CHAPTER

80 Metabolic and Endocrine Dysfunctions in Uremia

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PATHOMECHANISMS UNDERLYING ENDOCRINE DISORDERS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Disturbances of endocrine function in patients with chronic kidney disease may arise from a number of different causes, which are summarized in Table 80.1.

The clinician has at his or her disposal measurements of hormone concentration, which may or may not be abnormal. However, endocrinologic assessment is more than looking at plasma hormone concentrations. Hormone concentrations per se fail to provide a proper assessment of the adequacy of the hormonal state (e.g., hormone concentrations may be inappropriate to the stimulating or suppressing signal, the test may detect inactive hormone isoforms, or the response of the target organ may be abnormal). It is, therefore, indispensable to interpret hormone levels in the appropriate context (e.g., insulin concentration relative to glucose concentration, parathyroid hormone [PTH] in relation to serum ionized calcium concentration, and plasma 1,25-dihydroxycholecalciferol [$1,25(OH)_2D_3$] concentration).

DISORDERS OF CARBOHYDRATE METABOLISM IN PATIENTS WITH CHRONIC KIDNEY DISEASE

In patients with chronic kidney disease (CKD) abnormalities in carbohydrate metabolism are encountered at different levels of the insulin-glucose cascade (Table 80.2). Patients with chronic kidney disease almost always display resistance to the peripheral action of insulin, although the half-life of insulin is prolonged, because insulin removal by the damaged kidney and by the extrarenal organs is impaired so that plasma insulin concentrations tend to be higher.[1,2] The normal response of the β cell to insulin resistance is to increase the secretion of insulin and, therefore, hyperglycemia as a pointer to glucose intolerance is seen only when this adaptive response of β cells fails. In CKD patients, glucose intolerance is seen only in patients who have both insulin resistance and impaired insulin secretion.[3]

Peripheral Resistance to Insulin Action

Peripheral glucose uptake is reduced in uremic patients as shown by the euglycemic insulin clamp technique.[1,2] Peripheral resistance to insulin is seen even in patients with early stages of CKD. It is clinically important, because of its tight correlation to the enhanced cardiovascular risk[4] and to the rate of progression of CKD.[5]

Liver and skeletal muscles are the major sites of peripheral glucose uptake. The liver and, more recently appreciated, the kidney are the major sites of glucose production in the fasting state.[6] Glucose metabolism by the liver is usually not impaired in CKD: hepatic glucose production[2] as well as its suppression by insulin.[2]

The skeletal muscles are the primary sites of decreased insulin sensitivity. The defect is not at the level of the insulin receptor.[7] The defect is presumably at the postreceptor level. As a result, higher levels of insulin will be required to increase glucose uptake.[7]

The insulin-regulated glucose transporter (GLUT-4) in muscle and adipose tissue is unchanged in CKD.[8] In the heart of uremic rats, however, we observed (in unpublished studies) diminished insulin-dependent glucose uptake and unchanged total GLUT-4, but reduced GLUT-4 incorporation into the plasma membrane.

Peripheral resistance to insulin action is often found early in the course of renal disease and is present in the majority of patients with advanced CKD[9] and is markedly improved after several weeks of hemodialysis[10] and of peritoneal dialysis. Sera of uremic patients contain a compound that inhibits glucose metabolism by normal rat adipocytes.[11]

Insulin Secretion and Pancreatic Islet Metabolism

Glucose-induced insulin secretion starts with the uptake of glucose by the β cells, followed by its metabolism and production of adenine triphosphate (ATP), which facilitates closure of ATP-dependent K^+ channels, followed by cell depolarization, and subsequent activation of voltage-sensitive Ca^{++} channels. As a consequence, calcium enters the islets,

80.1 Different Pathomechanisms Underlying Endocrine Disorders in Chronic Kidney Disease

	Example
Abnormalities of Hormone Production/Catabolism	
Reduced production of hormone in the kidney	Diminished or inappropriate concentrations of $1,25(OH)_2D_3$ and erythropoietin
Reduced production of hormone in extrarenal production sites (testes, ovary)	Diminished concentrations of testosterone and estrogen(s)
Abnormal secretion pattern (pulsatility; circadian rhythm)	PTH, GH, LH
Reactive hypersecretion of hormone to reestablish homeostasis	PTH, FGF 23
Inappropriate hypersecretion due to disturbed feedback	LH, prolactin, corticotropin
Decreased metabolic clearance	Particularly peptide hormones (e.g., PTH, insulin, gastrin, MSH, ghrelin, leptin, adiponectin)
Abnormalities of Hormone Action	
Disturbed activation of prohormones	Proinsulin/insulin, proinsulinlike growth factor 1A, thyroxine (T_4)
Increased isoforms with potentially less bioactivity (from glycosylation, sialylation)	LH
Increased hormone binding proteins reducing availability of free hormone	IGF
Decreased hormone binding proteins increasing availability of free hormone	Leptin
Abnormal target organ response	
Inhibitory factors	$PTH_{1,84}$ versus $PTH_{7,84}$
Changed receptor number, structure, modification	Low parathyroid vitamin D receptor
Disturbed postreceptor steps	Insulin, GH

PTH, parathyroid hormone; GH, growth hormone; LH, luteinizing hormone; FGF 23, fibroblast growth factor 23; MSH, melanocyte stimulating hormone; IGF, insulinlike growth factor.

80.2 Glucose and Insulin Metabolism in Patients with Chronic Kidney Disease

Usually normal fasting blood glucose, but tendency for spontaneous hypoglycemia
Fasting hyperinsulinemia with prolonged insulin half-life and elevated blood levels of proinsulin and C peptide
Decreased requirement for insulin by diabetic patients
Usually decreased early, but exaggerated late-insulin response to hyperglycemia induced by oral or intravenous glucose administration
Elevated plasma immunoreactive glucagon concentration
Impaired glucose tolerance (decreased peripheral sensitivity to insulin action, but normal suppression of hepatic glucose production by insulin)

causing an acute rise in cytosolic Ca^{++} concentration and secretion of insulin.

PTH impairs insulin secretion in CKD and it is improved when PTH secretion is suppressed.[12] Glucose-induced insulin secretion by pancreatic islets is impaired in parathyroid intact but is normal in PTX uremic rats. Conversely, glucose-induced insulin secretion is impaired in rats with normal renal function treated with PTH.[13]

Islet cells express the vitamin D receptor.[14] Insulin secretion is impaired in vitamin D–deficient rats with normal renal function reversibly with the administration of vitamin D. An acute intravenous administration of $1,25(OH)_2D_3$ to dialysis patients improved early and late phases of insulin secretion.[15]

Insulin Clearance

Insulin is filtered by the glomeruli and reabsorbed in the proximal tubule.[16] Renal insulin clearance (200 mL per minute) exceeds glomerular filtration rate (GFR), indicating additional peritubular uptake.[17] Insulin removal by the kidney accounts for 25% to 40% of total removal.

A decreased metabolic clearance rate of insulin is seen at GFR < 40 mL per minute, and a significant prolongation of insulin half-life is observed at GFR < 20 mL per minute.[18] When dialysis is started, insulin clearance increases.

In CKD patients, diminished renal and extrarenal (liver and muscles) insulin clearance accounts for fasting hyperinsulinemia and higher insulin concentrations, fasting after administration of glucose, and decreased insulin requirements in diabetic patients with impaired renal function.[19]

Hypoglycemia

Episodes of spontaneous hypoglycemia may be seen in diabetic and even in nondiabetic CKD patients.[20] In diabetic patients, decreased degradation of administered insulin may cause excessive blood insulin levels; in diabetics, repeated episodes of hypoglycemia may be the first clinical sign of impaired renal function. Many sulfonylurea compounds or their active metabolites are cleared via the kidney.[21] Appropriate dose adjustment is again necessary, but it is even better to switch the patients to insulin. The sulfonylurea gliquidone is eliminated predominantly by the liver and does not accumulate.

Spontaneous hypoglycemia is also occasionally seen in nondiabetic CKD patients.[20,22] The underlying mechanism is not clear. Poor nutritional status, diminished gluconeogenesis, impaired glycogenolysis, and impaired degradation in insulin may all contribute.[22]

Hypoglycemia may exacerbate the cardiovascular risk via increased adrenergic activity, coronary ischemia, and arrhythmia.[20]

Clinical Consequences

Hyperglycemia and insulin resistance may contribute to accelerated atherogenesis in renal failure. Shinohara et al.[4] followed 183 nondiabetic hemodialysis patients for more than 5 years. Cumulative cardiovascular deaths were significantly more frequent in subjects in the top tertile of insulin resistance assessed by the homeostasis model assessment of insulin resistance (HOMA) technique. The adverse effect of insulin resistance on mortality was independent on body mass, hypertension, and dyslipidemia. Hyperinsulinemia and insulin-resistance contribute to hypertension[23] and lipid abnormalities.

