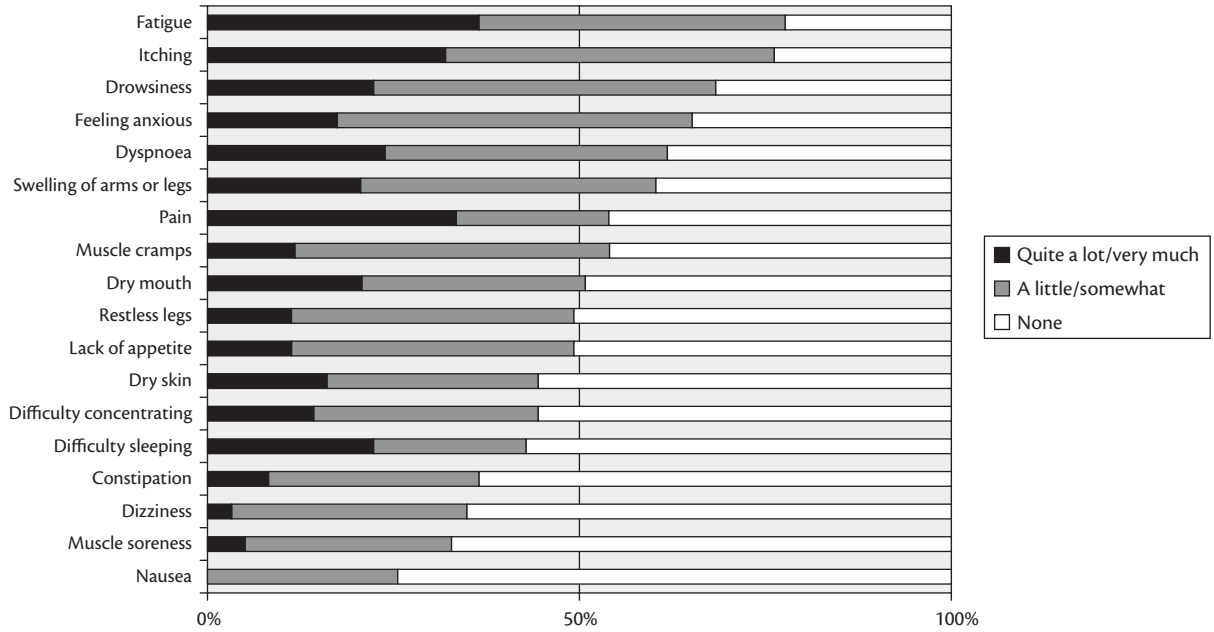

Fig. 145.2 Symptom prevalence in CM patients (N = 66).

2004). Renal impairment places a major constraint on use of medication, since many medicines are renally excreted, and may therefore accumulate substantially in renal impairment. Fig. 145.2 shows the prevalence of the most common symptoms in CM patients (Murtagh et al., 2007a), and Table 145.1 outlines the management strategies for these symptoms, with more detailed discussion of the most challenging symptoms in the following text.

Management of fatigue

Fatigue is multidimensional (Lee et al., 2007), with physical, cognitive, and emotional elements (O'Sullivan and McCarthy, 2007). There is a complex but poorly understood relationship between fatigue, sleep disturbance, physical functioning, and depression in those with renal disease (Brunier and Graydon, 1992; McCann and Boore, 2000). It is not clear whether the reduced physical functioning which occurs with renal disease itself causes fatigue, or whether the symptom of fatigue is because of poor function. Fatigue is an important symptom because it is very common, highly distressing to patients, and there are a number of causes which are potentially treatable. These causes can be classified as related to the renal disease, to dialysis itself, or related to co-morbid conditions. The renal disease may cause anaemia, hyperparathyroidism, and uraemia, all of which may directly contribute to fatigue. Secondary to these direct effects are dietary and fluid restrictions, impaired nutrition, and the side effects of medications (such as antihypertensives), all of which may contribute to fatigue, even if they are not the predominant cause. Conditions unrelated to renal disease, such as hypothyroidism, should be considered and excluded. Non-pharmacological managements of fatigue, such as exercise, cognitive and psychological approaches, and complementary treatments, are important, especially as pharmacological interventions become increasingly limited.

A systematic review of the use of erythroid-stimulating agents demonstrates that in renal patients there is a consistent relationship between haematocrit and energy/fatigue domains in quality of life (Ross et al., 2003); as haematocrit increases, so energy levels increase and fatigue reduces. It is not clear, however, how long treatment should be maintained in those who are nearing end of life; most clinicians continue treatment while the patient still continues to gain symptomatic benefit.

Management of pruritus or itch

The pathogenesis of pruritus in renal disease remains unclear, and treatment options have limited effectiveness. Pruritus is thought to arise in C fibres in the skin, separate from those which mediate pain (Schmelz et al., 1997). These transmit via the contralateral spinothalamic tract to the brain (thalamus and hypothalamus) via the reticular formation (Lugon, 2005). Connections to distinct cortical areas (the anterior cingulate process, supplementary motor area, and inferior parietal lobe) then mediate, via motor areas, the powerful, almost involuntary, desire to scratch. Pruritus could originate at any level in this pathway (in the skin at the level of the receptors, neuropathically in the afferent nerve pathway, neuropathically in central neural pathways, or centrally from psychogenic causes). In renal itch, complex interacting factors likely operate at more than one place in the pathway (Lugon, 2005), so elucidating any one discrete cause for itch is difficult. Current hypotheses postulate abnormal inflammatory/immune processes, dysfunction in the opioid receptor system, and/or neuropathic processes within the nervous system itself.

Immune modulators (such as ultraviolet (UV)-B light, tacrolimus, and thalidomide) have been proposed to treat itch. These act in various ways to decrease pro-inflammatory cytokines. Others have proposed disturbance in the endogenous opioids system as a cause of itch (Yosipovitch et al., 2003; Patel et al., 2007). κ-opioid receptor agonists have been shown to have antipruritic effects in animals, and κ-opioid receptor antagonists enhance itch in animal studies (Ikoma et al., 2006). Opioids such as butorphanol (which has μ-opioid antagonist and κ-opioid agonist action) (Dawn and Yosipovitch, 2006), and opioids antagonists such as naloxone and

Table 145.1 Management strategies for the most common symptoms in CM patients

Fatigue	Treat anaemia Exclude hypothyroidism, sleep apnoea, and over-zealous blood pressure control Consider exercise interventions, and cognitive and psychological approaches
Itching	Liberal topical skin moisturizers Antihistamines (limited evidence but may help sleep) Gabapentin Topical capsaicin cream 0.025–0.075% (especially if itch is localized) Consider psychological support with severe itch
Drowsiness	Treat anaemia Exclude sleep apnoea Consider exercise interventions, and cognitive and psychological approaches
Feeling anxious	Psychological support Assess mood and consider antidepressants Consider anxiolytics
Dyspnoea	Investigate and treat underlying cause Treat anaemia Consider increased diuretics, and consider fluid restriction with daily weights to achieve optimal dry weight
Swelling of arms or legs	Optimize diuretic therapy and heart failure treatment
Pain	Investigate and treat underlying cause(s) Treatment determined by cause: see 'Management of Pain' in text
Muscle cramps	Consider diuretic reduction Quinine sulphate 300 mg nocte (limited evidence)
Dry mouth	Review medication, consider reducing diuretic dose and other medications which exacerbate dry mouth Consider artificial saliva (or oral gels which may provide more prolonged benefit)
Restless legs	Correct phosphate, iron deficiency Review medication for any potential exacerbating drugs Consider gabapentin or clonazepam
Lack of appetite	Advise very small and attractive portions more frequently Dietetic and nutritional support Consider small doses of amitriptyline or mirtazapine (although both require caution in cardiac disease)
Dry skin	Liberal topical skin moisturizers
Difficulty concentrating	Treat anaemia Review and consider reducing medications, particularly analgesics and antihistamines
Difficulty sleeping	General sleep hygiene measures (see text) Exclude depression Actively manage restless legs and itch, if present Consider limited course of short-acting hypnotic Consider cognitive and psychological approaches
Constipation	Bulking agents (but beware potassium content) Moderate or persistent constipation best managed with a combination of 'softener' and 'stimulant' Oral laxatives often insufficient to address established constipation; rectal measures usually required alongside oral laxatives
Dizziness	Review antihypertensive medications Treat anaemia
Muscle soreness	Review need for statins Treat muscle cramp aggressively
Nausea	Determine cause (not always due to uraemia only). Consider investigating reversible cause, e.g. gastritis If delayed gastric emptying or gastroparesis, consider metoclopramide (reduced dose) Consider $5HT_3$ antagonists (side effect of constipation needs active management) Low-dose haloperidol or levomepromazine can be considered if other measures ineffective

naltrexone, have therefore been proposed to treat itch. There is increasing evidence that the relatively new κ-opioid agonist nalfurafine is effective (Wikstrom et al., 2005). There is also evidence to indicate that itch is a neuropathic process. Akhyani and colleagues report association between clinical neuropathy and itch in HD patients (Akhyani et al., 2005), and neuropathic agents (lidocaine, gabapentin, and capsaicin) have been effectively used to treat itch. However, the neuropathic component could be a secondary, rather than primary cause of renal pruritus. The role of histamine in acute itch is long established. Acute histamine-induced itch is well described, and histamine receptors sensitize at least some of the C fibres which mediate itch. What is less clear is how this acute itch response relates to the chronic itch experienced in advanced renal disease. Nevertheless, antihistamines are widely used in renal itch, with varying results. A final important factor in renal itch is xerosis, or dry skin. Xerosis may be an important factor especially in older people (Keithi-Reddy et al., 2007). And although uraemia is the most likely cause of itch, other common causes need to be excluded if the symptom is not resolving, such as skin disorders, skin infections such as scabies, and liver impairment.

The first step in management is to optimize renal management; high phosphate may contribute to pruritus (Lugon, 2005), so attention to reducing phosphate levels may be important—consider dietary advice and the use of phosphate binders. Hyperparathyroidism may also be a contributory factor and should be considered. Dry skin should be treated actively, with liberal emollients used if dry skin is present. Older people living alone may find it hard to apply emollients easily; spray applications are often helpful in this instance. Preventive measures, such as nail care (keeping nails short) and keeping cool (light clothing, and tepid baths or showers), are useful concurrent measures.

The evidence as to which medications are effective is limited, often conflicting, and no one single preparation can be recommended above others. Choice of treatment should be influenced by the stage of disease—for instance, UV light may be practical for those who remain relatively well, while antihistamines may be more appropriate nearer end of life. Time should be taken to discuss with the patient the need to persist with any one medication, and to explaining and minimizing side effects where possible. A clear plan of management, and persistence in following treatment through, goes a long way to helping patients cope with the distress that this symptom can sometimes cause. The psychological and social dimensions of severe itch are considerable (Lugon, 2005) and psychological, family, and social support is an important component of management.

Management of pain

Pain is clearly an important symptom to alleviate in any patient. Its prevalence is high in those opting for CM. In general, non-steroidal anti-inflammatory drugs are harmful to residual kidney function and may cause or exacerbate gastrointestinal haemorrhage. Other analgesics, particularly opioids, accumulate or are metabolized differently in those with advanced CKD. Hence considerable caution needs to be exercised to eliminate pain without causing additional problems.

A detailed pain history (remembering there is frequently more than one distinct pain), together with clinical examination, should reveal, or at least indicate, the underlying cause. Removal or specific treatment of the underlying cause of pain (when feasible) is always the best approach, and only when this cannot be achieved should palliation be the main focus. Non-opioid, opioid, and adjuvant analgesics can be used in CM patients, but careful consideration needs to be given to (1) potential risk of adverse effects, which may be exacerbated by uraemia, (2) whether there is risk of nephrotoxicity (it is critically important not to risk remaining renal function), (3) the elimination of the drugs used, and (4) how this will be influenced by the renal impairment.

Selection of which non-opioid, opioid, or adjuvant analgesic (or which combination) depends on the cause of the pain; adjuvants such as gabapentin, for instance, are appropriate for neuropathic pain usually in conjunction with opioids, whereas musculoskeletal pain may respond to non-opioids such as paracetamol. Ischaemic pain may be particularly challenging to manage, needing opioids, adjuvants for neuropathic pain, plus a combination of other strategies. Because of the challenges of using opioids, the main World Health Organization step 2 and 3 opioids (see <http://www.who.int/cancer/palliative/painladder/en/>) are briefly considered below; the reader is referred to extensive reviews of analgesic use for more detail (Davies et al., 1996; Dean, 2004; Mercadante and Arcuri, 2004; Murtagh et al., 2007c).

There are reports of serious side effects following codeine use in patients with advanced renal failure, in particular persistent hypotension (Chan and Matzke, 1987), respiratory arrest (Talbott et al., 1997), and profound narcolepsy (Davies et al., 1996). Dihydrocodeine has similar metabolism and elimination to codeine, and there are reports of prolonged narcosis (Barnes and Goodwin, 1983; Chan and Matzke, 1987). For these reasons, use of codeine and dihydrocodeine is not recommended in CM patients.

Ninety per cent of tramadol is excreted via the kidneys (Murtagh et al., 2006), and in renal impairment, there is an approximately twofold increase in the elimination half-life (King et al., 2011). Because of this, it is recommended that the dose interval be increased to 12-hourly, and the dose reduced. Uraemia also lowers the fit threshold, and tramadol may be more epileptogenic in these patients (Ikoma et al., 2006). For these reasons, alternative analgesia is preferred, and if use of tramadol is unavoidable, a dose of 50 mg 12-hourly should not be exceeded in stage 5 CKD.

Morphine and diamorphine are not recommended, because of the problems with metabolite accumulation, and because at least some of these metabolites are clinically active (Murtagh et al., 2007b).

Less than 10% of fentanyl is excreted unchanged in the urine. In renal failure, no dose modification appears necessary when fentanyl is given as a bolus injection (Coral et al., 1980), but there is limited evidence on the pharmacokinetics when it is administered either in repeated doses or by continuous infusion. One study suggests accumulation with sustained administration, and a further study demonstrates reduced clearance (Coral et al., 1980; Scholz et al., 1996). Despite these concerns about accumulation, fentanyl is, on present limited evidence, one of the preferred opioid in renal impairment, because the metabolites are inactive. Some authorities suggest 50% normal dose if creatinine clearance is < 10 mL/min (Davies et al., 1996). Careful monitoring for any gradual development of accumulation and toxicity is advised with sustained administration (beyond 1 or 2 days), and there may be some basis for gradual dose reduction if fentanyl is used over days or weeks. Transdermal patches can be used, but careful review and frequent checks for accumulation are needed. The very wide individual

variation in the pharmacokinetics of fentanyl would also support a cautious approach.

Alfentanil is shorter acting than fentanyl, and is both less potent and less lipid soluble. Like fentanyl, it is highly protein bound and its protein binding is reduced by a high urea, but despite this the volume of distribution and elimination half-life appears unchanged in patients with renal failure (Chauvin et al., 1987). Alfentanil is therefore also one of the preferred opioids for use in CM patients, but is limited to end-of-life use given that it is only available for parenteral use.

Buprenorphine is metabolized in the liver to norbuprenorphine, and buprenorphine-3-glucuronide, and these metabolites are principally excreted via the biliary system (Davies et al., 1996). Because of its high systemic clearance and largely hepatic metabolism to non-toxic metabolites, buprenorphine has the potential to be reasonably safe in patients with renal failure, but evidence is very limited; some shows no change in the pharmacokinetics of buprenorphine in renal impairment, but other work shows accumulation of metabolites (Hand et al., 1990; Boger, 2006), although adverse effects have not been reported. Buprenorphine also has the advantage of being available in sublingual, transdermal, and injectable preparations, although it is not available in some countries.

A single-dose study indicates hydromorphone accumulation in renal impairment (Babul et al., 1995) (with proportionately greater accumulation in severe renal impairment), and a further detailed pharmacokinetic case study over 14 days (Durnin et al., 2001) demonstrated clear accumulation of hydromorphone-3 glucuronide (H-3-G). Since H-3-G is known to be a more potent neuro-excitant, there has been concern about the use of hydromorphone in severe renal impairment. However, a retrospective review by Lee and colleagues (Lee et al., 2001) suggests that it may be reasonably well tolerated but clear guidance on its use cannot be given until there is more evidence available.

Methadone is metabolized mostly in the liver, and excreted both renally and faecally (Dean et al., 2004). There is large inter-individual variation, but also considerable difference between acute and chronic phase dosing. Some evidence suggests that plasma concentrations are no higher than in those with normal renal function (Kreek et al., 1980; Chan and Matzke, 1987), suggesting that faecal excretion might compensate in those with renal impairment. Because of this, and the limited possibilities for use of other opioids, methadone has been used for patients with renal failure without adverse effects. However, caution should be exercised on two counts: firstly, because of the well-described risk of late accumulation and toxicity in normal renal function, experienced specialist supervision of methadone is required, and secondly, because of the wide individual variation, doses and effects should be closely monitored. The titration and use of methadone is fully described elsewhere (Morley and Makin, 1998; Blackburn et al., 2002), but in severe renal impairment (stage 5 CKD) a dose reduction of 50% is recommended (Broadbent et al., 2003) (although prescription and monitoring should only be undertaken by a specialist experienced in use of methadone).

Kirvela et al. demonstrated that elimination of oxycodone in renal failure is significantly prolonged, and excretion of its metabolites is severely impaired (Kirvela et al., 1996), with wide inter-individual variation. There is also evidence that some of the effects of oxycodone may be mediated through its metabolites, with reports of central nervous system toxicity and sedation with oxycodone in renal failure (Foral et al., 2007). This raises queries about the use of oxycodone in renal impairment, and there is insufficient evidence to determine whether or not it is safe to use in end-stage renal disease patients. Some clinicians use it with caution, reducing the dose and increasing the dose interval, while others avoid using it. Broadbent et al. suggest the use of 75% of normal dose when creatinine clearance is 10–50 mL/min, and 50% when creatinine clearance < 10 mL/min (with unchanged dose intervals) (Broadbent et al., 2003).

Management of restless legs

RLS is characterized by urge to move the legs, uncomfortable sensations in the legs, and worsening of symptoms at rest, especially during the night. The formal International Restless Legs Syndrome Study Group (IRLSSG) criteria are (1) urge to move the legs, usually with unpleasant sensations in the legs; (2) worse during periods of rest or inactivity like resting or sitting; (3) partial or total relief by physical activity; and (4) worse symptoms in the evening or night rather than the day (Medcalf and Bhatia, 2006). The exact cause for restless legs is not well understood but the dopaminergic system in the central nervous system is somehow disrupted (Manenti et al., 2009). There is limited evidence in uraemic RLS that iron deficiency (O'Keeffeet al., 1993), low parathyroid hormone (Rijsman et al., 2004), hyperphosphataemia, and psychological factors (Takaki et al., 2003) may play a role. Treatment should involve correction of these factors, and reduction of potential exacerbating agents, such as caffeine, alcohol, nicotine, and certain drugs (sedative antihistamines, metoclopramide, tricyclic antidepressants, selective serotonin uptake inhibitors, lithium, and dopamine antagonists) (Manenti et al., 2009). Calcium antagonists may also exacerbate RLS (Telarovic et al., 2007).

There is very limited evidence about treatment of restless legs in CKD patients, and much of the evidence is extrapolated from patients with idiopathic restless legs (Silber et al., 2004). Gabapentin, dopamine agonists, co-careldopa, and clonazepam (a short-acting benzodiazepine) are the treatments most commonly used, with varying results. All need dose reduction, and gabapentin in particular accumulates rapidly in CM patients; dose reduction, increased dose interval, and close monitoring are required.

Management of sleep disturbance

A detailed history of any sleep disturbance is important, in order to identify sleep apnoea, RLS, and pruritus, which may be the underlying reason for the sleep disturbance; these each need treating in their own right initially to resolve any sleep problems. General sleep hygiene measures are important in addressing sleep disturbance: avoiding caffeine after lunch, reducing overall caffeine intake, avoiding alcohol (which is both depressant and stimulant), and avoiding daytime sleeping. If sleep apnoea is excluded, other exacerbating symptoms are treated optimally, and general measures are unsuccessful, then hypnotics may be necessary, ideally short term to attempt to re-establish sleep patterns. For those with a longer prognosis, hypnotics carry risk of dependence, and this needs consideration in management. The shorter-acting hypnotics, such as zolpidem 5–10 mg or temazepam 7.5–10 mg, are preferable. CM patients may be more sensitive to benzodiazepines in general, and lower doses are often required.

Management of nausea and vomiting

Nausea and vomiting are extremely unpleasant symptoms, and are often multifactorial. Assessment requires a thorough history

including establishing the history and pattern of both nausea and vomiting separately. Profound nausea and/or repeated vomiting will prevent absorption of any medications taken orally, and alternative routes (such as sublingual, rectal, or subcutaneous routes) need to be considered, at least until nausea and vomiting is controlled.

The first step is to identify the specific cause of nausea and vomiting where possible, since cause-directed treatment is most likely to succeed. Uraemia, and a variety of drugs (including opioids, anticonvulsants, antibiotics, and antidepressants), may cause persistent nausea. Gastroparesis or delayed gastric emptying, (which may be caused by drugs such as opioids, as well as occurring secondary to diabetes mellitus, for instance), usually presents with a history of post-prandial nausea or vomiting of undigested food which relieves nausea. Bloating, epigastric fullness, flatulence, hiccough, or heartburn may accompany this. Nausea related to gastritis is often associated with heartburn, dyspepsia, or epigastric pain. Constipation may exacerbate nausea and vomiting.

For delayed gastric emptying or gastroparesis, metoclopramide can be used, although doses should be reduced by 50%, and there is increased risk of dystonia. Haloperidol or levomepromazine are often used for persistent nausea related to uraemia or drug-related nausea, although there is increased cerebral sensitivity in CM patients, and both drugs need dose reduction. 5-hydroxytryptamine ($5HT_3$) antagonists can also be used, although the side effect of constipation will need active management. Because gastritis is common among uraemic patients, there should also be a low threshold for treatment with a proton pump inhibitor if gastritis could be a contributory factor.

Management of breathlessness towards end of life

The most common causes of breathlessness or dyspnoea in the renal patient are anaemia, pulmonary oedema (related to fluid overload or to coexisting cardiovascular disease), or co-morbidity (cardiac or respiratory disease). It is important to identify the underlying cause of breathlessness, since treating the underlying cause is almost always the most appropriate and effective first line of management. If treatment of the underlying cause has been exhausted, then symptomatic measures to relieve breathlessness will be required. These include general and non-pharmacological measures, psychological support, and pharmacological measures.

General measures in advanced disease include sitting upright rather than lying (which maximizes vital capacity), using a fan or stream of cool air which can provide effective symptom relief (Booth et al., 2004a), inhaled oxygen if hypoxia is confirmed or suspected (Booth et al., 2004b), and a calm, settled environment. For the patient whose mobility is limited by breathlessness, physiotherapy and occupational therapy can help to maximize mobility and provide appropriate aids to improve function constrained by breathlessness. Since breathlessness is a profoundly unpleasant symptom, assessment and management of the underlying psychological state is important. Breathlessness is very commonly associated with anxiety, often in an escalating cycle (anxiety causing worsening dyspnoea, which triggers worsening anxiety, and so on). Information, education, and support of patient and family are therefore critical.

As prognosis worsens, general and non-pharmacological measures will have less to offer, and pharmacological measures directed at the symptom of breathlessness itself may be more appropriate. Untreated moderate or severe dyspnoea at the end of life is very distressing, and should be treated as actively as pain or any other distressing symptom. Breathlessness is an increasingly important and dominant symptom in renal patients towards the end of life (Murtagh et al., 2007b), so it is important to try and anticipate and plan for future episodes. Not all patients will, for instance, choose to be admitted for maximal treatment with intravenous diuretics in the last days or weeks of life.

Pharmacological treatments directed specifically at breathlessness include opioids and benzodiazepines (especially if there is moderate or severe associated anxiety). Low-dose opioids are helpful in relieving breathlessness near the end of life in end-stage cardiac and respiratory disease (Jennings et al., 2001, 2002), and clinical experience suggests that this is true for renal patients too. However, there are considerable constraints on the use of opioids in renal patients; the guidance as for pain management should be followed, although dose of opioids for breathlessness is likely to be notably smaller (usually half or quarter the starting dose for pain) and titration upwards is undertaken to a lesser degree. If small doses are not at least partly effective, combining an opioid such as fentanyl with low-dose midazolam towards the end of life (last few days or hours) may bring relief where either alone is only partially effective. This is often a better strategy than increasing the dose, since adverse effects quickly increase as doses rise.

Benzodiazepines are useful when there is coexisting anxiety (as there often is), but again need to be used with care and in reduced doses. Shorter-acting benzodiazepines are recommended, such as lorazepam 0.5 mg orally or sublingually four times a day (if used sublingually, it has a quicker onset of action and may more readily restore a sense of control to the frightened and anxious patient). If the patient is in the last days of life, midazolam (at 25% of normal dose if eGFR < 10 mL/min) can be given subcutaneously and titrated according to effect.

Conclusions

People with advanced renal disease who received CM have extensive needs for symptom control, psychological and social support, and optimal disease management to minimize complications and maintain their residual renal function as long as possible. They therefore need significant medical, nursing, psychological, and social care as their illness advances towards end of life. We have not addressed in detail the considerable psychological, spiritual, and practical care that these patients need, nor the high level of coordination between providers that is important for ensuring effective and accessible care. But for this reason, multidisciplinary team management, with excellent coordination of care, is perhaps the best way to deliver healthcare. Collaborative working between nephrology, palliative, and primary care professionals will likely deliver best care to patients following the CM pathway.

References

Akhyani, M., Ganji, M. R., Samadi, N., *et al.* (2005). Pruritus in hemodialysis patients. *BMC Dermatol*, 5, 7.

Allen, R. P., Burchell, B. J., MacDonald, B., *et al.* (2009). Validation of the self-completed Cambridge-Hopkins questionnaire (CH-RLSq) for ascertainment of restless legs syndrome (RLS) in a population survey. *Sleep Med*, 10(10), 1097–100.

Babul, N., Darke, A. C., and Hagen, N. (1995). Hydromorphone metabolite accumulation in renal failure. *J Pain Symptom Manage*, 10, 184–6.

Bailie, G. R., Mason, N. A., Bragg-Gresham, J. L., *et al.* (2004). Analgesic prescription patterns among hemodialysis patients in the DOPPS: potential for underprescription. *Kidney Int*, 65(6), 2419–25.
Barnes, J. N. and Goodwin, F. J. (1983). Dihydrocodeine narcosis in renal failure. *Br Med J (Clin Res Ed)*, 286, 438–9.
Beck, A. T. and Steer, R. A. (1984). Internal consistencies of the original and revised Beck Depression Inventory. *J Clin Psychol*, 40(6), 1365–7.
Blackburn, D., Somerville, E., and Squire, J. (2002). Methadone: an alternative conversion regime. *Eur J Palliat Care*, 9, 93–6.
Boger, R. H. (2006). Renal impairment: a challenge for opioid treatment? The role of buprenorphine. *Palliat Med*, 20, s17–s23.
Booth, S., Farquar, M., Gysels, M., *et al.* (2004a). The impact of a breathlessness intervention service (BIS) on the lives of patients with intractable dyspnea: a qualitative phase 1 study. *Palliat Support Care*, 4(3), 287–93.
Booth, S., Wade, R., Johnson, M., *et al.* (2004b). The use of oxygen in the palliation of breathlessness. A report of the expert working group of the Scientific Committee of the Association of Palliative Medicine. *Respir Med*, 98(1), 66–77.
Broadbent, A., Khor, K., and Heaney, A. (2003). Palliation and chronic renal failure: opioid and other palliative medications – dosage guidelines. *Prog Palliat Care*, 11, 183–90.
Brunier, G. and Graydon, J. (1992). The relationshop of anemia, nonspecific uremic symptoms, and physical activity to fatigue in patients with end stage renal disease on hemodialysis. *ANNA J*, 19(2), 157.
Calvin, A. O. (2003). Hemodialysis patients and end-of-life medical treatment decisions: a theory of personal preservation. *J Adv Nurs*, 46, 558–66.
Carson, R. (2012). Deny dialysis or 'D-NI' dialysis? The case for 'do not initiate; do not ignore' orders. *Clin Am Soc Nephrol*, 7(12), 1924–6.
Carson, R. C., Juszczak, M., Davenport, A., *et al.* (2009). Is maximum conservative management an equivalent treatment option to dialysis for elderly patients with significant comorbid disease? *Clin J Am Soc Nephrol*, 4(10), 1611–19.
Chan, C. H., Noble, H., Lo, S. H., *et al.* (2007). Palliative care for patients with end-stage renal disease: experiences from Hong Kong. *Int J Palliat Nurs*, 13, 310–14.
Chan, G. L. C. and Matzke, G. R. (1987). Effects of renal insufficiency on the pharmacokinetics and pharmacodynamics of opioid analgesics. *Drug Intell Clin Pharm*, 21(10), 773–83.
Chandna, S. M., Da Silva-Gane, M., Marshall, C., *et al.* (2011). Survival of elderly patients with stage 5 CKD: comparison of conservative management and renal replacement therapy. *Nephrol Dial Transplant*, 26(5), 1608–14.
Chandna, S. M., Schulz, J., Lawrence, C., *et al.* (1999). Is there a rationale for rationing chronic dialysis? A hospital based cohort study of factors affecting survival and morbidity. *BMJ*, 318(7178), 217–23.
Chauvin, M., Lebrault, C., Levron, J. C., *et al.* (1987). Pharmacokinetics of alfentanil in chronic renal failure. *Anesthes Analg*, 66, 53–6.
Cohen, L. M., Germain, M. J., and Poppel, D. M. (2003). Practical considerations in dialysis withdrawal: 'to have that option is a blessing'. *JAMA*, 289(16), 2113–19.
Coral, I. M., Moore, A. R., and Strunin, L. (1980). Plasma concentrations of fentanyl in normal surgical patients with severe renal failure. *Br J Anaesth*, 52, 101P.
Da Silva-Gane, M., Wellsted, D., Greenshields, H., *et al.* (2012). Quality of life and survival in patients with advanced kidney failure managed conservatively or by dialysis. *Clin J Am Soc Nephrol*, 7(12), 2002–9.
Daut, R. L., Cleeland, C. S., and Flanery, R. C. (1983). Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain*, 17(2), 197–210.
Davies, G., Kingswood, C., and Street, M. (1996). Pharmacokinetics of opioids in renal dysfunction. *Clin Pharmacokinet*, 31(6), 410–22.
Davison, S. N. (2003). Pain in hemodialysis patients: prevalence, cause, severity, and management. *Am J Kidney Dis*, 42(6), 1239–47.
Davison, S. N., Jhangri, G. S., and Johnson, J. A. (2006a). Cross-sectional validity of a modified Edmonton symptom assessment system in dialysis patients: a simple assessment of symptom burden. *Kidney Int*, 69(9), 1621–5.
Davison, S. N., Jhangri, G. S., and Johnson, J. A. (2006b). Longitudinal validation of a modified Edmonton symptom assessment system (ESAS) in haemodialysis patients. *Nephrol Dial Transplant*, 21(11), 3189–95.
Davison, S. N. and Torgunrud, C. (2007). The creation of an advance care planning process for patients with ESRD. *Am J Kidney Dis*, 49(1), 27–36.
Dawn, A. G. and Yosipovitch, G. (2006). Butorphanol for treatment of intractable pruritus. *J Am Acad Dermatol*, 54(3), 527–31.
Dean, M. (2004). Opioids in renal failure and dialysis patients. *J Pain Symptom Manage*, 28(5), 497–504.
Delanaye, P. and Cohen, E. P. (2008). Formula-based estimates of the GFR: equations variable and uncertain. *Nephron Clin Pract*, 110(1), c48–53.
Dimkovic, N. and Oreopoulos, D. G. (2008). Assisted peritoneal dialysis as a method of choice for elderly with end-stage renal disease. *Int Urol Nephrol*, 40(4), 1143–50.
Dinneen, B., Peasgood, J., Johnston, S., et al. (eds.) (2011). Elderly Patients with CKD Stage V Managed Conservatively Report Considerable Daily Variation in Symptom Burden: A Pilot Study. Renal Association British Renal Society Combined Conference, Birmingham, UK.
Durnin, C., Hind, I. D., Wickens, M. M., *et al.* (2001). Pharmacokinetics of oral immediate-release hydromorphone (Dilaudid IR) in subjects with renal impairment. *Proc West Pharmacol Soc*, 44, 81–2.
Eriksen, B. O. and Ingebretsen, O. C. (2006). The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int*, 69(2), 375–82.
Esposito, C. and Dal Canton, A. (2010). Functional changes in the aging kidney. *J Nephrol*, 23 Suppl 15, S41–5.
Fliser, D. (2008). [The kidneys and old age]. *Dtsch Med Wochenschr*, 133(37), 1835–8.
Fliser, D., Laville, M., Covic, A., *et al.* (2012). A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. *Nephrol Dial Transplant*, 27(12), 4263–72.
Fogo, A. B. (2011). Relativity and the kidney: observations regarding glomerular density. *Nephrol Dial Transplant*, 26(11), 3425–6.
Foral, P. A., Ineck, J. R., and Nystrom, K. K. (2007). Oxycodone accumulation in a hemodialysis patient. *South Med J*, 100, 212–14.
Fujimaki, H., Kasuya, Y., Kagami, S., *et al.* (2003). [Acceptance of dialysis therapy in elderly patients with chronic renal failure]. *Nihon Ronen Igakkai Zasshi*, 40, 41–6.
Gill, T. M., Gahbauer, E. A., Han, L., *et al.* (2010). Trajectories of disability in the last year of life. *N Engl J Med*, 362, 1173–80.
Gonçalves, A. R., Khwaja, A., Ahmed, A. K., *et al.* (2011). Stopping renin-angiotensin system inhibitors in chronic kidney disease: predictors of response. *Nephron Clin Pract*, 119(4), c348–54.
Hand, C. W., Sear, J. W., Uppington, J., *et al.* (1990). Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites. *Br J Anaesth*, 64, 276–82.
Hines, S. C., Glover, J. J., Babrow, A. S., *et al.* (2001). Improving advance care planning by accommodating family preferences. *J Palliat Med*, 4(4), 481–9.
Holley, J. L., Finucane, T. E., and Moss, A. H. (1989). Dialysis patients' attitudes about cardiopulmonary resuscitation and stopping dialysis. *Am J Nephrol*, 9, 245–51.
Ikoma, A., Steinhoff, M., Stander, S., *et al.* (2006). The neurobiology of itch. *Nat Rev Neurosci*, 7(7), 535–47.
Isaacs, A., Burns, A., and Davenport, A. (2012a). Is dialysis a viable option for the older patient? Outcomes for patients starting dialysis aged 80 years or older. *Blood Purif*, 33(4), 257–62.
Isaacs, A., Burns, A., and Davenport, A. (2012b). Should maximum conservative management be the standard paradigm for very elderly adults with chronic kidney disease or is there a role for dialysis? *J Am Geriatr Soc*, 60(7), 1376–8.