Insulin is also an important regulator of lipoprotein lipase activity and its activity is reduced by insulin deficiency as well as insulin resistance.[24] Lipoprotein lipase plays a major role in triglyceride removal. In patients with CKD, lipoprotein lipase activity is impaired and this is the major cause of hypertriglyceridemia in these patients.

Insulin resistance may also contribute to malnutrition, commonly found in CKD[25] by inflammatory mechanisms.[26,27] Insulin deficiency stimulates muscle breakdown and activates the ubiquitin–proteasome system.[28] Insulin resistance increases salt sensitivity via increased tubular sodium reabsorption and contributes to hypertension.[29]

An interesting link between insulin resistance, metabolic syndrome, and kidney disease as a result of excessive fructose ingestion has recently been proposed by Johnson et al.[30]

DISORDERS OF LIPID METABOLISM IN CHRONIC KIDNEY DISEASE

In the 19th century, Richard Bright[31] commented on the milky aspect of the serum of patients suffering from kidney diseases. After this early observation, dyslipidemia and hyperlipidemia of renal patients had become well known, but only in the recent decades did it attract more general interest after it had been recognized that atherosclerotic complications are extremely frequent in patients with impaired renal function, at least partially as the result of dyslipidemia.

It had long been underappreciated how severe dyslipidemia actually is because measurements were usually restricted to the determination of total cholesterol and triglycerides in plasma. Only today's more sophisticated analyses of lipid subfractions, postprandial lipid changes, apolipoprotein (apo) concentrations, and modification by oxidation, glycation, and carbamylation have fully disclosed the profound and highly atherogenic character of the lipid changes in uremia (Fig. 80.1).

Dyslipoproteinemia was initially attributed to reduced renal function, but it has increasingly been recognized that concomitant pathologies (diabetes, metabolic syndrome, proteinuria, steroid treatment, and genetic background) play an important ancillary role.

Lipid Abnormalities in Kidney Disease

The Spectrum of Dyslipidemia in Uremia

Dyslipidemia in uremia is mainly characterized by:

- Hypertriglyceridemia
- Higher remnant lipoproteins (chylomicron remnants, intermediate density lipoproteins [IDLs])
- Lower high density lipoprotein (HDL) cholesterol
- Higher small dense low density lipoproteins [sd(LDL)], lipoprotein (a) [Lp(a)], apolipoprotein A-IV (apo A-IV)
- Normal plasma LDL cholesterol (except in nephrotic syndrome and in peritoneal dialysis)

(For details, see Table 80.3.)

Exogenous and Endogenous Pathways

The plasma–lipid spectrum is influenced through two different pathways. In the exogenous pathway, dietary lipids transported from the intestine into the systemic circulation yield triglyceride-rich chylomicrons, which are quickly metabolized by endothelium-associated lipoprotein lipase. Chylomicron remnants are taken up by the liver. Chylomicrons, that is, large triglyceride-rich particles of intestinal origin, are only transiently present in plasma in the postprandial state under physiologic conditions. In CKD patients, the

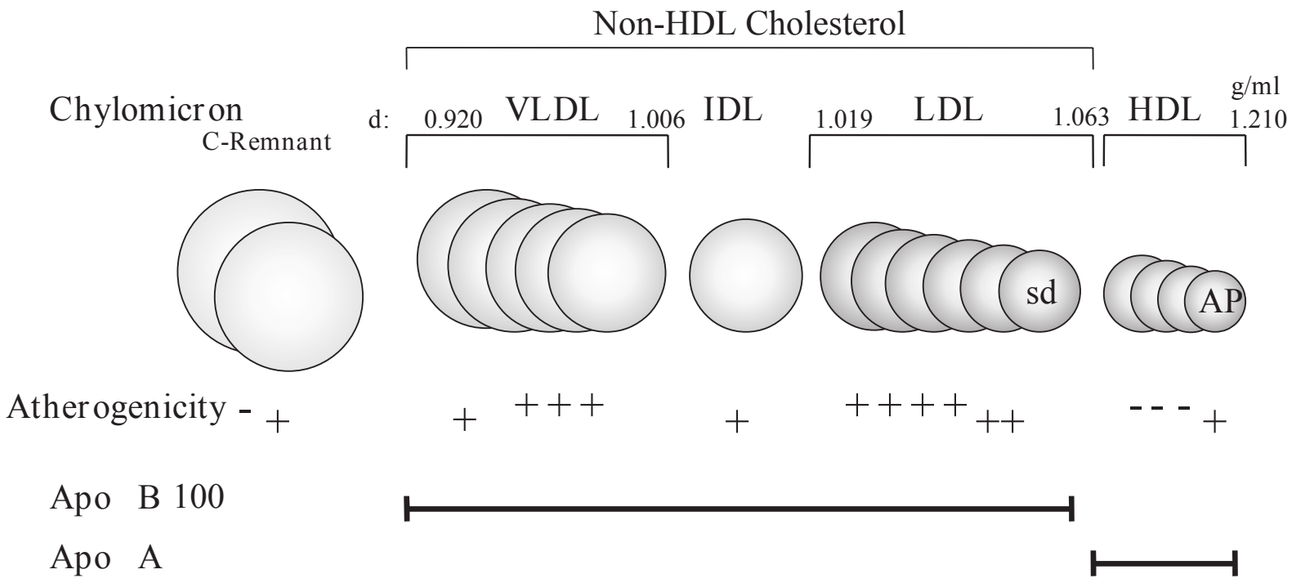

FIGURE 80.1 The atherogenicity of major lipoprotein classes. *HDL*, high density lipoprotein; *Apo,* apolipoprotein; *VLDL*, very low density lipoprotein; *IDL*, intermediate density lipoprotein; *LDL*, low density lipoprotein. (From Otvos J. Measurement of triglyceride-rich lipoproteins by nuclear magnetic resonance spectroscopy. *Clin Cardiol.* 1999;22:21, with permission.)

clearance of chylomicrons is severely impaired.[32] This abnormality contributes to the hypertriglyceridemia in CKD.

In the endogenous pathway, the liver synthesizes and secretes triglyceride-rich very low density lipoproteins (VLDLs) for export from the liver to peripheral tissues. Chylomicrons are metabolized stepwise to yield IDLs, which are either further converted into LDL particles or taken up by the liver (Fig. 80.2). This pathway is severely disturbed in CKD and end-stage renal disease (ESRD).

80.3 Abnormalities of Lipid Metabolism in Patients with Chronic Kidney Disease

Quantitative Changes in Plasma Lipid Profile
- Moderate elevation of plasma triglyceride concentrations
- Low plasma HDL cholesterol concentration
- High plasma VLDL and IDL cholesterol
- Normal plasma LDL cholesterol
- High ratio total cholesterol/HDL cholesterol
- High ratio LDL cholesterol/HDL cholesterol

Quantitative Changes in Plasma Lipoproteins
- Decreased plasma concentrations of apo A-I and A-II
- Normal or elevated plasma concentration of apo B
- High plasma concentrations of apo C-I, C-II, and C-III

Postprandial Changes in Plasma Lipoproteins
- Prolonged persistence of chylomicrons in the circulation postprandially

Qualitative Lipoprotein Changes
- Postribosomal modification of apolipoproteins by oxidation, glycation, and carbamylation
- Alteration in HDL component (changed it from antioxidant to pro-oxidant lipoprotein)
- Accumulation of small dense LDL
- Atherogenic apo A phenotype (low molecular weight)

LDL, low density lipoprotein; VLDL, very low density lipoprotein; IDL, intermediate density lipoprotein; HDL, high density lipoprotein; apo, apolipoprotein.

Lipid Spectrum

The lipid spectrum in kidney disease is characterized by quantitative and qualitative changes.

Triglycerides. Triglycerides start to increase in early stages of CKD.[33] They are more strikingly increased in advanced CKD and dialysis, specifically in peritoneal dialysis, and are highest in the nephrotic syndrome. Chylomicrons and VLDL are enriched in triglycerides. This reflects both abnormalities in particle production and in the low fractional catabolic rate of particles. Their reduced fractional catabolic rate is caused by the lower activity of lipoprotein lipase (LPL) and of the hepatic triglyceride lipase. In part, this is the result of the increased apo C-III/apo C-II ratio; apo C-III inhibits and apo C-II activates LPL. The result is an accumulation of intermediate particles, (e.g., chylomicron remnants and IDLs).

High density lipoprotein. In patients with CKD, HDL cholesterol concentrations are commonly reduced and this is accompanied by an abnormal spectrum of HDL subfractions resulting from low apo A-I levels and decreased lecithin:cholesterol acyltransferase (LCAT) activity with consecutive diminishing of esterification of free cholesterol and conversion of HDL_3 to HDL_2. In uremia, HDLs are modified by paraoxonase, inhibiting the oxidation of LDLs, and by inflammation, converting HDLs from antioxidant in pro-oxidant particles. HDL particles are involved in reverse cholesterol transport from the periphery (e.g., cell membranes) to the liver. The apo A lipoprotein in HDL activates LCAT, which esterifies cholesterol and facilitates transport.