Jennings, A. L., Davies, A. N., Higgins, J. P., *et al.* (2001). Opioids for the palliation of breathlessness in terminal illness. *Cochrane Database Syst Rev*, 4, CD002066.

Jennings, A. L., Davies, A. N., Higgins, J. P., *et al.* (2002). A systematic review of the use of opioids in the management of dyspnoea. *Thorax*, (11), 939–44.

Jing, Z., Wei-jie, Y., Nan, Z., *et al.* (2012). Hemoglobin targets for chronic kidney disease patients with anemia: a systematic review and meta-analysis. *PLoS One*, 7(8), e43655.

Keithi-Reddy, S. R., Patel, T. V., Armstrong, A. W., *et al.* (2007). Uremic pruritus. *Kidney Int*, 72(3), 373–7.

Kim, J. C., Kalantar-Zadeh, K., and Kopple, J. D. (2012). Frailty and protein-energy wasting in elderly patients with end stage kidney disease. *J Am Soc Nephrol*, 20.

King, S., Forbes, K., Hanks, G. W., *et al.* (2011). A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project. *Palliat Med*, 25, 525–52.

Kirvela, M., Lindgren, L., Seppala, T., *et al.* (1996). The pharmacokinetics of oxycodone in uremic patients undergoing renal transplantation. *J Clin Anesth*, 8, 13–18.

Kreek, M. J., Schecter, A. J., Gutjahr, C. L., *et al.* (1980). Methadone use in patients with chronic renal disease. *Drug Alcohol Depend*, 5, 197–205.

Kutner, N. G., Fair, P. L., and Kutner, M. H. (1985). Assessing depression and anxiety in chronic dialysis patients. *J Psychosom Res*, 29(1), 23–31.

Lee, B. O., Lin, C. C., Chaboyer, W., *et al.* (2007). The fatigue experience of haemodialysis patients in Taiwan. *J Clin Nurs*, 16(2), 407–13.

Lee, M. A., Leng, M. E., and Tiernan, E. J. (2001). Retrospective study of the use of hydromorphone in palliative care patients with normal and abnormal urea and creatinine. *Palliat Med*, 15, 26–34.

Lugon, J. R. (2005). Uremic pruritus: a review. *Hemodial Int*, 9(2), 180–8.

Lunney, J. R., Lynn, J., Foley, D. J., *et al.* (2003). Patterns of functional decline at the end of life. *JAMA*, 289, 2387–92.

Lunney, J. R., Lynn, J., and Hogan, C. (2002). Profiles of older Medicare decedents. *J Am Geriatr Soc*, 50, 1108–12.

Main, J. (2000). Deciding not to start dialysis—a one year prospective study in Teesside. *J Nephrol*, 13, 137–41.

Majeski, C. J., Johnson, J. A., Davison, S. N., *et al.* (2007). Itch Severity Scale: a self-report instrument for the measurement of pruritus severity. *Br J Dermatol*, 156(4), 667–73.

Manenti, L., Tansinda, P., and Vaglio, A. (2009). Uraemic pruritus: clinical characteristics, pathophysiology and treatment. *Drugs*, 69(3), 251–63.

Martin, C. R. and Thompson, D. R. (2000). Prediction of quality of life in patients with end-stage renal disease. *Br J Health Psychol*, 5, 41–55.

McCann, K. and Boore, J. R. (2000). Fatigue in persons with renal failure who require maintenance haemodialysis. *J Adv Nurs*, 32(5), 1132–42.

Medcalf, P. and Bhatia, K. P. (2006). Restless legs syndrome. *BMJ*, 333(7566), 457–8.

Melzack, R. (1975). The McGill Pain Questionnaire: major properties and scoring methods. *Pain*, 1(3), 277–99.

Mercadante, S. and Arcuri, E. (2004). Opioids and renal function. *J Pain*, 5(1), 2–19.

Meyer, B. R. (1989). Renal function in aging. *J Am Geriatr Soc*, 37(8), 791–800.

Moist, L. M., Lok, C. E., Vachharajani, T. J., *et al.* (2012). Optimal hemodialysis vascular access in the elderly patient. *Semin Dial*, 25(6), 640–8.

Molony, D. A. and Stephens, B. W. (2011). Derangements in phosphate metabolism in chronic kidney diseases/endstage renal disease: therapeutic considerations. *Adv Chronic Kidney Dis*, 18(2), 120–31.

Morton, R. L., Snelling, P., Webster, A. C., *et al.* (2012). Dialysis modality preference of patients with CKD and family caregivers: a discrete-choice study. *Am J Kidney Dis*, 60(1), 102–11.

Morley, J. S. and Makin, M. K. (1998). The use of methadone in cancer pain poorly responsive to other opioids. *Pain Rev*, 5, 51–8.

Murphy, E. L., Murtagh, F. E., Carey, I., *et al.* (2009). Understanding symptoms in patients with advanced chronic kidney disease managed without dialysis: use of a short patient-completed assessment tool. *Nephron Clin Pract*, 111(1), c74–80.

Murtagh, F. E., Addington-Hall, J. M., Donohoe, P., *et al.* (2006). Symptom management in patients with established renal failure managed without dialysis. *EDTNA ERCA J*, 32, 93–8.

Murtagh, F. E., Addington-Hall, J. M., Edmonds, P. M., *et al.* (2007a). Symptoms in advanced renal disease: a cross-sectional survey of symptom prevalence in stage 5 chronic kidney disease managed without dialysis. *J Palliat Med*, 10(6), 1266–76.

Murtagh, F. E., Addington-Hall, J., and Higginson, I. J. (2007b). The prevalence of symptoms in end-stage renal disease: a systematic review. *Adv Chronic Kidney Dis*, 14(1), 82–99.

Murtagh, F. E., Addington-Hall, J. M., and Higginson, I. J. (2011a). End-stage renal disease: a new trajectory of functional decline in the last year of life. *J Am Geriatr Soc*, 59(2), 304–8.

Murtagh, F. E., Chai, M. O., Donohoe, P., *et al.* (2007c). The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. *J Pain Palliat Care Pharmacother*, 2007(2), 5–16.

Murtagh, F. E., Marsh, J. E., Donohoe, P., *et al.* (2007d). Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. *Nephrol Dial Transplant*, 22(7), 1955–62.

Murtagh, F. E., Preston, M., and Higginson, I. (2004). Patterns of dying: palliative care for non-malignant disease. *Clin Med*, 4, 39–44.

Murtagh, F. E., Sheerin, N. S., Addington-Hall, J., *et al.* (2011b). Trajectories of illness in stage 5 chronic kidney disease: a longitudinal study of patient symptoms and concerns in the last year of life. *Clin Am Soc Nephrol*, 6(7), 1580–90.

Nadeau-Fredette, A. C., Goupil, R., Montreuil, B., *et al.* (2013). Arteriovenous fistula for the 80 years and older patients on hemodialysis: is it worth it? *Hemodial Int*, 17(4), 594–601.

NHS Kidney Care (2012). Getting it Right: End of Life Care in Advanced Kidney Disease. London: NHS Kidney Care.

O'Keeffe, S. T., Noel, J., and Lavan, J. N. (1993). Restless leg syndrome in the elderly. *Postgrad Med J*, 69(815), 701–3.

O'Sullivan, D. and McCarthy, G. (2007). An exploration of the relationship between fatigue and physical functioning in patients with end stage renal disease receiving haemodialysis. *J Clin Nurs*, 16(11C), 276–84.

Patel, T. S., Freedman, B. I., and Yosipovitch, G. (2007). An update on pruritus associated with CKD. *Am J Kidney Dis*, 50(1), 11–20.

Rijsman, R. M., de Weerd, A. W., Stam, C. J., *et al.* (2004). Periodic limb movement disorder and restless legs syndrome in dialysis patients. *Nephrology*, 9(6), 353–61.

Rodin, G. M., Chmara, J., Ennis, J., *et al.* (1981). Stopping life-sustaining medical treatment: psychiatric considerations in the termination of renal dialysis. *Can J Psychiatry*, 26(8), 540–4.

Ross, S. D., Fahrbach, K., Frame, D., *et al.* (2003). The effect of anemia treatment on selected health-related quality-of-life domains: a systematic review. *Clin Ther*, 25(6), 1786–805.

Saini, T., Murtagh, F. E., Dupont, P. J., *et al.* (2006). Comparative pilot study of symptoms and quality of life in cancer patients and patients with end stage renal disease. *Palliat Med*, 20(6), 631–6.

Schmelz, M., Schmidt, R., Bickel, A., *et al.* (1997). Specific C-receptors for itch in human skin. *J Neurosci*, 17(20), 8003–8.

Scholz, J., Steinfath, M., and Schulz, M. (1996). Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update. *Clin Pharmacokinet*, 31, 275–92.

Silber, M. H., Ehrenberg, B. L., Allen, R. P., *et al.* (2004). An algorithm for the management of restless legs syndrome. *Mayo Clinic Proc*, 79(7), 916–22.

Singer, P. A., Martin, D. K., Lavery, J. V., *et al.* (1998). Reconceptualizing advance care planning from the patient's perspective. *Arch Intern Med*, 158(8), 879–84.

Smith, C., Silva-Gane, M., Chandna, S., *et al.* (2003). Choosing not to dialyse: evaluation of planned non-dialytic management in a cohort

of patients with end-stage renal failure. *Nephron Clin Pract*, 95(2), c40–c46.

Solano, J. P., Gomes, B., and Higginson, I. J. (2006). A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. *J Pain Symptom Manage*, 31(1), 58–69.

Takaki, J., Nishi, T., Nangaku, M., *et al.* (2003). Clinical and psychological aspects of restless legs syndrome in uremic patients on hemodialysis. *Am J Kidney Dis*, 41(4), 833–9.

Talbott, G. A., Lynn, A. M., Levy, F. H., *et al.* (1997). Respiratory arrest precipitated by codeine in a child with chronic renal failure. *Clin Pediatr*, 36, 171–3.

Telarovic, S., Relja, M., and Trkulja, V. (2007). Restless legs syndrome in hemodialysis patients: association with calcium antagonists. A preliminary report. *Eur Neurol*, 58(3), 166–9.

Tonkin-Crine, S., Okamoto, I., Leydon, G. M., *et al.* (2015). Understanding by older patients of dialysis and conservative management for chronic kidney failure. *Am J Kidney Dis*, 65(3), 443–50.

Weiner, S. (2010). End of life care discussions: a survey of dialysis patients and professionals. *J Pain Symptom Manage*, 39(2), 395–96.

Weisbord, S. D., Carmody, S. S., Bruns, F. J., *et al.* (2003). Symptom burden, quality of life, advance care planning and the potential value of palliative care in severely ill haemodialysis patients. *Nephrol Dial Transplant*, 18(7), 1345–52.

Weisbord, S. D., Fried, L., Mor, M. K., *et al.* (2007). Renal provider recognition of symptoms in patients on maintenance hemodialysis. *Clin J Am Soc Nephrol*, 2, 960–7.

Weisbord, S. D., Fried, L. F., Arnold, R. M., *et al.* (2004). Development of a symptom assessment instrument for chronic hemodialysis patients: the Dialysis Symptom Index. *J Pain Symptom Manage*, 27(3), 226–40.

Wikstrom, B., Gellert, R., Ladefoged, S. D., *et al.* (2005). Kappa-opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. *J Am Soc Nephrol*, 16(12), 3742–7.

Williams, B., McDaid, L., Walker, R., *et al.* (2002). Maximum Conservative Management of End Stage Renal Failure; What Can Patients and Their Families Expect? presented at The Renal Association, UK, Conference, Royal College of Physicians, London.

Yang, H. and Fogo, A. (2010). Cell senescence in the ageing kidney. *J Am Soc Nephrol*, 21, 1436–9.

Yosipovitch, G., Greaves, M. W., and Schmelz, M. (2003). Itch. *Lancet*, 361(9358), 690–4.

Zhou, X. J., Rakheja, D., Yu, X., *et al.* (2008). The aging kidney. *Kidney Int*, 74(6), 710–20.

CHAPTER 146

Palliative care in end-stage renal disease

Katie Vinen, Fliss E. M. Murtagh, and Irene J. Higginson

Introduction

The World Health Organization defines palliative care as 'an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual' (Moss et al., 2004).

In the past, nephrology has been viewed as a highly active speciality where the death of a patient was perceived as a medical failure. When dialysis was rarely offered to those over 40 or suffering from diabetes, this may have been understandable. With changing demographics, however, nephrology patients are older and 70% of those over 65 starting dialysis have at least one co-morbidity most frequently ischaemic heart disease or diabetes (Webb et al., 2011). Despite this, dialysis is now offered even to those in their 80s or 90s, some of whom do well. Many more, however, cannot be cured of their renal disease or their co-morbidities so all treatment is essentially palliative and, as research suggests that their quality of dying is not optimal (Davison and Torgunrud, 2007), a change in focus of care is needed. Treatment should focus on symptom management, advance care planning, and family and patient education and support. These form part of a long process of renal palliative care of which the dying or terminal care phase is only one part.

Groups who might benefit from renal palliative care

Three groups of patients may benefit from renal palliative care. In those over 75 with extensive co-morbidity, dialysis does not extend life (Murtagh et al., 2007c; Chandna et al., 2011) (see Fig. 146.1) and may reduce quality of life with increased time in hospital and a reduced chance of achieving a non-medicalized death (Carson et al., 2009). For those beginning dialysis from nursing homes, only 13% of patients are alive with maintained functional status 1 year after starting dialysis (Kurella et al., 2009). Here, end-stage renal failure is often a reflection of more extensive multisystem failure where dialysis cannot improve diabetic control, combat vascular disease, or reverse dementia. Whilst some older patients do benefit from dialysis, it is interesting that the best predictors of success in the over 80s are age, ambulatory status, and co-morbidity, and not the biochemical targets and blood pressure control so often sought by renal physicians (Feest, 2010). These patients may prefer to forgo dialysis and follow the conservative care pathway described in Chapter 145. Instead of beginning dialysis, care focuses on slowing the decline in existing kidney function (by measures such as good blood pressure control) and treating the symptoms and complications of renal failure. This approach focuses on improving symptoms and quality of life, advance care planning, and building a network of care to support the patient. Here, the palliative phase may last for months or up to 1–2 years (Paniagua et al., 2002; Chandna et al., 2011) and the challenge is to optimize quality of life as well as plan for their later death.

Improvements in treatment have supported a second population of patients who begin dialysis in relative good health, but over years of different treatment modalities gradually become frailer. Such dialysis patients remain with the same clinician, but require a change in the focus of care towards greater emphasis on symptom control, a reduction in unnecessary tablet burden or even in dialysis frequency, and detailed attention to quality of life and planning for end-of-life care. Since we know that intensive dialysis regimens aimed at reducing morbidity and mortality are often ineffective (Eknoyan et al., 2002; Paniagua et al., 2002), maximizing health-related quality of life (HRQOL) may be a more beneficial goal.

Finally, a third smaller group of younger dialysis patients suffer devastating renal/multisystem disorders (e.g. severe poorly controlled diabetes) where, despite their relative youth, prognosis is poor and there is a relentless and steady deterioration in health. Whilst in these cases dialysis is frequently offered, a parallel symptom control and palliative approach may also be beneficial.

In each group of patients, traditional goals such as control of blood pressure and phosphate are replaced with symptom management and a greater focus on quality of life. Patients who dialyse may also wish to consider their ultimate treatment choice of dialysis withdrawal (Cohen et al., 2000b; Ashby et al., 2005; Cohen and Germain, 2005; Chater et al., 2006). This allows them to time their own demise, plan their place of care, say their final goodbyes, and receive excellent symptom control. With a mean survival of approximately 8 days (Cohen et al., 2000b) in those with no residual urine output, palliative care needs to be highly focused. The goal of care has changed from saving or extending life to dying well.

The unique features of renal palliative care

Although the principles of palliative care apply to renal patients, a number of unique features suggest this care is best provided by

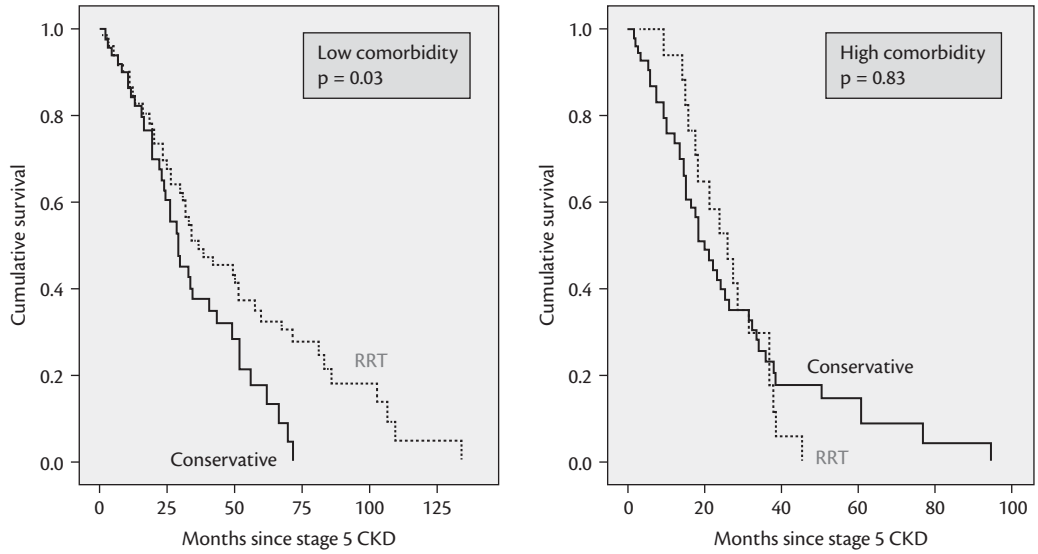

Fig. 146.1 Comparison of Kaplan–Meier survival curves by modality (renal replacement therapy (RRT) versus conservative non-dialytic management) in patients > 75 years, with low co-morbidity shown on the left and high co-morbidity on the right.
From Chandna et al. (2011).

a combined nephrology and palliative care approach. Firstly, renal patients have widespread complex co-morbidities with a particular burden of vascular disease (Webb et al., 2011) and frequent cognitive decline on dialysis. Thus, decisions about a patient's desire to continue dialysis after, for instance, a severe stroke need to be discussed early during an active dialysis phase if the patient's views are to be sought prior to such decline (Sekkarie and Moss, 1998; Davison, 2009). Nephrologists and families are limited in their ability to advocate about continuing dialysis in the face of severe dementia or life-limiting cancer with both groups tending to overestimate a patient's desire to continue (Miura et al., 2006). Secondly, the symptom burden is large, but some symptoms (e.g. pruritus, restless legs) are specific to (or at least more common in) advanced renal disease and are therefore not recognized, or well managed, by those with little renal experience (Cohen et al., 2000a; Murtagh et al., 2007a, 2007b). Thirdly, treatment of symptoms requires expert understanding of how drug modifications need to be made as renal function declines (Davison and Ferro, 2009). Fourthly, the trajectory to death is different in renal patients and the 'tipping point', where increased medical and supportive care is rapidly needed, may be missed by staff with little renal experience (Murray and Sheikh, 2008; Murtagh et al., 2011a, 2011b). In conservatively managed stage 5 chronic kidney disease (CKD), symptom scores and functional status can often be relatively stable until the first to second months preceding death, in marked contrast to trajectories for cancer patients or those with chronic obstructive pulmonary disease or heart failure. Finally, with longstanding relationships between patient and dialysis staff, continued care in this setting may avoid the sense of abandonment that transfer to another team might cause.

Honest communication with the patient and their family

Optimal supportive renal care starts with patients being given honest prognostic information yet we know such discussions are rare (Weiner, 2008). Research suggests that the majority of patients do value such information and that it should be offered even in the year before dialysis is initiated (Davison and Torgunrud, 2007). Those planning for a transplant, or without complex co-morbidity, may have an optimistic outlook and be spared such conversations, but others will benefit from more difficult discussions about the life-limiting nature of their illness.

Some patients believe they can be kept alive indefinitely on dialysis (Cohen et al., 1993, 1997; Holley et al., 1997; Davison, 2009). However, for the average 65-year-old starting dialysis, the mean life expectancy is 3.9 years compared to 17.2 years in an age-matched population not beginning dialysis. The annual mortality rate of haemodialysis patients is high, yet many renal patients are currently unaware of this, believing that renal failure is either curable with transplantation or treatable with dialysis.

Traditionally, nephrologists have struggled with the transition from active to palliative management, evidence suggesting that they find it difficult to address death and dying (Rodin et al., 1981; Cohen et al., 2003). In studies on advance care planning, Davison found that patients wanted more information about prognosis and the disease process and for this to be given in clear lay language and to include information about the impact of treatment on daily life (Davison, 2006). Although physicians perceive honest information about limited prognosis may remove hope, evidence suggests the opposite and that such discussions in fact build trust between patients and their medical teams (Davison, 2006).

Honest information must also be given as the patient declines on dialysis. Despite physician reluctance, one study has shown that 97% of patients felt that they wanted to be given information about life expectancy and treatment options and expected the physician to provide this without being prompted (Fine et al., 2005; Michel and Moss, 2005). Patient comments, referring to being 'too old' or 'too tired'to continue with dialysis, are often ignored by clinicians (Russ et al., 2007). Patients fully informed about the likely poor success of cardiopulmonary resuscitation (Moss et al., 1992), or the realities of their failing health may prefer to decline resuscitation

and adopt a more palliative approach to care yet without open discussion first, they have no choice but to continue active treatment.

In a survey of 584 stage 4 and 5 CKD patients (on conservative or dialysis pathways) about information needs (Davison, 2010), patients wanted greater education and support for staff, patients, and families in end-of-life issues. They also identified greater involvement of their family in both their care and decision-making as important. The patients themselves wanted to know more about what to expect clinically at the end of life, what palliative care and hospice services were available, and how to manage their symptoms. They also valued greater emphasis on pain and symptom management with < 18% of patients favouring extending life at the expense of prolonging pain and discomfort. As patients become frailer, clinicians may sensitively introduce the choice to withdraw from dialysis as many patients believe mistakenly that this would not be supported by their medical team (Cohen et al., 1993; Hines et al., 2001).

Although most clinicians agree that honest patient education is central to good renal palliative care, they often feel reluctant to have such discussions because offering a prognosis for an individual patient seems so full of uncertainty. We therefore report the significant recent progress in identifying those likely to be in the last part of life and, therefore, in most need of a more symptom-based approach.

Identification of those under nephrological care at risk of dying

Although there will always be some uncertainty, there are three broad categories of information to aid identification of dialysis patients who are likely to be in the last part of life and have most palliative and supportive care needs.

Firstly, demographic and laboratory data (such as age and serum albumin data) as well as co-morbidity data can guide prognosis (such as the Charlson co-morbidity index (Beddhu et al., 2000)). Vascular co-morbidity such as peripheral vascular disease, foot ulcers, cardiovascular disease, and dementia appear the most consistent clinical co-morbidities determining poor prognosis (Mauri et al., 2008; Couchoud et al., 2009; Cohen et al., 2010).

Secondly, patient-reported outcome measures such as symptom scores and quality of life measures have the additional advantage of identifying current need as well as contributing to prognosis and also helping to focus care on those areas most likely to help the patient. An example here is the Palliative care Outcome Scale—Symptom Module Renal Version (POS-S Renal), which has been shown to help identify those with greatest palliative care needs (NHS Kidney Care, 2012) (and see <http://www.pos-pal.org>). For the 25% of dialysis patients who die suddenly (Jadoul et al., 2012) and unexpectedly, such symptom and quality of life-based assessments direct care to need and are therefore valuable regardless of the accuracy of prognosis.

Thirdly, overall clinical judgement may be most helpful, provided the clinician is experienced and knows the patient well. One example is the surprise question (Would I be surprised if this patient died within the next 6–12 months?). This question shifts the emphasis from prognosis (Will this patient die within a year?) to clinical expectation (Would I be surprised if this patient were to die within a year?). By changing a clinician's focus to the possibility (not the likelihood) of death, it allows them to re-evaluate goals of care with the patient and helps to counter the tendency of physicians to over-estimate prognosis. In one study, the odds adjusted ratio for dying in the group for whom the surprise question was no was 3.5 times higher than that in the group where it was yes (Moss et al., 2008).

Cohen et al. studied 500 dialysis patients and found five variables associated with early mortality (Cohen et al., 2010). These were age, dementia, peripheral vascular disease, decreased albumin, and a 'no' response to the surprise question. In the UK Renal Registry data, the presence of ischaemic or neuropathic foot ulcers, or the presence of malignancy, were the co-morbidities associated with increased likelihood of death (Webb et al., 2011) in incident dialysis patients. Such features highlight the need for a parallel palliative approach in these patients, even from the outset of dialysis. Work continues to refine these tools and to create a simple quick predictive bedside test to identify those in greatest need of a palliative approach.

Good symptom management

Good symptom management first requires systematic identification and assessment of the symptoms experienced. This is sometimes neglected in nephrology, despite evidence that the symptom burden suffered by renal patients often exceeds that of cancer patients (Saini et al., 2006; Murtagh et al., 2007b) (see Fig. 146.2). Three- to four-monthly routine use of structured symptom assessment tools can improve identification of those with greatest symptom burden (NHS Kidney Care, 2012). Such symptom scores allow identification of common symptoms such as pain and breathlessness, as well as assessment of unusual renal symptoms such as restless legs or itching. In one American study, use of a symptom score tool among dialysis patients raised identification of symptoms over twofold, from an average of 4.1 symptoms to 10.5 symptoms per patient (Weisbord et al., 2003).

Physical symptoms

In the whole dialysis population, symptom burden accounts for 29% of their impairment in physical HRQOL and 39% in their impairment in mental HRQOL (Merkus et al., 1999). The main physical symptoms (see Fig. 146.2) are fatigue, itch, poor appetite and pain, and to a lesser extent sleep disturbance, anxiety, breathlessness, nausea, restless legs, and depression (Murtagh et al., 2007b). Renal physicians are often responsible for managing symptoms that are both renal and non-renal in origin, as their knowledge of drug dose adjustment makes them uniquely able to do this. Pain is a particularly undertreated symptom, with evidence showing that up to 50% of patients with CKD had pain and up to 82% of these patients described it as moderate to severe (Davison and Ferro, 2009). This symptom which can be both renal in origin (e.g. ischaemic hand from steal), or related to co-morbidity (such as diabetic neuropathy or ischaemic feet) should be treatable in all cases.

Psychological symptoms

Studies suggest 10–20% of prevalent dialysis patients have significant depression, whilst 40% may have raised levels of depressive affect (Craven et al., 1988). Formal screening tools may be needed to identify this, as symptoms can sometimes be mistaken for the effects of uraemia or side effects of medication. Depression is an

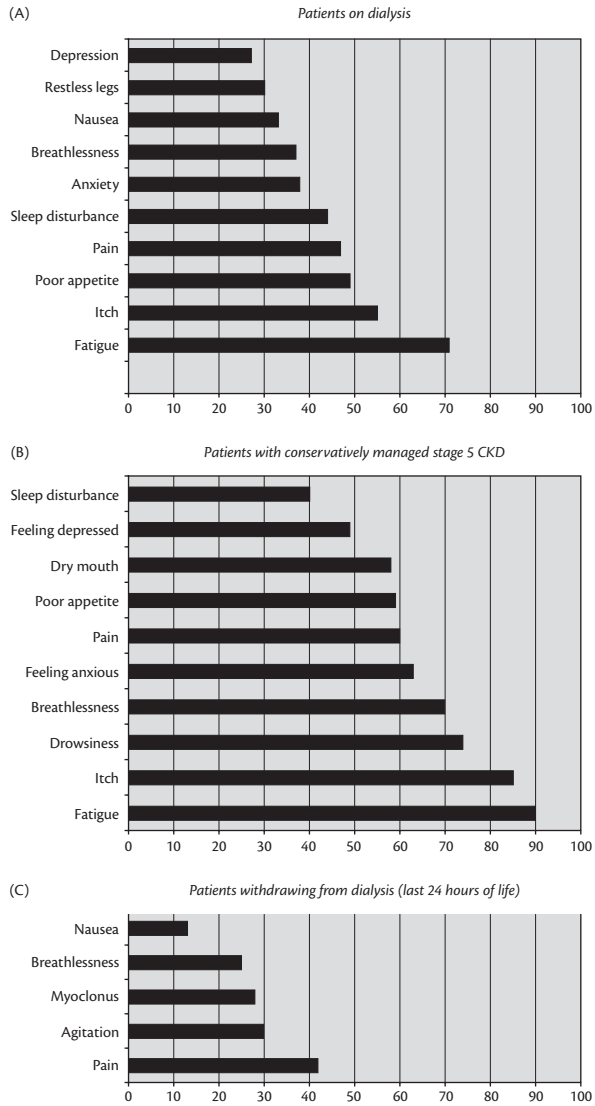

Fig. 146.2 Percentage of patients with common symptoms in renal disease. (A) Patients on dialysis. (B) Patients with conservatively-managed stage 5 CKD. (C) Patients withdrawing from dialysis (last 24 hours of life).
From Chambers et al. (2010).

independent risk factor for death in the end-stage renal failure population and is associated with a greater risk of hospitalization (Hedayati and Finkelstein, 2009), functional impairment, sexual dysfunction, and non-compliance with medical therapy (Drayer et al., 2006; Peng et al., 2007). Good treatment may not only improve the quality of life for the patient but may also improve compliance with treatment (Cukor et al., 2009). Pharmacological treatments are probably underused in this population due to concerns about the use of antidepressant medications in those with low glomerular filtration rate. Other treatments such as psychotherapy, cognitive behaviour therapy, and exercise therapy have all been shown to be effective in reducing levels of depression (Hedayati and Finkelstein, 2009). Anxiety is also common in dialysis patients with one-third experiencing at least moderate anxiety in the first year of treatment (Nichols and Springford, 1984). Treatment is complex and undoubtedly begins in pre-dialysis clinics with good education of both the patient and family and the involvement of peer supporters where possible. Cognitive behavioural therapy has been shown to be effective in anxiety disorders in other populations but has never been trialled in this population (Rachman, 2009).

Rationalization of tablets and dialysis provision

The benefit of honest communication with patients and families is that it allows goals of care to be changed, with subsequent improvement in a patient's quality of life. Treatment schedules can hamper many aspects of a patient's life through limitations on travel and social life and restrictions on fluid intake and diet. Heroic pharmacological efforts to minimize cardiovascular risk and repeated hospitalizations for yet further surgical access attempts add further constraints and contribute to poor quality of life (Valderrabano et al., 2001). As patients approach the end of their lives, this disease-focused model should gradually be replaced by patient-centred care that minimizes symptoms, optimizes functional capacity, and helps patients to cope with their illness. Unnecessary oral medication can be removed and diet and fluid restrictions eased. Even dialysis hours can be relaxed where all parties acknowledge that optimal toxin clearance is no longer as important as celebrating a birthday with a loved one or even visiting a lawyer to make a will.