Apo lipoprotein A-IV. Apo A-IV is synthesized in the small intestine and protects against atherosclerosis by promoting reverse cholesterol transport from the periphery to the liver. It is an activator of LCAT. The beneficial effect of high plasma apo A-IV levels is illustrated by the inverse relationship between apo A-IV and coronary artery disease in healthy individuals and in uremia.[34] Low apo A-IV also correlates to progression in CKD.[35]

Low density lipoprotein. Elevated LDL is not a typical feature in CKD and ESRD (except in patients with nephrotic syndrome). Behind normal LDL concentrations are hidden

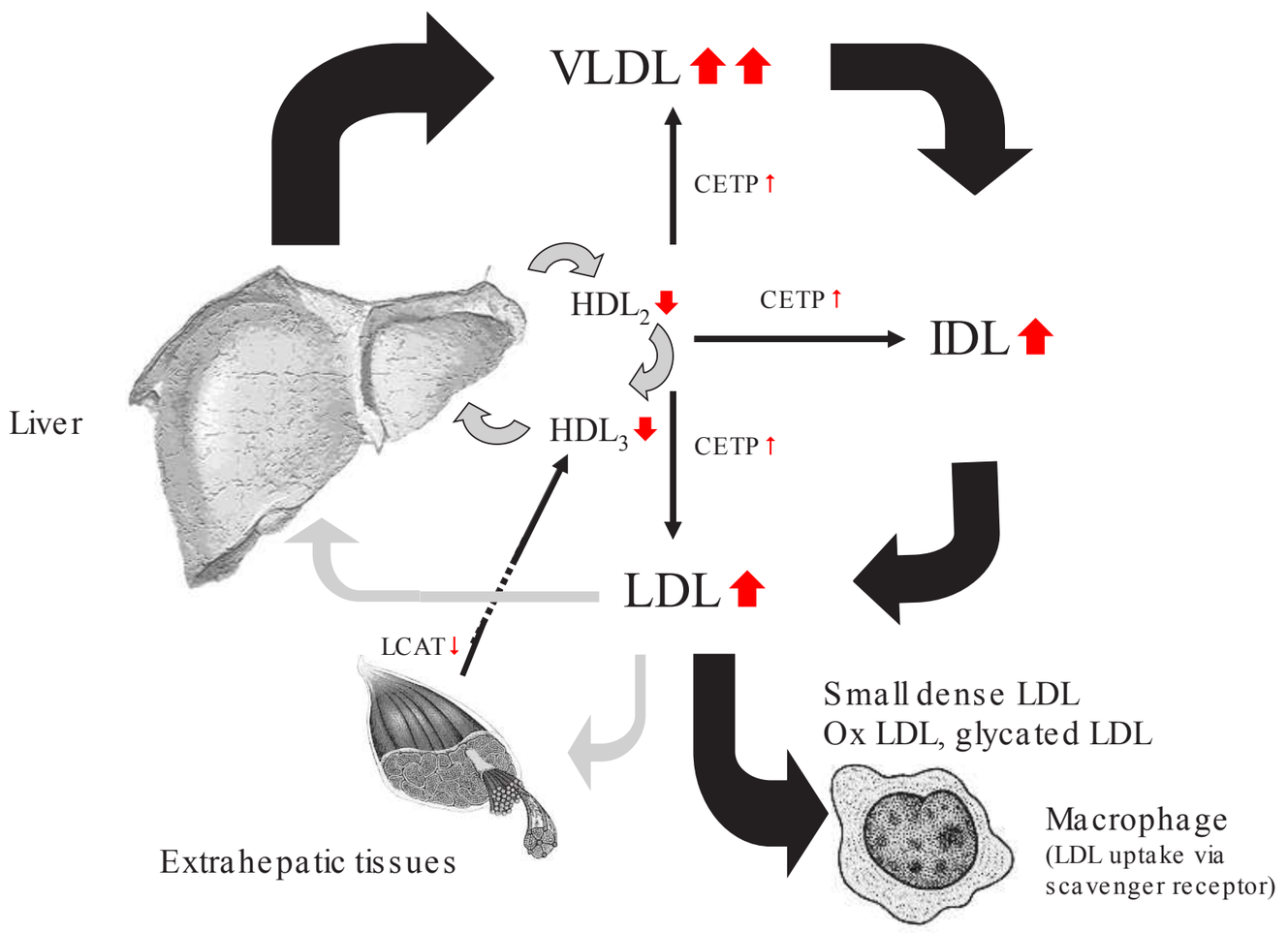

FIGURE 80.2 Lipoprotein metabolism in chronic kidney disease patients. *LCAT,* lecithin-cholesterol acyltransferase; *CETP,* cholesterol ester transfer protein; *LPL,* lipoprotein lipase; *VLDL,* very low density lipoproteins; *IDL,* intermediate density lipoprotein; *LDL,* low density lipoproteins.

qualitative changes, particularly an increased proportion of atherogenic sdLDL and IDL. Not only the activity of lipoprotein lipase, however, but also the activity of hepatic triglyceride lipase is decreased in animal models and patients with CKD.[36,37] The decreased activities of both lipases cause a major defect in the catabolism of triglyceride-rich lipoproteins. Reduced lipoprotein lipase activity explains the disturbed first step in the breakdown of both chylomicrons (circulating after the absorption of fat from the gut) and of VLDL (synthesized and secreted by the liver). Because of the reduced activity of the hepatic triglyceride lipase, the second step (i.e., the clearance of partially metabolized lipoproteins and chylomicrons) is disturbed as well. The VLDL receptor is expressed in skeletal muscle, the heart, the brain, and adipose tissue, which use fatty acids for energy production or storage. The expression of the VLDL receptor was reduced in experimental uremia.[38] In addition to quantitative changes in lipoprotein particles, several qualitative lipoprotein changes have been demonstrated to occur in CKD. These include postribosomal modification of apos by oxidation, glycation, and carbamylation. Modified lipoproteins are not recognized by their respective receptors.[39] Their half-life in the circulation is increased. The prolonged residence time in the circulation permits their uptake by the nonsaturable scavenger receptor pathway. Oxidation does not reduce the affinity of oxidized LDL to the scavenger receptor, and oxidized LDL uptake by the macrophage scavenger receptor is increased, thus favoring the formation of foam cells. In addition to its pivotal role in foam cell formation, oxidized LDL exhibits additional atherogenic properties, including cytotoxicity and stimulation of thrombotic as well as inflammatory events.[40] LDL oxidation is currently considered as an early key event in the pathogenesis of atherosclerosis. HDL protects against oxidation of LDL. In hemodialysis patients, the capacity of HDL to prevent LDL oxidation is reduced, however.

Lipoprotein (a). Lipoprotein (Lp)(a) is an LDL-like lipoprotein consisting of apo A covalently bound to an LDL particle. The plasma Lp(a) concentrations are strongly determined by genetic factors: individuals with the high molecular weight isoform have lower plasma Lp(a) concentrations and plasma Lp(a) levels begin to start to rise early in CKD. The increase is more delayed in individuals with low molecular weight isoforms. The level of Lp(a) is determined by the degree of proteinuria.[41,42] Furthermore, the turnover of Lp(a) is reduced, causing increasing residence time.[43] In prospective studies, Kronenberg et al.[44] and Longenecker et al.[45] found in hemodialysis patients that the small apo A genotype predicted coronary events and total mortality.

Predictive Parameters

Disorders of lipid metabolism in chronic kidney disease are not adequately reflected by the simple conventionally measured parameters (i.e., plasma concentrations of total cholesterol, LDL-cholesterol, and triglycerides). The previous parameters do not provide information on further lipid abnormalities, which almost certainly impact on the atherogenic risk: (1) abnormal concentrations of apolipoproteins (low apo A-I and apo A-II; and high apo B, apo C-II, and apo E serum concentrations); (2) postribosomal modification of apolipoproteins by oxidation, glycation, and carbamylation; (3) inflammation-induced alterations of HDL (transforming HDL from an antioxidant to a prooxidant lipoprotein); (4) accumulation of IDL and small, dense LDLs; (5) prolonged postprandial persistence of chylomicrons in the circulation; and (6) atherogenic apo A genotypes (Table 80.3).

Shoji et al.[46] demonstrated that the plasma IDL concentration is an independent risk factor for aortic atherosclerosis as determined by pulse-wave Doppler sonography and proposed non-HDL cholesterol (i.e., the sum of LDL and VLDL cholesterol, as a predictor [target < 130 mg per deciliter]).

Epidemiology

The constellation of (1) high plasma LDL cholesterol, (2) low HDL cholesterol, and (3) high triglycerides increase the risk of cardiovascular atherosclerosis.[47] The correlation between lipid concentrations and cardiovascular (CV) events is not very strong, however, possibly because apos may be more important than the lipid parts of the particles or because prolonged residence time permits the modification of the particles.