Advance care planning

Advance care planning is a dynamic process that involves understanding the patient, their life, and their family before discussions about future priorities and preferences for care. Davison describes aspects of early advance care planning, which allow clinicians to gain background information to help them to plan subsequent optimal care with the patient. These are providing a realistic prognosis, establishing how involved the patient wishes to be and who else they wish to include in decisions, and exploring the expectations of patient and family regarding the health and future of the patient, to guide realistic goals of care. The values of the patient need to be taken into account, with discussions focusing on everyday aspects of life, such as family relationships, and enjoyed or difficult activities. Patients may also wish to think about their own balance for the importance of maximizing comfort, maintaining function, or prolonging life.

Subsequent discussions may then allow naming of a surrogate decision-maker, clarification of preferences, and the development of a unique patient-centred individual care plan (Davison and Torgunrud, 2007). In the early stages of advance care planning, the focus should be on maximizing quality of life by, for instance, allowing the patient to dialyse flexibly enough to attend a 50th wedding anniversary celebration or travel to see a new grandchild abroad. It may focus on identifying social care needs that maximize independence and reduce the burden on loved ones (often a cause of considerable concern for these patients). Towards the last stage of life, planning will move to focus on preparing for death and expressing a preference for the location of end-of-life care, strengthening relationships with loved ones, and achieving very good symptom management, allowing the patient a sense of autonomy and control even at the end of life. Advance care plans may contain an advance directive about a patient's wish to be dialysed after diagnoses of, for instance, moderate or severe stroke or dementia and may nominate

a formal lasting power of attorney (or other nominated advocate). Others may prefer to discuss with family and leave decisions more open, with one study showing that 43% of elderly patients on dialysis units had not completed an advance directive, preferring family to make decisions if necessary (Holley et al., 1997).

Advance care planning is often started late when a patient's cognitive decline may impair their ability to be involved. Unlike cancer patients, where decline is often more rapid in the last few months of life, renal patients often experience physical and cognitive decline over several years with 'punctuated' episodes of life-threatening illness making the dying phase harder to identify. If research is followed and patients do have honest discussions in the pre-dialysis setting, then ongoing advance care planning in the haemodialysis setting should follow more easily (Davison and Torgunrud, 2007).

Many believe that, as a minimum, advance care planning should start when the answer to the surprise question is 'no'. Advance care planning should be reviewed at least annually and after any significant change in a patient's health. Whilst advance care planning may be poorly defined, research suggests it is highly valued by patients (Davison, 2006) although they feel it is often begun too late and needs to be more individualized. Contrary to what healthcare professionals often believe, patients also feel it should be the responsibility of the physician or nurse to initiate these discussions and not for the patient to raise this subject (Davison, 2006).

Successful use of advance care planning can be measured objectively through improvements in quality of life and psychological distress scores, measures of quality of death (such as preferred location and absence of symptoms), and family satisfaction with care.

Social and family considerations and building a network for care

As patients become frailer, they may benefit from help from occupational therapists, social workers, dieticians, counsellors, and chaplains, all of whom may help either the patient or their carer or both. They will also need to be linked to their family doctor and associated community nurses, and at the end of their life to palliative care nurses and the local hospice or palliative care services. Such complex networks of care can be achieved by regular multidisciplinary meetings which link nephrological (secondary or tertiary care) with primary and community-based care. A team based approach is the most realistic route to achieve such complex care and to ensure families feel well supported.

Achieving their preferred place of care at the end of life is a priority for many renal patients, with 36% of stage 4 and 5 kidney disease patients preferring to die at home, 29% in a hospice, and 27% in a hospital setting (Davison, 2010). When patients choose conservative care rather than dialysis, studies suggest we are close to achieving such preferences, at least in the United Kingdom, with one study showing that only one-third of conservative patients die in hospital compared to 73% of dialysis patients (Carson et al., 2009). There are perhaps two principal reasons why dialysis patients still die in hospital despite not wishing to—first, because clinicians or family do not recognize or acknowledge that the patient is dying and the second, because we simply do not ask them where they wish to die. Honest recognition of a patient reaching the end of life may allow them to die peacefully at home rather than in an impersonal hospital ward after a futile intervention or procedure. For those who withdraw from dialysis through their own request, knowing that they wish to die at home or in a hospice may influence the timing of a last dialysis session so that services are available to support the patient in their preferred place of care.

Dying with renal disease

For those who die purely due to renal failure (those on the conservative care pathway and where the patients withdraw from active dialysis), three common complications of renal failure (volume overload, hyperkalaemia and uraemia) may finally result in death. Fluid overload is the most symptomatic of these—aggressive fluid restriction with significant doses of diuretics should be used in the conservative population and dialysis patients may be brought to their dry weight before dialysis withdrawal to prevent breathlessness. With appropriate management, uraemia may allow the patient to pass into a coma with relatively few symptoms. Hyperkalaemia by contrast can result in cardiac dysrhythmia and a less predictable timescale of death. Many other patients who continue dialysis, however, will end their lives as a result of the common co-morbidities where patients succumb to cerebrovascular or cardiovascular disease or sepsis.

In the United Kingdom, withdrawal from dialysis accounts for 14% of deaths in patients on dialysis. However, rates vary in different parts of the world according to cultural norms and clinical practice and reach approximately 30% in Australia and up to 40% in New England in the United States (Cohen and Germain, 2005; Ansell and Tomson, 2009). Studies suggest that in approximately 50% of cases of dialysis withdrawal, the decision to stop treatment is made by the family or clinicians rather than by the patient (Chater et al., 2006).

Work by Cohen et al. suggests that dying renal patients do experience significant symptoms in the 24 hours before death with pain in 40% of patients, agitation in 30%, and breathlessness in 25% (Cohen et al., 2000a). Other work (Chater et al., 2006) has shown that formal palliative care at this time can significantly improve the quality of dying with reductions in pain (from 53% to 20% after intervention), agitation (from 68% to 33%), and dyspnoea (from 46% to 26%).

Care at the end of life does not of course simply extend to the patient but also to their family, friends, and those close to them. The family needs emotional support, honest prognostic information, and helpful information about local hospices and other sources of community support, especially if caring for the patient at home.

A good death is difficult to define and sometimes a clinician's priorities can differ from those of the patient. Studies suggest both patients and clinicians value symptom management, clear decision-making, achieving a sense of completion, contributing to others, and the patient being treated as a whole person. Patients themselves, however, put more weight on remaining mentally alert sometimes at the cost of symptom control, preparing funeral arrangements or making a will, and not being a burden to loved ones (Steinhauser et al., 2000a, 2000b).

Care of the bereaved after death

Over many years of care, the families of renal patients and staff have often come to know one another very well so care does not end with the death of the patient. Many families value recognition of the

death of a loved one in the form of an obituary placed in the dialysis unit or a letter of condolence from staff. Some units hold an annual non-religious service of remembrance for those who have died in the last year. Rather than feeling that the renal unit has given up on the patient and abandoned the family, such gestures allow closure for families and clinicians, with a sense that the relationship has been completed. In addition, many hospices or palliative care services offer bereavement care both to families of those who have died under their care or to the families of those who have died elsewhere which can be invaluable.

Conclusions

Renal palliative care has come a long way in the past 10 years. We now recognize that there will always be those we cannot cure and whose lives we cannot extend but that we can still offer them very valuable care. With the right tools we are starting to identify these patients and their priorities and preferences for care allowing us to work with them to try to achieve their goals. Good guidelines are being created for symptom control and the focus of care is shifting from aggressive, disease-focused care, to a more personalized approach which reflects the needs and priorities of the individual, and is in accord with their own illness trajectory. We are just beginning to acknowledge that our final duty to these often long-standing patients is to try to ensure that just as they have lived well under our care, they should also die well under it.

References

Ansell, D. and Tomson, C. R. (2009). UK Renal Registry 11th Annual Report (December 2008): Chapter 15 The UK Renal Registry, UKRR database, validation and methodology. *Nephron Clin Pract*, 111 Suppl 1, c277–85.

Ashby, M., Op't Hoog, C., Kellehear, A., *et al*. (2005). Renal dialysis abatement: lessons from a social study. *Palliat Med*, 19, 389–96.

Beddhu, S., Bruns, F. J., Saul, M., *et al*. (2000). A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. *Am J Med*, 108, 609–13.

Carson, R. C., Juszczak, M., Davenport, A., *et al*. (2009). Is maximum conservative management an equivalent treatment option to dialysis for elderly patients with significant comorbid disease? *Clin J Am Soc Nephrol*, 4, 1611–19.

Chandna, S. M., Da Silva-Gane, M., Marshall, C., *et al*. (2011). Survival of elderly patients with stage 5 CKD: comparison of conservative management and renal replacement therapy. *Nephrol Dial Transplant*, 26, 1608–14.

Chater, S., Davison, S. N., Germain, M. J., *et al*. (2006). Withdrawal from dialysis: a palliative care perspective. *Clin Nephrol*, 66, 364–72.

Cohen, L. M. and Germain, M. J. (2005). Psychosocial factors in patients with chronic kidney disease: the psychiatric landscape of withdrawal. *Semin Dial*, 18, 147–153.

Cohen, L. M., Germain, M. J., and Poppel, D. M. (2003). Practical considerations in dialysis withdrawal: 'to have that option is a blessing'. *JAMA*, 289, 2113–19.

Cohen, L. M., Germain, M., Poppel, D. M., *et al*. (2000a). Dialysis discontinuation and palliative care. *Am J Kidney Dis*, 36, 140–4.

Cohen, L. M., Germain, M. J., Poppel, D. M., *et al*. (2000b). Dying well after discontinuing the life-support treatment of dialysis. *Arch Intern Med*, 160, 2513–18.

Cohen, L. M., Germain, M., Woods, A., *et al*. (1993). Patient attitudes and psychological considerations in dialysis discontinuation. *Psychosomatics*, 34, 395–401.

Cohen, L. M., McCue, J. D., Germain, M., *et al*. (1997). Denying the dying. Advance directives and dialysis discontinuation. *Psychosomatics*, 38, 27–34.

Cohen, L. M., Ruthazer, R., Moss, A. H., *et al*. (2010). Predicting six-month mortality for patients who are on maintenance hemodialysis. *Clin J Am Soc Nephrol*, 5, 72–9.

Couchoud, C., Labeeuw, M., Moranne, O., *et al*. (2009). A clinical score to predict 6-month prognosis in elderly patients starting dialysis for end-stage renal disease. *Nephrol Dial Transplant*, 24, 1553–61.

Craven, J. L., Rodin, G. M., and Littlefield, C. (1988). The Beck Depression Inventory as a screening device for major depression in renal dialysis patients. *Int J Psychiatry Med*, 18, 365–74.

Cukor, D., Rosenthal, D. S., Jindal, R. M., *et al*. (2009). Depression is an important contributor to low medication adherence in hemodialyzed patients and transplant recipients. *Kidney Int*, 75, 1223–9.

Davison, S. (2009). Advance care planning in patients with end-stage renal disease *Prog Palliative Care*, 17, 170–8.

Davison, S. N. (2006). Facilitating advance care planning for patients with end-stage renal disease: the patient perspective. *Clin J Am Soc Nephrol*, 1, 1023–8.

Davison, S. N. (2010). End-of-life care preferences and needs: perceptions of patients with chronic kidney disease. *Clin J Am Soc Nephrol*, 5, 195–204.

Davison, S. and Ferro, C. (2009). Management of pain in chronic kidney disease. *Prog Palliative Care*, 17, 186–95.

Davison, S. N. and Torgunrud, C. (2007). The creation of an advance care planning process for patients with ESRD. *Am J Kidney Dis*, 49, 27–36.

Drayer, R. A., Piraino, B., Reynolds, C. F., *et al*. (2006). Characteristics of depression in hemodialysis patients: symptoms, quality of life and mortality risk. *Gen Hosp Psychiatry*, 28, 306–12.

Eknoyan, G., Beck, G. J., and Cheung, A. K. E. A. (2002). Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med*, 347, 2010–19.

Feest, T. (2010). What determines a good outcome? The selection of patients for renal replacement therapy? In J. Chambers, E. A. Brown, and M. J. Germain, (eds.) *Supportive Care for the Renal Patient*, pp. 75–90. Oxford: Oxford University Press.

Fine, A., Fontaine, B., Kraushar, M. M., *et al*. (2005). Nephrologists should voluntarily divulge survival data to potential dialysis patients: a questionnaire study. *Perit Dial Int*, 25, 269–73.

Hedayati, S. S. and Finkelstein, F. O. (2009). Epidemiology, diagnosis, and management of depression in patients with CKD. *Am J Kidney Dis*, 54, 741–52.

Hines, S. C., Glover, J. J., Babrow, A. S., *et al*. (2001). Improving advance care planning by accommodating family preferences. *J Palliat Med*, 4, 481–9.

Holley, J. L., Stackiewicz, L., Dacko, C., *et al*. (1997). Factors influencing dialysis patients' completion of advance directives. *Am J Kidney Dis*, 30, 356–60.

Jadoul, M., Thumma, J., Fuller, D. S., *et al*. (2012). Modifiable practices associated with sudden death among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Clin J Am Soc Nephrol*, 7, 765–74.

Kurella, T., Covinsky, K., Chertow, G. M., *et al*. (2009). Functional status of elderly adults before and after initiation of dialysis. *N Engl J Med*, 361, 1539–47.

Mauri, J. M., Cleries, M., Vela, E., *et al*. (2008). Design and validation of a model to predict early mortality in haemodialysis patients. *Nephrol Dial Transplant*, 23, 1690–6.

Merkus, M. P., Jager, K. J., Dekker, F. W., *et al*. (1999). Physical symptoms and quality of life in patients on chronic dialysis: results of The Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD). *Nephrol Dial Transplant*, 14, 1163–70.

Michel, D. M. and Moss, A. H. (2005). Communicating prognosis in the dialysis consent process: a patient-centered, guideline-supported approach. *Adv Chronic Kidney Dis*, 12, 196–201.

Miura, Y., Asai, A., Matsushima, M., *et al*. (2006). Families' and physicians' predictions of dialysis patients' preferences regarding life-sustaining treatments in Japan. *Am J Kidney Dis*, 47, 122–30.

Moss, A. H., Ganjoo, J., Sharma, S., *et al*. (2008). Utility of the 'surprise' question to identify dialysis patients with high mortality. *Clin J Am Soc Nephrol*, 3, 1379–84.

Moss, A. H., Holley, J. L., Davison, S. N., *et al.* (2004). Palliative care. *Am J Kidney Dis*, 43, 172–3.

Moss, A. H., Holley, J. L., and Upton, M. B. (1992). Outcomes of cardiopulmonary resuscitation in dialysis patients. *J Am Soc Nephrol*, 3, 1238–43.

Murray, S. A. and Sheikh, A. (2008). Palliative care beyond cancer: care for all at the end of life. *BMJ*, 336, 958–9.

Murtagh, F. E., Addington-Hall, J. M., Edmonds, P. M., *et al.* (2007a). Symptoms in advanced renal disease: a cross-sectional survey of symptom prevalence in stage 5 chronic kidney disease managed without dialysis. *J Palliat Med*, 10, 1266–76.

Murtagh, F. E., Addington-Hall, J., and Higginson, I. J. (2007b). The prevalence of symptoms in end-stage renal disease: a systematic review. *Adv Chronic Kidney Dis*, 14, 82–99.

Murtagh, F. E., Addington-Hall, J. M., and Higginson, I. J. (2011a). End-stage renal disease: a new trajectory of functional decline in the last year of life. *J Am Geriatr Soc*, 59, 304–8.

Murtagh, F. E., Marsh, J. E., Donohoe, P., *et al.* (2007c). Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. *Nephrol Dial Transplant*, 22, 1955–62.

Murtagh, F. E., Sheerin, N. S., Addington-Hall, J., *et al.* (2011b). Trajectories of illness in stage 5 chronic kidney disease: a longitudinal study of patient symptoms and concerns in the last year of life. *Clin J Am Soc Nephrol*, 6, 1580–90.

NHS Kidney Care (2012). Getting it Right: End of Life Care in Advanced Kidney Disease. London: Department of Health.

Nichols, K. A. and Springford, V. (1984). The psycho-social stressors associated with survival by dialysis. *Behav Res Ther*, 22, 563–74.

Paniagua, R., Amato, D., Vonesh, E., *et al.* (2002). Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol*, 13, 1307–20.

Peng, Y. S., Chiang, C. K., Hung, K. Y., *et al.* (2007). The association of higher depressive symptoms and sexual dysfunction in male haemodialysis patients. *Nephrol Dial Transplant*, 22, 857–61.

Rachman, S. (2009). Psychological treatment of anxiety: the evolution of behaviour therapy and cognitive behaviour therapy. *Ann Rev Clin Psychol*, 5, 97–119.

Rodin, G. M., Chmara, J., Ennis, J., *et al.* (1981). Stopping life-sustaining medical treatment: psychiatric considerations in the termination of renal dialysis. *Can J Psychiatry*, 26, 540–4.

Russ, A. J., Shim, J. K., and Kaufman, S. R. (2007). The value of 'life at any cost': talk about stopping kidney dialysis. *Soc Sci Med*, 64, 2236–47.

Saini, T., Murtagh, F. E., Dupont, P. J., *et al.* (2006). Comparative pilot study of symptoms and quality of life in cancer patients and patients with end stage renal disease. *Palliat Med*, 20, 631–6.

Sekkarie, M. A. and Moss, A. H. (1998). Withholding and withdrawing dialysis: the role of physician specialty and education and patient functional status. *Am J Kidney Dis*, 31, 464–72.

Steinhauser, K. E., Christakis, N. A., Clipp, E. C., *et al.* (2000a). Factors considered important at the end of life by patients, family, physicians, and other care providers. *JAMA*, 284, 2476–82.

Steinhauser, K. E., Clipp, E. C., McNeilly, M., *et al.* (2000b). In search of a good death: observations of patients, families, and providers. *Ann Intern Med*, 132, 825–32.

USRDS (2001). Annual Data Report. Bethesda, MD: The National Institute of Health, National Institute for Diabetes and Digestive and Kidney Disease.

Valderrabano, F., Jofre, R., and Lopez-Gomez, J. M. (2001). Quality of life in end-stage renal disease patients. *Am J Kidney Dis*, 38, 443–64.

Webb, L., Gilg, J., Feest, T., *et al.* (2011). UK Renal Registry thirteenth annual report (December 2010). Chapter 4: Co-morbidities and current smoking status amongst patients starting renal replacement therapy in England, Wales and Northern Ireland from 2008–2009. *Nephron Clin Pract*, 119 Suppl 2, c85–c96.

Weiner, S. (2008). National Kidney Foundation: a survey of dialysis patients and professionals. *J Nephrol Social Work*, 28, 52–8.

Weisbord, S. D., Carmody, S. S., Bruns, F. J., *et al.* (2003). Symptom burden, quality of life, advance care planning and the potential value of palliative care in severely ill haemodialysis patients. *Nephrol Dial Transplant*, 18, 1345–52.

CHAPTER 147

Patient selection when resources are limited

Bernadette A. Thomas and Christopher R. Blagg

Introduction

Development of the Teflon shunt by Scribner, Quinton, and Dillard in March 1960 converted the diagnosis of chronic kidney failure from a death sentence to a treatable chronic disease (Quinton et al., 1960). Since then, renal replacement therapy (RRT) in the form of haemodialysis, peritoneal dialysis, and kidney transplantation has become a viable option for the majority of patients with end-stage renal disease (ESRD) in developed countries and in many developing countries progress is being made in providing treatment for at least a portion of the population. As a result, there are now more than 2 million patients worldwide living on dialysis or with a kidney transplant.

Scribner faced three major problems in early 1961: where to establish a unit to treat more patients than the first four who were being treated at the University of Washington Hospital in Seattle, how to find funding support for the unit and the patients, and how to select patients for dialysis when only a very few could be treated (Blagg, 2012). The first two problems were quickly solved in early 1961 when Scribner approached the King County Medical Society (KCMS) for help. The unit would be attached to Seattle's Swedish Hospital in what had been the hospital's nurses' residence, with initial funding from the John A. Hartford Foundation. Once funding was secured the KCMS and the Seattle Area Hospital Council appointed a committee to guide implementation of what was called the Kidney Treatment Centre Program, and in particular to discuss patient selection. Their decision was to set up a Medical Advisory Committee to set strict medical criteria for consideration of new patients and an Admissions and Policies Committee to make the final decisions.

The Medical Advisory Committee, faced with an estimate of between 5 and 20 ideal candidates for dialysis per million population (pmp) per year and a centre that could treat only nine patients, established very strict medical standards. These included age between 18 and 45, absence of long-standing hypertension and its complications and of other non-renal diseases including diabetes, and willingness to cooperate with the treatment and dietary restrictions. Patients who met these criteria were referred to the anonymous Admissions and Policies Committee that consisted of seven members: a lawyer, a housewife, a business man, a labour leader, a minster, and two physicians who did not care for kidney patients. Their role was to develop criteria for final selection on a non-medical basis, protect the centre from pressures to take a given patient, and represent the Centre to the community. They could investigate candidates in any way they thought appropriate, but were not told their names and could not meet with either candidates or their physicians. Their decisions were based on such aspects as sociological and economic factors, including relative worth of candidates to family and community in terms of dependence of others on the patient's continuing existence, their rehabilitation potential, and their moral values and worth.

Possible alternatives to the Seattle system included strictly medical selection, but this would have lacked diversity of viewpoints, provided the possibility of prejudices in the committee, and allowed outside pressures; first-come, first-served could have been arbitrary with too many candidates and could make possible selection of poor candidates if medical criteria were not used; and treatment of all candidates was obviously impractical and would have resulted in financial failure of the project. Choice by lottery might have been the least controversial option and would have increased public awareness of the issues with dialysis and with other new technologies.

In the first year, 30 candidates were referred to what came to be called the Seattle Artificial Kidney Center (SAKC), 17 of whom were judged medically acceptable; nine of these were accepted for treatment, the remainder died.

The dilemma and its solution gained national attention when *Life Magazine* published an article by Shana Alexander entitled 'They Decide Who Lives, Who Dies: Medical miracle and a moral burden of a small committee' (Alexander, 1962). This discussed in detail the selection process and its implications and was followed in 1965 by an NBC TV documentary entitled 'Who Lives? Who Dies?'. Reactions to this publicity generated criticism from nephrologists, lawyers, psychiatrists, philosophers, and theologians (Blagg, 1998) and was a major factor in development of the discipline of bioethics (Jonsen, 1998). However, no other programme in the United States used a primarily lay committee to select patients for dialysis, the decisions generally being made by nephrologists or by a group of one of more nephrologists, a psychiatrist or psychologist, and a social worker.

The Seattle committee continued to function until 1971, by which time private insurance, funding from the State of Washington, and support from donations was sufficient that all patients referred to the SAKC could be treated, although at the time very few diabetics or patients older than 60 were being referred. Establishment of almost universal entitlement to federal funding for dialysis and transplantation in the United States in July 1973 through the

Medicare End-Stage Renal Disease (ESRD) Program abrogated the need for selection other than on purely medical grounds.

Current practices in developing countries

In many developing countries the practice of patient triage for RRT is a contemporary issue. Such nations face the challenge of allocating limited health-related financial resources towards infectious diseases such as AIDS and malaria and other widespread acute and chronic conditions in the population. Such financial limitations often result in limiting dialysis resources to portions of the population thought to benefit most directly. Factors contributing to this selection process often involve socioeconomic status, functional status, and ability to perform the modality, as is the case for peritoneal dialysis. Often, the factors of race, age, and gender are integrally tied into the social factors that permit patients to access treatment. For countries with profoundly limited therapy options, cost is the ultimate deciding factor in determining provision of care (El Nahas, 2005).

Africa

Africa is the second most populous continent in the world, with profoundly low prevalence estimates for dialysis. In 2007, it was estimated to have a dialysis prevalence of 74 patients pmp, compared to the global estimate of 250 patients pmp (Abu-Aisha and Elamin, 2010). Accurate estimates are incredibly challenging to determine, as there are no known current dialysis registries within the continent (Bamgboye, 2006; Benghanem Gharbi, 2010). The majority of dialysis is delivered in the more affluent African regions of South Africa and northern Africa, typically in the form of haemodialysis (Naicker, 2003, 2009, 2010; Bamgboye, 2006; Abu-Aisha and Elamin, 2010; Benghanem Gharbi, 2010). Kidney transplantation occurs in select countries such as South Africa, Mauritius, Nigeria, Sudan, Egypt, and Ghana, with Egypt having the highest rates (Naicker, 2003, 2009, 2010; Benghanem Gharbi, 2010) and is mainly living donor transplantation in these countries except in South Africa (Dirks and Levin, 2006). Limitations to the rate of transplantation include lack of a universal definition of death together with religious and cultural factors (Naicker, 2010).

Within the continent, patients generally cover the cost of dialysis themselves except in the Sudan, Mauritius, and South Africa where dialysis costs for some patients are partially subsidised (Abu-Aisha and Elamin, 2010). South Africa provides an example of the interplay between resource, race, and patient selection. In 1997, the National Department of Health in South Africa formalized a selection process, with the ultimate decision of whether to offer RRT to a patient being left to regional selection committees. Patients are not accepted for dialysis if they do not qualify for transplantation (Naicker, 2003, 2009, 2010; Dirks and Levin, 2006). Statistics from a report describing South Africa's experiences with dialysis for the period of 1988 to 2003 identify 2442 patients with ESRD referred for dialysis, 48% of whom ultimately were accepted to receive care. Poverty was identified as the fundamental reason for refusing treatment in most cases, as it was linked to poor insight, limited ability to travel to care centres, unsanitary conditions for performance of peritoneal dialysis, and illiteracy (Dirks and Levin, 2006). This process selects against black people, women, the aged, and the poor.

Southeast Asia

Practice patterns of patient selection for ESRD treatment in Southeast Asia vary widely by country and are more a reflection of national economics than medical practice (Jha, 2004, 2009; Lo, 2009).

India

India is the second most populous country in the world, with a high incidence of infectious glomerulonephritis, and a rapidly expanding prevalence of diabetes and hypertension (Jha, 2004). Factors influencing access to RRT include lack of governmental support and a nationwide healthcare system, and timely referral. From the societal standpoint, limiting factors for patient access to care include extreme poverty, and limited access to any form of healthcare (Jha and Chugh, 2003; Jha, 2004, 2009; Rajapurkar and Dabhi, 2010). Haemodialysis is the standard acute and chronic care, yet most of the institutions that offer chronic haemodialysis are private institutions that cater to patients who can afford it. Living-related donor transplantation is viewed as a more practical form of treatment, but the costs of immunosuppression make this prohibitive for the great majority of the population. Thus, cost is the ultimate deciding factor for access to care, which is limited by a paucity of healthcare infrastructure (Jha, 2004, 2009; Rajapurkar and Dabhi, 2010).

Pakistan

Pakistan has important lessons to impart regarding ethical decision-making in a resource-poor setting. Considered a developing country, Pakistan has an estimated ESRD incidence of 100 pmp (Rizvi et al., 2011). Specific limitations of poverty, rural dwelling and poor government health infrastructure create challenges to providing ESRD care for all patients who qualify. Presently only 10% receive dialysis and the transplant rate is < 5 pmp (Rizvi et al., 2011). Although private centres have developed to address these needs their charges are high, with dialysis costs of $20–25 per session and transplantation ranging from $6000 to $10,000. Since national per capita income is $2335 and 60% of the population live on < $2 a day these charges are beyond the reach of most of the ESRD population. Unfortunately even those who can afford such rates are unable to sustain the costs beyond 1–2 years (Khanna, 2009). Against this backdrop attempts were made to address ESRD needs with a model of government–community partnership. Units developed through this partnership deliver dialysis and transplantation free of charge to all patients, with lifelong immunosuppression and follow-up (Sakhuja and Sud, 2003; Rizvi et al., 2011). This collaboration offers 650 dialysis sessions per day and 10–12 transplants per week, consisting of half of all transplants in the country. Despite these efforts by government and community (Rizvi et al., 2011) a large population remains disenfranchised for ESRD therapy. The need can best be fulfilled by replicating this model throughout the country and once renal replacement becomes available to all will open the door to deceased organ donation.

Thailand and Vietnam

For Thailand and Vietnam, programmes such as the 'PD First' initiative have made RRT more widely available to the general population (Lo, 2009). Prior to 1990, cost was the prohibitive factor for Thai patients with ESRD but in the mid-1990s the Thai government began to support haemodialysis for civil servants. In December

2007, the government announced a 'PD First' initiative, whereby any patients with ESRD could receive peritoneal dialysis but would have to pay if they opted for haemodialysis. A similar programme was started in Vietnam, and the numbers of patients receiving treatment has steadily increased (Li et al., 2007; Jha, 2009; Lo, 2009). Because these countries took the initiative to initiate RRT primarily with peritoneal dialysis, they have achieved lower costs in comparison to peritoneal dialysis use in other developing countries where costs can sometimes exceed those of haemodialysis (Jha, 2004, 2009; Li et al., 2007).

Latin America

In Latin America, creation of a renal registry has played a significant role in monitoring incidence and prevalence of dialysis and transplantation for select countries. Universal RRT access is available in Argentina, Brazil, Chile, Uruguay, Venezuela, and Cuba; all countries in the higher economic bracket (Cusumano et al., 2006, 2010; Lugon et al., 2010). Data from 20 Latin American countries compiled in this registry has reported RRT prevalence in the form of haemodialysis, peritoneal dialysis, or renal transplant has increased from 162 patients pmp in 1991 to 478 patients pmp in 2006 (Cusumano et al., 2010). For the remaining Latin American countries, access to care is regionally limited and governed by similar trends of healthcare infrastructure, poverty, and access to care.

Mexico does not have a national registry, but has performed national surveys to document ESRD treatment prevalence (Paniagua et al., 2007). In the early 1990s, the prevalence of patients receiving RRT was 200 pmp, with peritoneal dialysis being the dominant form of treatment. The United States Renal Data System (USRDS) 2011 Report listed the Mexican states of Morelos and Jalisco as having the highest ESRD incidence in the world, with 597 and 419 p.m.p, respectively (USRDS, 2010). There is limited national insurance coverage, with half of the population being covered by three social security programmes. An additional programme recently has been started by the government to assist in providing coverage for the lower-income portion of the population. Only patients covered by one of these systems are financially covered for RRT, amounting to less than half of the population (Paniagua et al., 2007).

China

China has experienced rapid economic growth in the past decade, but still shows a significant divide between wealth and poverty. One of the most populous regions on earth, haemodialysis is offered predominantly in major cities such as Shanghai and Beijing (Zuo and Wang, 2006; Yao et al., 2009). The point prevalence of ESRD patients on haemodialysis in mainland China at the end of 2007 was estimated to be 51.7 pmp, increasing to 79.1 pmp by 2008, from results of a facility-level survey (Zuo and Wang, 2010). Beijing and Shanghai maintain dialysis registries, enabling evaluation of the growth of RRT for these regions in recent years.

Estimates of ESRD prevalence for Shanghai are available from 2000 and 2005. In 2000, the point prevalence was estimated to be 175 pmp, compared with 404 pmp in 2005 (Yao et al., 2009). Beijing reported a point prevalence for 2003 of 235.9 pmp, which increased to 268.9 pmp by 2004 (Zuo and Wang, 2006).

Peritoneal dialysis was started in China for acute kidney injury treatment in the 1960s (Zuo and Wang, 2006), and chronic peritoneal dialysis was started during the 1970s (Wang and Wan, 2003). It is estimated that today about 25,000 patients are on continuous ambulatory peritoneal dialysis (CAPD) (T. Wang, personal communication, 2012). In Shanghai alone there were reported to be 677 patients receiving peritoneal dialysis, increasing to 993 by 2005 (T. Wang, personal communication, 2012). In Hong Kong, since the 1960s peritoneal dialysis has been the modality of choice, and since the 'PD First' initiative, 80% of dialysis patients are maintained on peritoneal dialysis (Yu et al., 2007). China's pending efforts to provide universal health coverage may significantly improve the possibility to provide RRT to a larger portion of the population.

Current practices in high-income countries

Europe

Western and Eastern European countries have differed with regard to RRT; the differences having hinged on economic growth (Rutkowski, 2006; Viklicky et al., 2006). Most countries in Western Europe provide universal dialysis access for their populations and supply data to the ERA–EDTA Registry. Eastern and Central European countries have experienced dramatic changes in infrastructure and dialysis delivery within the past 20 years, particularly after the dissolution of the socialist bloc (Rutkowski, 2006). Between 1990 and 1996 alone, the number of haemodialysis units more than doubled, and Central and Eastern Europe experienced an explosion of peritoneal dialysis facilities (Rutkowski, 2006). The current challenges facing Europe are the global challenges of increasing numbers of patients requiring dialysis as diabetes, hypertension and obesity become increasingly more prevalent in the setting of relatively limited renal transplantation rates.

Australia and New Zealand

Australia and New Zealand provide universal dialysis access for their populations. The ANZDATA registry records RRT activity for modality of dialysis, transplantation, and survival. Australia has documented a 321% increase in RRT between 1990 and 2009 Australia and New Zealand Dialysis & Transplant Registry (2010). Possible cited explanations of increased longevity, and increased prevalence of diabetes mellitus (Grace, 2012).