The recently proposed index of non-HDL cholesterol reflects the sum of LDL and VLDL particles and appears to be more sensitive. It is a superior predictor of cardiovascular risk (Table 80.3).[48,49]

Dialysis modalities and lipid profile. In hemodialyzed patients, the improvement of dyslipidemia has also been documented in patients with the studies addressing alternative dialysis treatment modalities (e.g., comparing of conventional hemodialysis against hemodialysis using high-flux membranes)[50] and also nocturnal hemodialysis.[51] A randomized crossover study showed that treatment with high-flux polysulfone and modified cellulose membranes significantly lowered serum triglyceride concentration when compared with low-flux dialysis with polysulfone membrane.

In patients treated with continuous ambulatory peritoneal dialysis (CAPD), the concentrations of total plasma cholesterol, LDL cholesterol, and triglycerides are even higher than in hemodialysis patients.[52,53] Such aggravation is most likely due to two additional factors: a loss of protein (7 to 14 g per day) with peritoneal dialysate and the absorption of glucose (150 to 200 mg per day) from the dialysis fluid. The protein loss may concern not only albumin, but also apolipoproteins, and possibly further lipoprotein-regulating substances, as occurs in the nephrotic syndrome. The glucose load increases the availability of free fatty acids and stimulates the synthesis of triglycerides and lipoproteins by the liver. This hypothesis is supported by the observation that conversion of patients from conventional glucose-containing dialysis fluids to icodextrin-containing dialysis fluids in the overnight dwell reduced plasma cholesterol concentrations.[54]

Dyslipidemia and Outcome—An Example of Reverse Epidemiology

Following the seminal report of Degoulet et al.,[55] numerous investigators found a paradoxical inverse relationship between plasma cholesterol concentration and overall mortality, as well as cardiovascular mortality.[56,57] Usually a U- or J-shaped relationship was noted between plasma cholesterol concentration and cardiovascular mortality (i.e., a higher mortality at low as well as high plasma cholesterol concentrations).[56] The most plausible explanation for this paradox is that this represents an example of reverse epidemiology[58] (i.e., a relationship that is reversed by a confounding factor). The work of Liu et al.[59] is important in this respect.[59] They identified microinflammation as a major confounding factor. In dialysis patients with low high sensitivity C-reactive protein (hs) CRP concentrations, a direct positive relation was noted between LDL cholesterol and cardiovascular mortality as in individuals with no renal disease. In contrast, in patients with high hsCRP concentrations, the mortality was higher at low LDL cholesterol concentrations.[59] This finding is important because in such circumstances, serum cholesterol and LDL cholesterol concentrations may no longer be a valid guide to establish the indication for lipid-lowering therapy.

Treatment of Dyslipidemia in Renal Failure

In the treatment of dyslipidemia in patients with CKD and ESRD, the best documented intervention of high current interest is the administration of statins. Because of the negative outcome of past intervention trials in dialysis patients (4D and AURORA), the indication for lipid lowering had not been evidence based until recently. There is no doubt that in early stages of renal dysfunction, lipid lowering by statins provides a benefit by significantly lowering cardiovascular events and possibly even the progression of CKD.[60,61,62] In dialysis patients, however, the overall outcome (cardiovascular mortality) in two underpowered studies on the use of statins (i.e., atorvastatin in the 4D study[63] and rosuvastatin in the AURORA study[64]) was negative. But, after approximately 3 years, there was a delayed nonsignificant tendency for fewer coronary events. A major drawback was that coronary events (the primary treatment target) accounted only for approximately 10% of mortality, whereas the contribution of sudden death and other noncoronary causes of cardiac death was approximately 30%.

Today, the results of the sufficiently powered Study of Heart and Renal Protection (SHARP) have clarified the dilemma. The SHARP study recruited about 8,000 patients (i.e., CKD patients or dialysis patients).[65] A significant overall survival benefit was found in patients treated with atorvastatin (± ezetimibe) and this will be reported soon.

Which other intervention strategies do we have? There is no doubt that dyslipidemia in patients with advanced CKD can be modified by dietary interventions. A reduced intake of saturated fatty acids and carbohydrates reverses VLDL overproduction by the liver and thus lowers plasma triglyceride levels.[66] Caloric restriction will also achieve weight loss and improve lipid levels in obese patients with advanced CKD. Both interventions have not gained universal acceptance,[67] however, because of their obvious side effects, particularly catabolism. Another nonpharmacologic approach is physical exercise, which has been shown to reduce insulin resistance and improve the lipid pattern in CKD patients, just as it does in nonrenal patients.[68] In our experience, however, adherence to this intervention is less than optimal.

What is the role of alternative pharmacologic treatments?

The spectrum of dyslipidemia of renal patients is mainly characterized by low HDL and high triglycerides. This constellation would require an a priori call for medications that increase HDL and decrease triglyceride concentrations.

Current efforts in cardiology target cholesteryl ester transfer protein (CETP) to raise HDL cholesterol levels in order to overcome residual dyslipidemia despite statin therapy.[69] Although the outcome of the effect of torcetrapib on glucose, insulin, and hemoglobin A1c in subjects in the ILLUMINATE study was negative,[70] presumably resulting from "off target" side effects of torcetrapib, novel agents also targeting CETP (e.g., dalcetrapib, anacetrapib) are currently under investigation.[69]

There are further interesting approaches (e.g., maturation of HDL with the orally absorbable amphipathic apo A-I mimetic peptide 4F).[71]

The pattern of hypertriglyceridemia associated with low-plasma HDL cholesterol concentration appears, at first sight, as an ideal indication for peroxisome proliferator-activated receptor alpha (PPAR-α) agonists (i.e., fibrates). Fibrates mimic the structure of free fatty acids and increase the HDL cholesterol concentration up to 20%, in part by reducing plasma CETP activity as a result of modulating CETP gene expression through the activation of PPAR-α.[69] Fibrates reduce inflammation markers independently of effects on lipid and glucose metabolism.[72] The problem is that fibrates accumulate in renal insufficiency. Therefore, except for gemfibrozil, the dose must be reduced in CKD patients depending on the level of GFR.[73] Fibrates may cause massive rhabdomyolysis with acute renal failure[74,75] and deterioration of kidney function even in the absence of rhabdomyolysis.[76] Therefore, fibrates are no longer recommended for treatment in CKD patients.

Nicotinic acid (niacin) lowers elevated concentrations of triglyceride-rich lipoproteins, (i.e., IDL, LDL, and Lp[a]); in addition, it raises HDL dose dependently by up to 30%.[77] Upregulation of apo A-I at HDL-C is the result of (1) the upregulation of apo A-I production, (2) the inhibition of hormone-sensitive triglyceride lipase in adipose tissue, and (3) the reduction of plasma CETP activity. Unfortunately, nicotinic acid frequently causes side effects, particularly flushing and occasionally worsening glucose tolerance and hepatotoxicity. Studies investigating the effect of nicotinic acid in hemodialysis patients are sparse.[78,79,80] Currently, nicotinic acid analogs with fewer side effects are under investigation.

DISORDERS OF PROTEIN AND AMINO ACID METABOLISM IN CHRONIC KIDNEY DISEASE

Nutrients can be divided into six general classes: proteins, lipids, carbohydrates, minerals, vitamins, and water. The first three classes serve as sources of energy required for carrying out the biochemical and functional activities of organs and cells. In addition to being an energy source, proteins in the diet provide the amino acids that are used to synthesize body proteins. Proteins and their constituent amino acids are essential to life.

The protein requirement of an individual is defined as the lowest level of dietary protein intake that will balance the losses of nitrogen from the body and maintain energy balance at modest levels of physical activity. The need for dietary protein largely arises because turnover of tissue and organ proteins is accompanied by an inefficient capture of their constituent amino acids to form new body proteins. The amino acids are lost via oxidative metabolism. Most estimates of protein and amino acid requirements in humans have been obtained directly or indirectly from measurements of nitrogen balance. In the course of carrying out their functional roles, proteins and amino acids turn over, and part of their nitrogen and carbon is lost via excretory pathways. This includes carbon dioxide in expired air and urea and ammonium in urine. Thus, to maintain an adequate protein and amino acid balance, these losses must be replaced by an appropriate dietary supply of a usable source of nitrogen and by indispensable and conditionally indispensable amino acids. These are required to replace amino acids that are lost during the course of metabolic processes or those that are deposited during growth and tissue replacement. Adults in stable conditions synthesize and degrade approximately 3.5 to 4.5 g of protein per kilogram of body weight (i.e., 245 to 315 g of protein in a 70-kg adult person) each day.[81] The protein content of muscle is about 20%. Therefore, the daily protein turnover is the equivalent of 1.2 to 2 kg of muscle. Because protein turnover is so large, even a small increase in protein degradation or a decrease in the protein synthesis rate, persisting for longer periods, can cause a marked loss of lean body mass.

The essential amino acids are valine, leucine, isoleucine, threonine, methionine, phenylalanine, lysine, tryptophan, and histidine. The nonessential amino acids are glycine, alanine, serine, cystine, aspartic acid, glutamic acid, and hydroxyproline. A third category, conditionally indispensable, is based on the observation that under specific dietary conditions, function is best maintained when these amino acids are part of nutrient intake. These conditionally indispensable amino acids are glycine, cystine, tyrosine, proline, arginine, citrulline, glutamine, and taurine.[82]

Recently, the concept of protein-energy wasting (PEW) has been introduced by The International Society Of Clinical Nutrition and Metabolism.[83] PEW is characterized by the loss of adequate nutrient intake, decreased body protein, and reduced body energy reserves as a cause of malnutrition and/or inflammation. PEW is estimated to be present in 6% to 8% of ESRD patients. The diagnostic criteria for PEW are given in Table 80.4.

In catabolic conditions, Du et al.[84] identified activation of caspase 3 as the initial step triggering accelerated muscle proteolysis in catabolic conditions of different causes (including fasting, cancer cachexia, streptozotocin diabetes,

80.4 Indices of Protein–Energy Wasting in Patients with Chronic Kidney Disease

Biochemical Parameters
Plasma albumin concentration < 3.8 g/dL
Plasma transthyretin concentration < 30 mg/dL
Plasma cholesterol concentration < 100 mg/dL
Body Mass
Body mass index < 22 kg/m^2 (for ≤ 65 years) or < 23 kg/m^2 (for > 65 years)
Unintentional weight loss over time; ≥ 5% in 3 months or ≥ 10% in 6 months
Total body fat percentage < 10%
Muscle Mass
Muscle wasting; reduced muscle mass ≥ 5% in 3 months or ≥ 10% in 6 months
Reduced midarm muscle circumference area; > 10 % reduction in relation to 50th percentile of reference population
Dietary Intake
Unintentional low dietary protein intake < 0.80 g/kg/d for at least 2 months for maintenance dialysis patients or < 0.60 g/kg/d for patients with CKD stages 2 to 5 with ≤ 5g/d of urinary protein loss
Unintentional low dietary energy intake < 25 kcal/kg/d for at least 2 months

CKD, chronic kidney disease.

and uremia induced by subtotal nephrectomy).[85] A common set of genes (atrogenes) was affected in these catabolic states, including polyubiquitins, ubiquitin ligases, and others, suggesting that different types of muscle atrophies shared a common transcription program.[86]

Abnormalities in Plasma and Intracellular Amino Acid Concentrations in Chronic Kidney Disease

Some disturbances in the amino acids' plasma concentrations are observed in chronic kidney disease even before renal replacement therapy is started.[87] The severity of amino acid abnormalities is related to the degree of chronic kidney disease and the presence of uremic symptoms.[88]

Plasma concentrations of tryptophan, tyrosine, and the branched-chain amino acids, particularly valine, are low in chronic renal failure[87] and plasma concentrations of citrulline, methylhistidine, and the sulfur-containing amino acids, cystine, and methionine, are high.[87,89,90] In summary, plasma concentrations of essential amino acids, with some exceptions, tend to be decreased, whereas plasma concentrations of the nonessential amino acids tend to be increased. The pattern of the plasma amino acid concentrations does not accurately reflect the intracellular pattern.[91] The intracellular concentrations of valine, threonine, tyrosine, and taurine in muscle are decreased[92] as a result of acidosis. The concentrations of phenylalanine, alanine, arginine, and citrulline are increased.[92] The molecular pathways of muscle wasting with CKD have been reviewed by Workeneh and Mitch.[93]

In CKD patients, low plasma amino acid concentrations and low intracellular amino acid concentrations may be due to: (1) anorexia, (2) decreased amino acid synthesis, (3) increased catabolism, (4) loss during the dialysis procedure, and (5) impaired binding to serum albumin caused by substances that accumulate in the blood in uremia.

As in nonuremic individuals, in CKD patients, poor dietary intake of protein and nutrients leads also to decreased concentrations of such amino acids as histidine, isoleucine, leucine, valine, and tyrosine.[94] In CKD patients, the plasma concentrations of several amino acids are inversely correlated with protein intake.[95]

In rats with experimental chronic renal disease, the principal cause of low plasma concentrations of branched-chain amino acids (valine, leucine, isoleucine) is increased catabolism.[92] This is stimulated by acidosis and is caused by increased activity of branched-chain keto acid dehydrogenase, a key enzyme in the amino acid degradation pathway.[92] The correction of metabolic acidosis increases the concentration of the previous three amino acids in muscle.[96] Reduced binding by albumin probably accounts for the low total plasma tryptophan concentration.[97] Also, low intracellular levels of taurine with normal or slightly elevated concentrations of this amino acid in plasma are found in CKD patients. Because the plasma concentration of precursors of taurine, such as cystine, methionine, and cystine sulfonic acid are elevated, a selective metabolic block at the level of cystine sulfonic acid decarboxylase has been proposed to explain the decrease in intracellular taurine.[98] In addition, low intracellular levels of threonine and lysine and low ratios of essential to nonessential amino acids (valine–glycine and phenylalanine–tyrosine) have been found in patients with CKD.[99]

Protein Metabolism in Chronic Kidney Disease

The detailed observations of renal patients by Richard Bright[100] pointed to an important role of inanition in kidney disease. More recently, a high prevalence of protein malnutrition has been reported in hemodialysis patients as well. Mild-to-moderate protein malnutrition occurs in approximately 33% of hemodialysis patients and severe malnutrition occurs in an additional 6% to 8% of these individuals.[101] The interpretation, however, of what constitutes malnutrition and how it relates to patient outcome remains controversial.[102] Pure-energy protein malnutrition (kwashiorkor) is not associated with accelerated atherogenesis and cardiovascular events. These events, however,

are commonly found in wasted dialysis patients and are associated with markers of microinflammation, such as high hsCRP, low plasma concentrations of albumin and fetuin, as well as high plasma concentrations of interleukin (IL)-6, IL-18, and tumor necrosis factor (TNF)-α.[103] This constellation has been rephrased as the malnutrition, inflammation, and atherosclerosis (MIA) syndrome.[104] It has remained uncertain, however, whether low muscle and body mass per se[105] or rather the process of active wasting have negative effects on outcome.[104] The paradoxical finding that survival is best in dialysis patients with a high body mass index (BMI), even in the range of frank obesity, may indicate that obesity increases tolerance toward episodes of catabolism. Energy expenditure is increased in uremia.[105] In addition, some factors common in uremic patients may trigger catabolism, such as fasting resulting from a loss of appetite. Acidosis or insulin resistance activates the ubiquitin proteasome system as the final common pathway of protein breakdown.[86] It is important that proteolytic mechanisms, not malnutrition caused by loss of muscle mass in chronic renal failure[106] with insulin resistance, triggered the activation of the ubiquitin proteasome pathway as an upstream component.[107] There is also evidence that the dialysis procedure per se is a catabolic stimulus.[108] A study by Pupim at al.[109] confirmed that dialysis causes whole body and muscle proteolysis, which can be overcome, at least acutely, by an intravenous infusion of amino acids, glucose, and lipids.

The rates of synthesis and degradation of proteins can be quantitated by the infusion of either radiolabeled or stable isotopes bearing amino acids. This allows the calculation of total body protein synthesis and total average proteolysis, as well as amino acid oxidation.[110] Patients with stable CKD have been studied using this methodology when ingesting either of two different levels of dietary protein: 0.6 g per kilogram of body weight or 1.0 g per kilogram of body weight. Studies were performed both after overnight fasting and in the fed state. No differences were found in either the rate of protein turnover or the amino acid oxidation as compared to control subjects. Thus, the dynamics of amino acid metabolism are apparently normal at the whole body level in stable, nonacidotic patients with chronic kidney disease.[111]

In contrast to nondialyzed, stable CKD patients, nitrogen balance studies indicate that hemodialysis patients are unable to conserve nitrogen normally and have increased dietary requirements.[112] The increased protein needs are higher than accounted for by a loss of amino acids, peptides, and proteins into the dialysate. These findings are consistent with the existence of a chronic, low-grade catabolic state in hemodialysis patients. Such a catabolic state may be due to the presence of chronic inflammation, acidosis, insulin resistance, or a combination of these conditions.[113]

When protein intake is restricted, supplemental calories may improve nitrogen balance.[114] If calorie intake is inadequate in patients eating a low protein diet, the risk of catabolizing body protein is increased.[114]

Caloric Requirements in Patients with Chronic Kidney Disease

Inadequate caloric intake may be present when energy requirements are increased, when caloric intake is decreased, or when a combination of both is present.