Japan

Japan has a universal healthcare system in place that also allows for universal access to dialysis. Tight structuring and regulation of healthcare delivery are credited for competitive survival rates for patients receiving dialysis. Access to transplantation is limited, and dialysis is viewed as the primary means of RRT (Akizawa, 2010).

Canada

Canada provides universal healthcare that includes RRT provision. The country has experienced a 57% increase in RRT between 1999 and 2008 (Canadian Organ Replacement Register, 2010). The predominant form of replacement therapy is haemodialysis, followed by transplantation, though in some parts of the country transplantation is the primary means of RRT (Mendelssohn, 2009).

United States

The need for patient selection ended when Medicare began its programme for patients with ESRD in July 1973. Currently all patients requiring dialysis or kidney transplantation because of ESRD are funded for these treatments by the government. Yet the literature

documents evidence of disparate care within minority groups, specifically in regards to transplantation rates, and early referral (Alexander and Sehgal, 1998; Ifudu et al., 1999; Hall et al., 2008; Prakash et al., 2010). The reasons for these findings are complex, but suggest that even with universal coverage there are barriers to aspects of renal care that are still resource limited, such as transplantation. As the population of patients anticipated to require ESRD care grows, stricter legislation has been contemplated for specific portions of the population that pose unique challenges to reimbursement for care, such as the rapidly increasing population of undocumented immigrants (Hurley et al., 2009; Campbell et al., 2010).

Ethical considerations

Both developed and developing countries are facing the pending challenges of increasing burdens of ESRD secondary to diabetes and hypertension as well as of ageing populations in the setting of improved infectious disease management (Moosa and Kidd, 2006).

The ethical challenges for developing countries are extreme. Competing priorities for governmental funds and a lack of health infrastructure create formidable challenges to providing a costly form of chronic life support. Problems include how much of GDP should go to RRT and how much to major public health problems such as malnutrition, clean water, sanitation, child health, malaria, HIV, and other infectious diseases. Especially in low-income countries where most patients with chronic kidney failure will not have access to dialysis or transplantation, prevention should be the key objective compatible with limited resources. In India, Mani was the first to show that using non-physician healthcare workers and the cheapest available diagnostic tests and drugs it was possible to significantly reduce the rate of decline of renal function in patients with hypertension, diabetes, and other kidney diseases and extend life by as much as 10 years or more (Mani, 2010).

When it comes to the role of ethical issues with RRT in developing countries, patient selection requires consideration of what age limits should be set and whether aetiology or complications should affect selection, just as in Seattle in the 1960s. Another issue is whether it is better to treat more patients with haemodialysis twice or once a week even though they feel less well, are less rehabilitated, and have a poorer quality of life, or is it better to treat fewer patients thrice weekly? What should be the role of kidney transplantation? What about peritoneal dialysis? Recently this has been increasingly used in India, China, Southeast Asia, and Latin America, particularly when fluids can be manufactured locally rather than imported. In Hong Kong in 2008, the ESRD prevalence rate was 1065 pmp, the eighth highest in the world, and 79.4% of the patients were treated by peritoneal dialysis (USRDS, 2010). In India, CAPD has been used in both cities and rural areas for a number of years, is increasing as new payment, insurance, and home support schemes are being developed and now accounts for > 7000 patients (Reddy et al., 2011).

As use of RRT grows around the world the various issues need to be resolved in conjunction with the individual country's political institutions, public health programmes, nephrologists and transplant surgeons, the public, and, in some countries, religious institutions. The need is for national planning to contain costs and promote equity in resource allocation, clear policies for who is and who is not eligible for RRT, and for the latter how to provide conservative management to prolong life. Domestic production of equipment, consumables, and relevant generic drugs and use of peritoneal dialysis first whenever possible should be encouraged. There is also need for national efforts to increase organ donation, legislate criteria for brain death, consent, donor registration, ethical regulation of institutions and professionals, and prevention or control of commercial transplantation including consideration of legislation to provide and regulate payment for kidneys.

Those developing countries that have enjoyed the most success to date have involved governmental and private sector collaboration, improved health infrastructure, as well as providing implementation of unique solutions to reaching those portions of the population in need (Jha, 2004; Lo, 2009). As economics will fundamentally drive either the progress or stalemate of RRT development, poverty will ultimately be a deciding factor for patient selection in developing countries.

In coming years, developed countries will have to consider re-implementation of selection as well. For example, in the United States, nephrologists are becoming increasingly concerned with being asked to provide dialysis for patients who they believe will benefit only marginally from the treatment. Also, with the changing dialysis population, withdrawal from dialysis has become increasingly common over the last 20 years or so (Latos and Lucas, 2011). In 2006, 24.5% of deaths were due to patient withdrawal from dialysis. Reported withdrawal is less in other developed countries, perhaps reflecting more conservative selection for treatment and the greater legal and cultural emphasis on patient autonomy in the United States. Factors such as the growing burden of kidney disease and of other chronic diseases, increased lifespan, and growing numbers of undocumented immigrants will challenge current healthcare capacity. If such restrictions are implemented, it will require significant effort to ensure that the most vulnerable portions of the population do not bear the brunt of such healthcare restriction.

References

Abu-Aisha, H. and Elamin, S. (2010). Peritoneal dialysis in Africa. *Perit Dial Int*, 30, 23–8.

Akizawa, T. (2010). Current status of dialysis therapy and related clinical guidelines in Japan. *JMAJ*, 53(3), 185–7.

Alexander, G. C. and Sehgal, A. R. (1998). Barriers to cadaveric renal transplantation among blacks, women, and the poor. *JAMA*, 280, 1148–52.

Alexander, S. (1962). Medical miracle and a moral burden of a small committee: they decide who lives, who dies. *Life*, 53, 102–25.

Australia and New Zealand Dialysis & Transplant Registry (2010). Annual Report. Australia and New Zealand Dialysis & Transplant Registry.

Bamgboye, E. L. (2006) End-stage renal disease in sub-Saharan Africa. *Ethn Dis*, 16, S2-5–9.

Benghanem Gharbi, M. (2010). Renal replacement therapies for end-stage renal disease in North Africa. *Clin Nephrol*, 74 Suppl 1, S17–19.

Blagg, C. R. (1998). Development of ethical concepts of dialysis: Seattle in the 1960s. *Nephrology*, 4, 235–8.

Blagg, C. R. (2012). 50th anniversary of the opening of the world's first out-of-hospital dialysis unit, January 8, 1962. *Hemodial Int*, 16(1), 122–7.

Campbell, G. A., Sanoff, S., and Rosner, M. H. (2010). Care of the undocumented immigrant in the United States with ESRD. *Am J Kidney Dis*, 55, 181–91.

Canadian Organ Replacement Register (2010). Annual Report: Treatment of End-Stage Organ Failure in Canada 1998 to 2008. Canadian Organ Replacement Register.

Cusumano, A., Garcia-Garcia, G., Di Gioia, C., *et al.* (2006). End-stage renal disease and its treatment in Latin America in the twenty-first century. *Ren Fail*, 28, 631–7.

Cusumano, A. M., Gonzalez Bedat, M. C., Garcia-Garcia, G., *et al.* (2010). Latin American Dialysis and Renal Transplant Registry: 2008 report (data 2006). *Clin Nephrol*, 74 Suppl 1, S3–8.

Dirks, J. H. and Levin, N. W. (2006). Dialysis rationing in South Africa: a global message. *Kidney Int*, 70, 982–4.

El Nahas, M. (2005).The global challenge of chronic kidney disease. *Kidney Int*, 68, 2918–29.

Grace, B., Clayton, P., and McDonald, S. (2012). Increases in renal replacement therapy in Australia and New Zealand: understanding trends in diabetic nephropathy. *Nephrology*, 17, 76–84.

Hall, Y. N., O'Hare, A. M., Young, B. A., *et al.* (2008). Neighborhood poverty and kidney transplantation among US Asians and Pacific Islanders with end-stage renal disease. *Am J Transplant*, 8, 2402–9.

Hurley, L., Kempe, A., Crane, L. A., *et al.* (2009). Care of undocumented individuals with ESRD: a national survey of US nephrologists. *Am J Kidney Dis*, 53, 940–9.

Ifudu, O., Dawood, M., Iofel, Y., *et al.* (1999). Delayed referral of black, Hispanic, and older patients with chronic renal failure. *Am J Kidney Dis*, 33, 728–33.

Jha, V. (2004). End-stage renal care in developing countries: the India experience. *Ren Fail*, 26, 201–8.

Jha, V. (2009). Current status of end-stage renal disease care in South Asia. *Ethn Dis*, 19, S1-27–32.

Jha, V. and Chugh, K. S. (2003). The practice of dialysis in the developing countries. *Hemodial Int*, 7, 239–49.

Jonsen, A. R. (1998). The Birth of Bioethics. New York: Oxford University Press.

Khanna, U. (2009). The economics of dialysis in India. *Indian J Nephrol*, 19(1), 1–4.

Latos, D. L. and Lucas, J. (2011). Geriatric nephrology: a paradigm shift in the approach to renal replacement therapy. *Adv Chron Kidney Dis*, 18, 412–19.

Li, P. K., Lui, S. L., Leung, C. B., *et al.* (2007). Increased utilization of peritoneal dialysis to cope with mounting demand for renal replacement therapy—perspectives from Asian countries. *Perit Dial Int*, 27 Suppl 2, S59–61.

Lo, W. K. (2009). Peritoneal dialysis in the far East—an astonishing situation in 2008. *Perit Dial Int*, 29 Suppl 2, S227–9.

Lugon, J. R. and Strogoff de Matos, J. P. (2010). Disparities in end-stage renal disease care in South America. *Clin Nephrol*, 74 Suppl 1, S66–71.

Mani, M. K. (2010). Treating renal disease in India's poor: the art of the possible. *Semin Nephrol*, 30, 74–80.

Mendelssohn, D. and Wish, J. (2009). Dialysis delivery in Canada and the United States: a view from the trenches. *Am J Kidney Dis*, 54(5), 954–64.

Moosa, M. R. and Kidd, M. (2006). The dangers of rationing dialysis treatment: the dilemma facing a developing country. *Kidney Int*, 70, 1107–14.

Naicker, S. (2003). End-stage renal disease in sub-Saharan and South Africa. *Kidney Int* Suppl, S119–22.

Naicker, S. (2009). End-stage renal disease in sub-Saharan Africa. *Ethn Dis*, 19, S1-13–15.

Naicker, S. (2010). Burden of end-stage renal disease in sub-Saharan Africa. *Clin Nephrol*, 74 Suppl 1, S13–16.

Paniagua, R., Ramos, A., Fabian, R., *et al.* (2007). Chronic kidney disease and dialysis in Mexico. *Perit Dial Int*, 27, 405–9.

Prakash, S., Rodriguez, R. A., Austin, P. C., *et al.* (2010). Racial composition of residential areas associates with access to pre-ESRD nephrology care. *J Am Soc Nephrol*, 21, 1192–9.

Quinton, W., Dillard, D., and Scribner, B. H. (1960). Cannulation of blood vessels for prolonged hemodialysis. *Trans Am Soc Artif Intern Organs*, 6, 104–13.

Rajapurkar, M. and Dabhi, M. (2010). Burden of disease—prevalence and incidence of renal disease in India. *Clin Nephrol*, 74 Suppl 1, S9–12.

Reddy, Y. N. V., Abraham, G., Mathew, M., *et al.* (2011). An Indian model for cost-effectiveness CAPD with minimal man power and economic resources. *Nephrol Dial Transplant*, 26, 3089–91.

Renal Physicians Association (2010). Shared Decision-Making in the Appropriate Initiation and Withdrawal from Dialysis: Clinical Practice Guideline (2nd ed.). Rockville, MD: Renal Physicians Association.

Rizvi, S. A., Naqvi, S. A., Zafar, M. N., *et al.* (2011). A renal transplantation model for developing countries. *Am J Transplant*, 11, 2302–7.

Rutkowski, B. (2006). Highlights of the epidemiology of renal replacement therapy in Central and Eastern Europe. *Nephrol Dial Transplant*, 21, 4–10.

Sakhuja, V. and Sud, K. (2003). End-stage renal disease in India and Pakistan: burden of disease and management issues. *Kidney Int Suppl*, 83, S115–18.

United States Renal Data System (2011). USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Viklicky, O., Pokorna, E., and Vitko, S. (2006). Commentary on the highlights of the epidemiology of renal replacement therapy in Central and Eastern Europe. *Nephrol Dial Transplant*, 21, 2025–6.

Wang, T. and Wan, H. Y. (2003). [Peritoneal dialysis in China: problem and prospects]. *Zhonghua Nei Ke Za Zhi*, 42, 757–9.

Yao, Q., Zhang, W., and Qian, J. (2009). Dialysis status in China: a report from the Shanghai Dialysis Registry (2000–2005). *Ethn Dis*, 19, S1-23–6.

Yu, A. W., Chau, K. F., Ho, Y. K., *et al.* (2007). Development of the 'peritoneal dialysis first' model in Hong Kong. *Perit Dial Int*, 27, S53–5.

Zuo, L. and Wang, M. (2006). Current status of hemodialysis treatment in Beijing, China. *Ethn Dis*, 16, S2-31–4.

Zuo, L. and Wang, M. (2010). Current burden and probable increasing incidence of ESRD in China. *Clin Nephrol*, 74 Suppl 1, S20–2.

CHAPTER 148

Acidosis in chronic kidney disease

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Introduction

Progressive reduction in the capacity to generate ammonia in advanced chronic kidney disease (CKD) impairs the ability of kidneys to excrete the approximately 1 mmol/kg body weight of hydrogen ions produced daily in adults at physiological pH. When the excretion of hydrogen ions by kidneys is reduced, a new steady state can only be achieved at the cost of a permanent reduction in blood pH resulting in metabolic acidosis (MA).

MA is a relatively common complication in patients with advanced CKD particularly when the glomerular filtration rate (GFR) falls below 30 mL/min (Jeffrey and Kurtz, 2005). It adversely affects protein and muscle metabolism, bone turnover, and compounding mineral bone disorders of uraemia. MA is also associated with increased inflammatory mediators, insulin resistance, increased corticosteroid production, and parathyroid production.

This may result in stunted growth in children, loss of bone and muscle mass, negative nitrogen balance, and possible acceleration of progression of chronic failure due to hormonal and cellular abnormalities (Mitch, 1997). Currently, there is good experimental but limited clinical evidence that MA contributes to protein-energy wasting (PEW) disorder in CKD patients (Verove et al., 2002). Acidosis is associated with increased protein catabolism (Ballmer et al., 1995), due to upregulation of the ubiquitin-proteasome system (Mitch et al., 1999), excessive oxidation of the branched chain amino acids (Löfberg et al., 1997), and reduced synthesis of visceral proteins including albumin (Bailey et al., 1996). Several clinical trials conducted in patients with end-stage renal disease (ESRD), despite being small in size and with short-term follow-up, have suggested that correction of acidosis is associated with increased serum albumin and pre-albumin levels, a reduction in normalized protein catabolic rate (Torres et al., 1996; Torres et al., 1997; Williams et al., 1997) and an increase in the concentrations of both branched chain and total essential amino acids (Kooman et al., 1997; Dou et al., 1998).

Evidence from preclinical studies

However, the role of MA in more rapid decline of renal function of in pre-dialysis CKD is less convincing. Some experimental studies in few rodent models of CKD have indicated that the MA is associated with the development and worsening of proteinuria, tubulointerstitial fibrosis, and acceleration in the rate of decline in renal function (Nath et al., 1985; Torres et al., 2001; Gadola et al., 2004). Several speculative mechanisms have been put forward to explain the pathogenesis of renal damage due to MA. Single-nephron ammoniagenesis increases as compensation for the decreased functioning nephron mass to excrete acid load. Excessive ammonia production per nephron results in a non-enzymatic activation of the alternative complement pathway in the renal interstitium resulting in a chronic inflammatory state (Nath et al., 1985; Halperin et al., 1989). This observation was subsequently substantiated in a rat model of polycystic kidney disease (PKD). Rats with PKD demonstrated abnormal renal handling of citrate and ammonia. Citrate salts which have alkalinizing properties and abilities to reduce ammonia generation preserved renal function, reduced cyst growth, and prolonged lifespan of these animals (Tanner and Tanner, 2000). Moreover, casein diet-induced MA in rats with CKD induced by surgical renal mass reduction was associated with rapid decline of GFR. Interestingly, endothelin receptor A inhibitor was beneficial raising the issue of acidosis-induced excessive endothelin production as another potential mechanism (Phisitkul et al., 2008).