In a study on 10 hemodialysis patients, Ikizler et al.[108] found 7% higher than expected energy expenditure during both dialysis and nondialysis days, suggesting that uremia per se increases energy expenditure. This conclusion is controversial, however. Monteon et al.[115] measured energy expenditure of CKD patients during rest and exercise; CKD patients did not differ from control subjects. This issue may be clinically important, because a prospective study showed a correlation between high resting energy expenditure and increased mortality or cardiovascular death in patients on continuous ambulatory peritoneal dialysis.[116]

In CKD patients, caloric intake tends to be decreased.[117] CKD patients do not ingest a prescribed amount of calories despite dietary counseling: in the Modification of Diet in Renal Disease (MDRD) study, initial energy intake was below the recommended limit (30 to 35 kcal per kilogram of body weight per day) and, during the study, energy intake declined further despite intensive dietary counseling.[118]

Nutrition in Hemodialysis Patients

Hypercatabolism is common in dialysis patients and is presumably related to an intradialytic loss of amino acids, as well as cytokine activation, particularly IL-6. There is an interesting dichotomy: muscle protein breakdown increases during hemodialysis, whereas whole-body proteolysis is not increased.[119] It has been suggested that avoiding a negative protein balance requires both the provision of nutrients and the inhibition of inflammatory signals.[119] Hypoalbuminemia, negative nitrogen balance, loss of muscle mass, and wasting are commonly seen in long-term dialysis patients.[119] Several tests have been used to diagnose PEW, but they do not exactly measure the same abnormality.[102] The procedures range from the well-known anthropometric measurements, such as skinfold thickness and midarm muscle circumference, BMI, waist-to-hip ratio, to a subjective global assessment. Low plasma albumin concentrations are closely related to mortality,[120] whereas BMI and urine creatinine excretion as an index of muscle mass are not. Even small decrements in plasma albumin concentration (in the range of 3.5 to 3.9 g per deciliter) have been associated with increased mortality in hemodialysis patients. The plasma albumin concentration appears to be a late index of malnutrition. Because of its relatively long half-life (21 days) and the vast capacity of the liver to synthesize albumin, a decrease in serum albumin concentration lags behind the onset of malnutrition by several months.[121] Other indicators of PEW include prealbumin levels, plasma cholesterol concentrations (< 150 mg per deciliter), decreased plasma transferrin, and a decrease in body weight.[102] Indices of PEW in CKD patients undergoing renal replacement therapy are shown in Table 80.4.

80.5 Factors That Affect the Nutritional Status of Patients with Chronic Kidney Disease

Gastrointestinal Disturbances
- Anorexia
- Gastroparesis and delayed gastric emptying
- Malabsorption
- Esophagitis, gastritis
- Intestinal bacterial colonization
- Subjective feeling of fullness from dialysate in the abdomen (in peritoneal dialysis patients)

Biochemical Derangements
- Metabolic acidosis
- Low grade inflammation
- Insulin resistance

Iatrogenic Factors
- Dialysate amino acids, protein and glucose losses
- Bioincompatibility of dialysis membranes
- Multiple medications, particularly sedatives

Other Factors
- Long-term, low protein intake
- Low socioeconomic status
- Depression
- Underlying illness
- Frequent hospitalizations

Factors That Affect Nutritional Status in Chronic Kidney Disease

Several factors contribute to the high prevalence of PEW in CKD patients (Table 80.5). The catabolic factors that may participate in the pathogenesis of PEW in CKD are (1) metabolic acidosis, (2) inflammation, (3) insulin resistance, (4) dialysate loss of amino acids and glucose losses, and (5) bioincompatibility of dialysis membrane.

Metabolic acidosis is one of the most important factors causing excessive catabolism of amino acids and proteins in CKD patients. Metabolic acidosis activates the specific pathways involved in the degradation of branched-chain amino acids catalyzed by branched-chain keto acid dehydrogenase.[92] It also activates the ubiquitin–proteasome system, the final common pathway of muscle protein degradation.[122] Profound acidemia following the ingestion of ammonium chloride causes cachexia in humans without CKD.[123] Conversely, in CKD patients, correction of metabolic acidosis decreases protein degradation considerably.[124] Long-term therapy with a higher concentration of lactate buffer in peritoneal dialysate caused decreased expression of mRNA encoding ubiquitin in muscle.[125] Correction of metabolic acidosis by oral sodium bicarbonate supplementation in dialysis patients increases plasma albumin concentration and muscle mass,[126] and may even slow down progression in CKD.[127,128]

In a sizable proportion of hemodialyzed patients, high plasma concentration of proinflammatory cytokines are found[129] (e.g., high TNF-α, which are known to stimulate protein degradation in muscle). Another factor is insulin resistance. Absence of, and potentially resistance to, insulin stimulates the ubiquitin–proteasome system, that is, the common proteolytic pathway, in muscle.[28]

The hemodialysis procedure may also be catabolic. Protein breakdown is acutely stimulated during a dialysis session.[105] This effect may be mediated, at least in part, via complement activation by contact between blood and bioincompatible membranes.[130] The use of more biocompatible dialysis membranes may prevent PEW by reducing complement activation. Unfortunately, two long-term, prospective studies on this issue yielded conflicting results,[131,132] and the issue of the relation between bioincompatibility and malnutrition remains a matter of debate.

A further important factor contributing to malnutrition in CKD patients is a loss of appetite. Changes in the motility and function of the gastrointestinal tract, including gastroparesis, malabsorption, intestinal bacterial colonization, and constipation, are further contributory factors.

Dietary and Energy Intake Recommended in Patients Undergoing Dialysis Replacement Therapy

The recommended nutrient intake for patients undergoing maintenance hemodialysis or peritoneal dialysis is summarized in Table 80.6.[133]

ENDOCRINE DISORDERS IN CHRONIC KIDNEY DISEASE

Abnormalities in the Hormones of the Hypothalamic–Pituitary–Gonadal Axis

Both female and male CKD patients present a variety of derangements of the hypothalamic–pituitary–gonadal axis (Table 80.7). In males, these abnormalities are involved in the pathogenesis of impotence and gynecomastia. In females, these abnormalities account for anovulatory menstrual cycles and infertility.

The Hypothalamic–Pituitary–Gonadal Axis in Male Chronic Kidney Disease Patients

Luteinizing Hormone

In CKD, the lack of appropriate cyclic release of gonadotropin-releasing hormone (GnRH) by the hypothalamus leads to a loss of normal pulsatile luteinizing hormone (LH) release by the pituitary, which results in impaired ovulation in women and reduced testosterone and sperm production in men.[134] The cause of impaired cyclic release of GnRH is unclear, but

80.6 Recommended Dietary Protein and Energy Intake for Patients Undergoing Maintenance Hemodialysis or Peritoneal Dialysis

	Maintenance Hemodialysis	Continuous Ambulatory or Cyclic Peritoneal Dialysis
Protein	1.2 g/kg/d ≥50% high biologic-value protein	1.2–1.3 g/kg/d ≥50% high biologic-value protein Unless a patient has demonstrated adequate protein nutritional status on 1.2 g/kg/d diet, 1.3 g/kg/d should be prescribed
Energy	≥ 35 kcal/kg/d 30 to 35 kcal/kg/d for patients 60 years or older	

Based on Kidney diseases outcomes quality initiative clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2000;35[suppl 2].

hyperprolactinemia, elevated endorphins, and high levels of GnRH and LH caused mainly by reduced clearance may contribute.[134]

In the majority of CKD patients, basal plasma LH concentrations are higher by a factor of approximately 1.5 to 2 compared with healthy controls. Such concentrations approach the concentrations in patients with primary hypogonadism. High plasma LH concentrations in CKD are mainly due to a decreased rate of catabolism of LH[135] and, conversely, its half-life of LH in CKD is increased by a factor of 2 to 4 compared to normal subjects.[135] Apart from an abnormal basal LH concentration, there is also an abnormality of pulsatile LH secretion. Schaefer et al.[136] found decreased amplitudes of the secretory bursts of bioactive and immunoreactive LH, but no change in the number of bursts.

80.7 Abnormalities of the Hypothalamic–Pituitary–Gonadal Axis in Patients with Chronic Kidney Disease

	Male	Female
Basal prolactin	↑	↑
Prolactin response to TRH	↓	↓ and delayed
Prolactin suppression test	Impaired	Impaired
Basal FSH	↑	N
FSH response to GnRH	N but delayed	N
Basal LH	↑	↑
LH response to GnRH	N	N
Testosterone	↓	—
Estradiol	N	↓
Progesterone	—	↓

TRH, thyrotropin-releasing hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; N, normal.

LH stimulates the production of testosterone by the Leydig cells of the testes. Testosterone, in turn, exerts negative feedback control on the secretion of GnRH and, secondarily, on LH. Low plasma testosterone concentration in CKD[137] may, therefore, contribute to the elevation of LH concentration.

Follicle-Stimulating Hormone

In CKD patients, the basal plasma concentrations of follicle-stimulating hormone (FSH) are in the upper normal range or elevated.[134] FSH is important for spermatogenesis. It stimulates testicular growth and increases the production of testosterone-binding protein by Sertoli cells. In testicular tubules, FSH accounts for the high local concentrations of testosterone required for sperm maturation. In CKD patients, spermatogenesis is impaired despite elevated blood levels of FSH,[134] a finding that is consistent with the following explanations: (1) resistance of the testis to the action of FSH causes testicular damage with a consequent increase in FSH concentrations, and/or (2) testicular damage is the primary abnormality and the elevated FSH concentrations represent the normal response of the hypothalamic–pituitary axis. In either case, the negative feedback between testes and the hypothalamic–pituitary axis appears to be normal in CKD.

Prolactin

Plasma prolactin concentrations are elevated in the majority (40% to 70%) of male hemodialysis patients.[138] As CKD pro-

gresses, elevated plasma prolactin concentrations correlate with plasma creatinine concentration.[139] Apart from elevated basal prolactin concentrations, the circadian rhythm of prolactin secretion is also disturbed. Finally, the characteristic sleep-induced secretory bursts are not observed, although episodic secretion occurs during the daytime.[139]

It seems that both diminished prolactin clearance[140] and increased autonomous production rate contribute to hyperprolactinemia in CKD. The response to the stimulation or suppression of prolactin is diminished in CKD. This observation is consistent with the notion of increased autonomous production.[138,140] The underlying mechanism is presumably an inadequate dopaminergic inhibition of prolactin release from pituitary lactrotrophs.[141]

It is of interest that in some patients, correction of the hyperprolactinemia by bromocriptine also caused improvement of sexual dysfunction.[142]

Testicular Hormones

In most male hemodialysis patients, plasma testosterone concentrations are low.[143,144] In a recent paper, Carrero et al.[137] found that testosterone deficiency was present in 44% of the hemodialysis patients, whereas 33% showed testosterone insufficiency (10 to 14 nmol per liter), and only 23% had normal testosterone values (>14 nmol per liter). The normal circadian rhythm of plasma testosterone concentrations, with a peak at 4 to 8 AM and nadir at 8 to 12 PM is maintained in CKD patients.[145] It is unknown whether the decreased plasma testosterone concentrations are due to reduced synthesis, increased catabolism, or a combination of both. LH stimulates testosterone secretion; however, despite numerous studies, it is not clear whether the deranged LH metabolism accounts for the reduced testosterone concentrations. The reduced amplitude of pulsatile secretory LH bursts, found in CKD, may be more critical for testosterone secretion than the sustained elevation of LH concentration. Alternatively, LH resistance of testosterone-producing cells may lead to impaired testosterone production and/or secretion. A circulating LH-receptor inhibitor was found in CKD patients, which suggested that it might contribute to Leydig cell resistance and an impaired feedback mechanism at the hypothalamic–pituitary level.[146] In this context, it is also possible that elevated prolactin concentrations interfere with the action of LH on the testes and contribute to LH resistance.[147] The response to 4 days of administration of human gonadotropin is sluggish and delayed; no increase of testosterone concentration was seen after 8 hours, but a two- to threefold increase was seen after 4 days.[148] Malnutrition is also likely to participate in the reduction of plasma testosterone concentration in CKD male patients. In CKD patients on a low-protein diet, essential amino acids and keto analog supplementation raised low testosterone plasma concentration.[149]

With respect to the other androgens, increased plasma dihydrotestosterone and androstanediol concentrations[150] as well as decreased plasma concentration of androstenedione and dehydroepiandrosterone sulfate have been reported.[151]

Androgen deficit in CKD males may cause changes in body composition. Body fat increases while lean body mass is reduced. An androgen deficit may be associated with reduced muscle mass, osteoporosis, and a higher incidence of bone fractures.[147] In addition to its negative effects on body composition, the androgen deficit also may impair libido and sexual function and might lead to depression.[147] Moreover, testosterone was strongly and inversely correlated to inflammatory markers (CRP, IL-6, and fibrinogen).[137] Finally, it was recently shown that low testosterone concentrations were associated with worse outcomes in male hemodialysis patients.[143,144]

Abnormalities in the Hormones of the Hypothalamic–Pituitary–Gonadal Axis in Female Chronic Kidney Disease Patients

Luteinizing Hormone

Pulsatile secretion of GnRH at 90-minute intervals during the follicular phase of the cycle is essential for effective hypophyseal gonadotropin secretion. In healthy premenopausal females, the secretion of LH is pulsatile. In female CKD patients, the spontaneous pulsatile LH secretion is disturbed.[152] Plasma LH concentration is elevated in most premenopausal CKD patients. The response to stimulation with GnRH is delayed.[153] Diurnal pulsatile LH secretion and high preovulatory peaks of GnRH and LH plasma concentrations are absent in most female CKD patients. In healthy females, estradiol lowers the amplitude of LH pulses. In females with CKD, estradiol fails to influence the LH surge, suggesting impaired positive feedback.[153]

Follicle-Stimulating Hormone

In contrast to the abnormal plasma LH concentration, the plasma FSH concentration is normal in most premenopausal CKD patients[154] and the FSH/LH ratio is decreased. The decreased FSH/LH ratio argues against primary ovarian failure and suggests hypothalamic–hypophyseal dysregulation in CKD females.

Prolactin

Plasma prolactin concentrations are often elevated in female hemodialysis patients,[154] but the increase of plasma prolactin after the administration of thyrotropin-releasing hormone (TRH) is blunted.[154] In CKD females, amenorrhea is frequent in patients with high plasma prolactin concentrations, and conversely, in females with regular menstruation plasma prolactin, concentrations are lower.[155]

Estrogens

In female CKD patients, the plasma estradiol concentrations are normal or low[152,156] and are consistently lower in CKD females with hyperprolactinemia.[157] In the second half of the menstrual cycle, plasma progesterone concentrations are low because of defective luteinization of the follicles.[156] The

hormonal derangements of females with CKD are clearly the consequence of abnormal regulation at the level of the hypothalamus.

A major consequence of the low plasma estrogen concentration concerns bone disease. Weisinger et al.[158] studied young female hemodialysis patients. Amenorrheic patients had not only significantly lower plasma estrogen concentrations, but also significantly lower bone mineral density compared to normally menstruating female dialysis patients. Furthermore, in amenorrheic patients, a significant positive correlation was found between bone mineral density and both plasma estradiol concentration[158] and free estrogen index.[159] A causal role is suggested by the observation of Matuszkiewicz-Rowinska et al.[160] In a small group of postmenopausal women on dialysis, they showed that treatment with transdermal estradiol and cyclic addition of norethisterone acetate for 1 year increased lumbar spine bone mineral density significantly. Similarly, in a placebo-controlled randomized trial, 1 year of treatment with raloxifene, a selective estrogen receptor modulator (SERM), significantly increased bone mineral density of the lumbar spine in hemodialyzed postmenopausal females.[161] In view of concern about the potential adverse cardiovascular effects of hormonal replacement therapy, it must be emphasized that currently long-term studies on the effectiveness and safety of hormone replacement or SERM therapy in CKD female are not available.

80.8 Abnormalities in the Growth Hormone–Insulinlike Growth Factor (Somatotropic) Axis in Patients with Chronic Kidney Disease

Growth Hormone (GH)
Increased plasma GH concentration
Decreased plasma concentrations of high-affinity GH-binding protein
Peripheral resistance to GH due to defect in GH intracellular signal transduction
Insulinlike Growth Factor (IGF)
Slightly decreased IGF-1 and increased IGF-2 plasma concentration
Reduced free IGF-1 plasma concentration
Increased IGFBPs (IGFBP-1, -2, -3, -4, and -6) plasma concentration
Presence of low molecular weight (1,000 Da) inhibitor of IGF-1 in plasma
Peripheral resistance to IGF-1 probably due to postreceptor defect in IGF-1 action

IGFBP, IGF-binding protein.

Abnormalities in the Growth Hormone–Insulinlike Growth Factor (Somatotropic) Axis

The somatotropic axis comprises growth hormone (GH), insulinlike growth factor 1 and 2 (IGF-1 and -2), six IGF-binding proteins (IGFBP-1 to -6), and the IGFBP proteases (BP-Pr). All are involved in the modulation of somatic growth, cellular proliferation, metabolism, and numerous other processes. Poor growth and reduced final height are well-known complications of children with CKD. Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) 2005 database revealed that 36.9% of children with CKD had growth impairment.[162] It is not surprising that several abnormalities (Table 80.8) in the somatotropic axis have been reported in children and adults with CKD.