However, other studies in rats were to reproduce the beneficial effect of correction of acidosis on the progression of chronic renal failure. In a 5/6 nephrectomy rodent model of CKD, beneficial effect of sodium bicarbonate on proteinuria, interstitial fibrosis, or rate of decline of renal function was not seen (Throssel et al., 1995). In addition, in rodents with CKD on high phosphate intake, MA was actually protective by reducing the rate of progression of renal failure. This unusual but interesting finding was put down to inhibition of calcium phosphate deposition in the kidney (Jara et al., 2000, 2004).

Evidence from clinical observations

Few studies have examined the effects of amelioration of MA on renal function in humans. In a seminal report from 1931, Lyon et al. (1931) treated 17 patients with moderate renal failure with both low-acid diets and sufficient oral supplementation with sodium bicarbonate and potassium citrate to maintain an alkaline urine pH for a few weeks to months. This observation was instrumental in putting forward the idea that reducing acid burden on the kidney may stabilize or temporarily improve renal function. In subsequent short-term studies, administration of oral sodium bicarbonate to patients with mild to moderate renal failure led to reduced peptide catabolism, reduced ammonia production, and reduced tubular damage, as assessed by biochemical parameters (Rustom et al., 1998). Due to the short-term follow-up, no substantial impact on renal function could be demonstrated.

However, in a recent, small prospective observational study, MA was independently associated with acceleration of renal failure in CKD patients over a 2-year follow-up period (Ashurst et al., 2005). In a separate retrospective cohort study, > 5000 adult CKD patients attending an outpatient setting over a 2-year period between 2001

and 2003 were followed until 2007 and analysed for rate of decline of GFR (Shah et al., 2009). Progression of CKD was defined as either a decrease in estimated GFR by 50% or reaching below 15 mL/min (N = 337). In this ethnically diverse group of patients with heterogeneous causes of CKD, a bicarbonate level of 22 mEq/L or lower was associated with increased risk of primary renal endpoints. However, the retrospective observational nature of this study fell short of establishing cause and effect relationship between MA and progression of CKD.

A much needed randomized controlled clinical trial to examine the effect of administering oral sodium bicarbonate on progression of CKD in patients with non-dialysis-dependent CKD has now been reported by de Brito-Ashurst et al. (2009). In a single-centre study, the researchers randomized 134 patients with CKD and mean creatinine clearance (CrCl) around 20 mL/min to standard patient care plus administration of oral sodium bicarbonate titrated to reach a serum bicarbonate level of > 23 mmol/L. The two groups were similar in their baseline demographic characteristics and clinical and biochemical parameters, including blood pressure control and proteinuria. At 24 months the mean rate of decline of CrCl was significantly lower in the bicarbonate group compared to the control group (−1.88 ± 0.38 vs −5.93 ± 0.39, P <0.0001) despite similar blood pressures and proteinuria. In addition, incidence of ESRD was significantly lower in the intervention than control group suggesting that this inexpensive and readily available intervention could potentially be beneficial to patients with non-dialysis-dependent CKD (Fig. 148.1). In addition, there was an improvement in protein intake and in the anthropometrics, potassium levels, and other biochemical nutritional status of patients who received the bicarbonate supplement. In light of the known association of various markers of PEW disorder with mortality in patients with both moderate and advanced CKD, this finding raises the hope that the administration of sodium bicarbonate might also increase survival rates in patients with non-dialysis-dependent CKD.

This study had several strengths. The sample size of 134 patients was substantial for a single-centre study. Duration of follow-up was sufficiently long in patients with severe CKD to observe clinically meaningful outcomes. Moreover, the study was conducted from a busy pre-dialysis clinic and was close to a real-life setting. The patients were heterogeneous with respect to underlying disease, race and ethnic group, and duration of disease, making it likely that the findings can be translated to other populations with CKD. Clearly it cannot apply to those with associated morbid obesity, cognitive impairment, chronic sepsis, overt congestive heart failure, and uncontrolled hypertension as these co-morbidities were the exclusion criteria for this study. Nutritional parameters were assessed blindly by a single dietician and as expected from a single-centre study, data collection was complete. Compliance in the study was satisfactory as evident by consistent elevation of bicarbonate levels and urinary sodium excretion, and the endpoints were rigorous and clinically meaningful. However, this study can be criticized for a lack of placebo use and absence of a double-blind design. Like any other single-centre study, reproducibility and generalizability of this report will require further validation by a double-blind, placebo-controlled, multicentre trial.

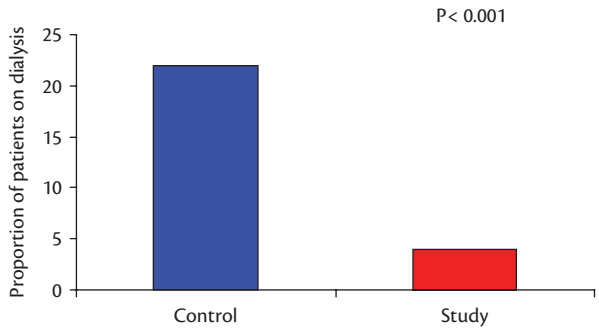

Fig. 148.1 Impact of treatment of metabolic acidosis with sodium bicarbonate on evolution to ESRD.
Modified from de Brito-Ashurst et al. (2009).

Phisitkul et al. (2010) reported their experience of correcting MA in 59 patients with hypertensive nephropathy after optimizing their blood pressure control with regimens that included angiotensin-converting enzyme inhibition. Thirty patients were then prescribed sodium citrate, and the remaining 29, unable or unwilling to take sodium citrate, served as controls. All were followed for 24 months with maintenance of their blood pressure reduction. Urine endothelin-1 excretion, a surrogate of kidney endothelin production, and *N*-acetyl-beta-D glucosaminidase, a marker of kidney tubulointerstitial injury, were each significantly lower, while the rate of estimated GFR decline was significantly slower in the citrate group. Even though this observation was not a randomized control study, it had the strength of providing some insight into the mechanism of renoprotection due to alkali treatment in hypertensive nephropathy patients with acidosis and moderately severe CKD.

More recently, another 5-year, prospective, randomized, placebo-controlled, and blinded interventional study tested if daily oral sodium bicarbonate slowed GFR decline in patients with hypertensive nephropathy with reduced but relatively preserved estimated GFR (eGFR) (mean 75 mL/min/1.73 m^2). Patients matched for age, ethnicity, albuminuria, and eGFR received daily placebo (N = 40) or equimolar sodium chloride (N = 40) or sodium bicarbonate (N = 40) while maintaining antihypertensive regimens (including angiotensin-converting enzyme inhibition) aiming for their recommended blood pressure targets. After 5 years, the rate of eGFR decline, estimated using plasma cystatin C, was slower and eGFR significantly higher in patients given sodium bicarbonate (baseline cysGFR (in mL/min/1.73 m^2) = 73.2; after 5 years 66.4) than in those given placebo (baseline 73.5; after 5 years 60.8) or sodium chloride (baseline 73.5; after 5 years 62.7). This interesting study calls for use of sodium bicarbonate in patients with early CKD even in the absence of overt acidosis (Mahajan et al., 2010).

Beneficial effects of alkali therapy were also supported by a recently published systematic review in which used a random-effects model meta-analyses to compute net changes (for continuous variables) and risk ratios (for binary variables) of two short-term (≤ 7 days) crossover trials and four long-term (62 months) parallel-design randomized controlled trials that compared sodium bicarbonate to standard-of-care therapy or placebo and reported kidney-related outcomes. The authors demonstrated that alkali therapy was associated with a net improvement in GFR and a lower incidence of dialysis initiation (Fig. 148.2). Alkali therapy was not associated with a higher likelihood of initiating or escalating antihypertensive medications (Susantitaphong et al., 2012).

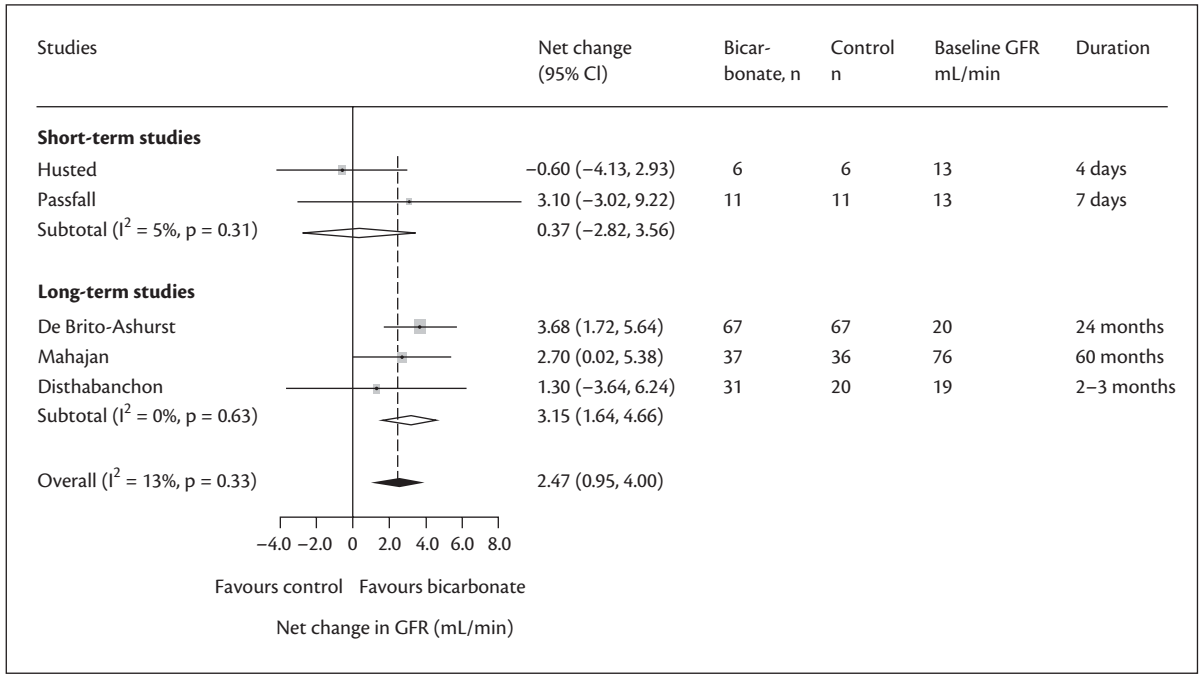

Fig. 148.2 Forest plot displaying the effect of bicarbonate therapy in parents with CKD on change in GFR (mL/min or mL/min/1.73 m^2).
Modified from Susantitaphong et al. (2012).

Concluding remarks

Recent studies have confirmed the majority of preclinical observations and suggested that correction of MA in patients with CKD slows the rate of decline of renal function and the development of ESRD. This cheap and simple strategy, which is in line with current renal recommendations, also improves the nutritional status of patients and has the potential of translating into significant economic and clinical benefits in an expanding pool of CKD patients.

References

Ashurst, I., Varagunam, M., and Yaqoob, M. M. (2005). The Effect of Metabolic Acidosis on the Rate of Decline of Glomerular Filtration Rate in Patients with Stage 4 CKD. Abstract presented at the World Congress Nephrology, 26–30 June, Singapore.

Bailey, J. L., Wang, X., England, B. K., *et al.* (1996). The acidosis of chronic renal failure activates muscle proteolysis in rats by augmenting transcription of genes encoding proteins of the ATP-dependent ubiquitin-proteasome pathway. *J Clin Invest*, 97(6), 1447–53.

Ballmer, P. E., McNurlan, M. A., Hulter, H. N., *et al.* (1995). Chronic metabolic acidosis decreases albumin synthesis and induces negative nitrogen balance in humans. *J Clin Invest*, 95, 39–40.

De Brito-Ashurst, I., Varagunam, M., Raftery, M. J., *et al.* (2009). Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol*, 20(9), 2075–84.

Dou, L., Brunet, P., Dignat-George, F., *et al.* (1998). Effect of uremia and haemodialysis on soluble L-selectin and leukocyte surface CD11b and L selectin. *Am J Kidney Dis*, 31, 67–73.

Gadola, L., Noboa, O., and Marquez, M. N. (2004). Calcium citrate ameliorates the progression of chronic renal injury. *Kidney Int*, 65, 1224–30.

Graham, K. A., Reaich, D., Channon, S. M., *et al.* (1996). Correction of acidosis in CAPD decreases whole body protein degradation. *Kidney Int*, 49, 1396–400.

Graham, K. A., Reaich, D., Channon, S. M., *et al.* (1997). Correction of acidosis in haemodialysis decreases whole body protein degradation. *J Am Soc Nephrol*, 8, 632–7.

Halperin, M. L., Ethier, J. H., and Kamel, K. S. (1989). Ammonium excretion in chronic metabolic acidosis: benefits and risks. *Am J Kidney Dis*, 14, 267–71.

Jara, A., Chacon, C., Ibaceta, M., *et al.* (2004). Effect of ammonium chloride and dietary phosphorus in the azotaemic rat. Part II—kidney hypertrophy and calcium deposition. *Nephrol Dial Transplant*, 19, 1993–8.

Jara, A., Felsenfeld, A. J., Bover, J., *et al.* (2000). Chronic metabolic acidosis in azotemic rats on a high phosphate diet halts the progression of renal disease. *Kidney Int*, 58, 1023–32.

Jeffrey, A. and Kurtz, I. (2005). Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment. *Am J Kidney Dis*, 45, 978–93.

Kooman, J. P., Deutz, N. E., Zijlmans, P., *et al.* (1997). The influence of bicarbonate supplementation on plasma levels of branched chain amino acids in haemodialysis patients with metabolic acidosis. *Nephrol Dial Transplant*, 12, 2397–401.

Löfberg, E., Wernerman, J., Anderstam, B., *et al.* (1997). Correction of acidosis in dialysis patients increases branched chain and total essential amino acid levels in muscle. *Clin Nephrol*, 48, 230–7.

Lyon, D. M., Dunlop, D. M., and Steward, C. P. (1931). The alkaline treatment of chronic nephritis. *Lancet*, 218, 1009–13.

Mahajan, A., Simoni, J., Sheather, S. J., *et al.* (2010). Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. *Kidney Int*, 78(3), 303–9.

Mitch, W. E. (1997). Influence of metabolic acidosis on nutrition. *Am J Kidney Dis*, 29, 16–18.

Mitch, W. E., Du, J., Bailey, J., *et al.* (1999). Mechanisms causing muscle proteolysis in uraemia: the influence on insulin and cytokines. *Mineral Electrolyte Metab*, 25, 216–9.

Nath, K. A., Hostetter, M. K., and Hostetter, T. H. (1985). Pathophysiology of chronic tubulo-interstitial disease in rats—interactions of dietary acid load, ammonia, and complement component-C3. *J Clin Invest*, 76, 667–75.

Phisitkul, S., Hacker, C., Simoni, J., *et al*. (2008). Dietary protein causes a decline in the glomerular filtration rate of the remnant kidney mediated by metabolic acidosis and endothelin receptors. *Kidney Int*, 73(2), 192–9.

Phisitkul, S., Khanna, A., Simoni, J., *et al*. (2010). Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR. *Kidney Int*, 77(7), 617–23.

Rustom, R., Grime, J. S., Costigan, M., *et al*. (1998). Oral sodium bicarbonate reduces proximal renal tubular peptide catabolism, ammoniogenesis, and tubular damage in renal patients. *Ren Fail*, 20, 371–82.

Shah, S. N., Abramowitz, M., Hostetter, T. H., *et al*. (2009). Serum bicarbonate levels and the progression of kidney disease: a cohort study. *Am J Kidney Dis*, 54(2), 270–7.

Susantitaphong, P., Sewaralthahab, K., Balk, E. M., *et al*. (2012). Short- and long-term effects of alkali therapy in chronic kidney disease: a systematic review. *Am J Nephrol*, 35(6), 540–7.

Tanner, G. A. and Tanner, J. A. (2000). Citrate therapy for polycystic kidney disease in rats. *Kidney Int*, 58(5), 1859–69.

Throssel, D., Brown, J., Harris, K. P., *et al*. (1995). Metabolic acidosis does not contribute to chronic renal injury in the rat. *Clin Sci*, 89, 643–50.

Torres, V. E., Cowley, B. D., Branden, M. G., *et al*. (2001). Long-term ammonium chloride or sodium bicarbonate treatment in two models of polycystic kidney disease. *Exp Nephrol*, 9, 171–80.

Verove, C., Maisonneuve, N., El Azouzi, A., *et al*. (2002). Effect of the correction of metabolic acidosis on nutritional status in elderly patients with chronic renal failure. *J Ren Nutr*, 12(4), 224–8.

Williams, A. J., Dittmer, I. D., McArley, A., *et al*. (1997). High bicarbonate dialysate in haemodialysis patients: effects on acidosis and nutritional status. *Nephrol Dial Transplant*, 12, 2633–7.