Growth Hormone

GH is produced and secreted by the somatotrophs of the pituitary glands. The secretion of GH is pulsatile. A diurnal rhythm also exists; the secretion is high before awakening and decreases toward the end of the day. The secretion of GH is mainly controlled by two opposing hypothalamic factors; growth hormone-releasing hormone (GHRH), which stimulates GH secretion, and somatostatin, which inhibits GH secretion. The kidney is the main site of GH degradation.[163]

In children and adult patients with CKD, the plasma concentration of GH is usually elevated.[164] The increase in plasma GH concentration is correlated negatively to GFR.[164] The increase in plasma GH concentration is caused by a reduction of the metabolic clearance rate and by an increase of GH secretion. In CKD, the metabolic clearance rate of GH is reduced[165] and the GH secretion rate is elevated, as documented in adult hemodialysis patients.[166] The latter finding is not consistent, however, and in pubertal patients with advanced CKD, the GH secretion rate was decreased.[167] Plasma GH concentrations are higher in CAPD than in hemodialysis patients.[168]

The dysregulation of GH secretion is explained by several abnormalities of the central neuroendocrine control mechanisms. This issue has been investigated by suppressing and stimulating maneuvers testing the hypothalamic–pituitary function in CKD patients. Hyperglycemia by glucose infusion suppresses GH secretion in normal individuals, but fails to do so in CKD patients.[169] Conversely, in CKD patients, the response of GH secretion to the administration of GHRH[169] or L-3,4-dihydroxyphenylalanine (L-DOPA)[170] is exaggerated. Exogenous TRH does not affect GH release in normal subjects, but stimulates GH secretion in CKD[170] and a sustained exaggerated increase of GH secretion is also seen after stimulatory maneuvers, such as arginine infusion and insulin-induced hypoglycemia.[170,171]

Approximately 45% of plasma GH is bound to plasma proteins. Decreased plasma concentrations of the high

affinity GH-binding protein have been found in CKD.[172] The constellation of increased concentrations of plasma GH and decreased concentrations of the high-affinity GH-binding protein implies that the fraction of free hormone is increased to which target tissues are exposed. When chondrocytes are isolated from bones of uremic rats and exposed to growth hormone or IGF-1, the response was blunted, however,[173] suggesting that in CKD the high concentrations of free GH are counteracted by peripheral resistance to GH.

The resistance appears to be both at the receptor and the postreceptor level. Determination of the concentration of serum growth hormone binding protein (GHBP), which is a cleaved product of the GH receptor, may be used to assess GH receptor density in tissues. GHBP plasma concentration is low in children and adults with CKD and proportionate to the degree of renal dysfunction.[162] Experiments of Rabkin et al.[174] suggest that resistance to GH is due to defective intracellular signal transduction. The authors found impaired phosphorylation and nuclear translocation of GH-activated signal transducer and activator of transcription (STAT) protein.[174]

Insulinlike Growth Factors

GH promotes linear growth partially by stimulating systemic and local concentrations of IGFs. The two most important IGFs are IGF-1 and IGF-2. These peptide growth factors are produced locally by most tissues, including the growth plate, but the liver is the main source of circulating hormones. The synthesis of IGFs is stimulated by GH. Conversely, as part of a negative feedback loop, IGF-1 inhibits GH presumably through stimulation of somatostatin secretion by the hypothalamus. Plasma IGF-1 forms complexes with six IGF-binding proteins (IGFBP-1 to -6). IGFBP-3 is the predominant IGFBP isoform in human plasma. Its main production site is the liver. IGFBP-3 binds IGF-1 and binding prolongs the half-life of IGF and serves as a reservoir of IGF-1.

In advanced CKD, the plasma concentration of total IGF-1 is slightly decreased and that of IGF-2 is increased.[175] The plasma concentration of free IGF-1 is lower by 50%.[176] Moreover, the so-called somatomedin bioactivity in blood, an index of IGF activity measured by sulfate incorporation into porcine costal cartilage, is reduced in uremia.[177]

The discrepancy between normal or elevated total IGF plasma concentration and low bioactivity in CKD may be explained by one or a combination of the following: (1) increased plasma concentration of IGFBPs, (2) circulating IGF inhibitor, and (3) receptor or postreceptor defect. There is some evidence for all three possibilities.

Plasma concentrations of five of the six IGF-binding proteins (IGFBP-1, -2, -3, -4, and -6) are markedly higher in CKD patients.[178] The increased binding capacity of IGF-1 decreases the concentration of free IGF-1.[179] This imbalance between plasma IGF-1 and plasma IGFBP concentrations seems to be relevant in the pathogenesis of growth failure in CKD. A significant negative correlation is found between plasma concentrations of IGFBP-1, -2, and -4, on the one hand, and standardized height in CKD children, on the other hand.[175,179]

A low molecular weight (1,000 Da) inhibitor of IGF-1 has been identified in the plasma of CKD patients,[180] but molecular details have not yet been characterized.

Finally, Ding et al.[181] characterized a postreceptor defect to the action of IGF-1 in the epitrochlearis muscle of uremic rats (i.e., both autophosphorylation of the IGF-1R tyrosine kinase and activity of the IGF-1R tyrosine kinase to the exogenous insulin receptor substrate 1 [IRS-1], a natural substrate for IGF-1 receptor tyrosine kinase, are diminished). These are in line with observations of Fouque et al.,[182] who found resistance to the metabolic effects of recombinant human IGF-1 in patients with advanced CKD.

Clinical Consequences

It was shown that growth failure in CKD is associated with increased morbidity and mortality. Furth et al.[183] demonstrated from the U.S. Renal Data System (USRDS) database that patients with severe-to-moderate growth failure had increased hospitalization rates and increased risk of death.[183]

Elevation of plasma GH concentration and low IGF bioactivity is compatible with the notion that growth failure in CKD is mainly due to end-organ hyporesponsiveness to growth hormone. The demonstration of the resistance to the action of GH and IGF-1 in CKD provides the rationale for the use of GH in the treatment of CKD children with retarded growth despite normal or elevated hormone concentrations. In a multicenter randomized double-blind placebo-controlled study, 2 years of administration of recombinant human GH in 125 prepubertal children with CKD caused an increase in growth rate and in standardized height without undue advancement of bone age or significant side effects.[184] Haffner et al.[185] studied the effect of GH treatment on the final adult height of children with CKD that, in contrast to the controls, had persistent growth failure; children treated with rhGH demonstrated sustained catch-up growth.[185]

Abnormalities in the Adrenocorticotropin–Cortisol Axis

The adrenocorticotropin–cortisol axis is only mildly affected in CKD. In CKD patients, plasma adrenocorticotropin (ACTH) concentrations are normal or elevated.[186,187] In CKD patients, ACTH secretion following the administration of corticotropin-releasing hormone (CRH) occurs earlier, but the magnitude of the response is blunted.[188,189]

In CKD patients, the basal blood levels of cortisol are normal[188] or modestly elevated.[189,190] No significant correlation was found between free cortisol concentrations and GFR.[191] The circadian rhythm of cortisol secretion is not disturbed. The cortisol half-life is prolonged in CKD patients,[190] and decreased catabolism may contribute to the mildly elevated basal levels of cortisol.

A reduced stimulated cortisol secretion to CRH despite prolonged elevation of ACTH has been observed in hemodialysis patients,[192] but the results are not uniform.

Zager et al.[186] found a normal cortisol response to exogenous ACTH.

In CKD patients, ACTH secretion cannot be suppressed by standard oral doses of dexamethasone.[190] This is probably due to reduced dexamethasone absorption in the gut, because higher doses of dexamethasone suppress ACTH secretion. Therefore, when Cushing syndrome is suspected in CKD patients, a 2-day dexamethasone test is recommended. Overall, the adrenocorticotropin–cortisol axis is either normal or only mildly altered in CKD; the clinical significance of this finding is unknown.

Abnormalities in Vasopressin

In CKD patients, the plasma vasopressin concentration is elevated.[193,194] The major cause is a decreased metabolic clearance rate.[195]

The main physiologic stimuli for vasopressin secretion are increased plasma osmolality and decreased cardiac output or arterial vasodilation. Most studies found an intact osmotic regulation of vasopressin secretion in CKD.[193] The vasopressin response to nonosmotic stimuli is apparently also normal. In hemodialyzed patients, the plasma vasopressin concentration increases during ultrafiltration[196] and plasma volume contraction.[197] Conversely, it decreases during central hypervolemia induced by water immersion.[194] It was shown that in hemodialysis patients, the hierarchy of stimuli-regulating vasopressin secretion is osmotic followed by nonosmotic factors.[197]

The clinical significance of the elevated blood levels of vasopressin in CKD is still uncertain. Experimental studies suggest that vasopressin (AVP) may participate in the genesis and exacerbation of renal damage and CKD. It was shown that a sustained stimulation of vasopressin receptors induces intrarenal renin–angiotensin system activation, podocyte alterations, glomerular hyperfiltration, and hypertrophy eventuating in proteinuria and kidney damage. Furthermore, AVP directly stimulates the contraction and proliferation of mesangial cells and the accumulation of extracellular matrix and glomerulo-sclerosis.[198]

Copeptin (or C-terminal proarginine vasopressin; CT-proAVP) is the C-terminal part of the vasopressin prohormone, which is secreted stoichiometrically with AVP and easier to estimate its plasma concentration than AVP itself. It was shown that in patients with diabetic nephropathy, CT-proAVP is directly associated with serum creatinine and predicts cardiovascular mortality.[199] Moreover Meijer et al.[200] found in a recent cohort study in 548 renal transplant patients that high CT-proAVP entails a negative renal prognosis. In this study, the plasma concentrations of this peptide predicted renal function loss over 3.2 years.[200] Selective and nonselective AVP type 2 antagonists, also denominated aquaretic agents, have already been tested in various hyponatremia-related disorders such as chronic heart failure. However, no clinical trial has been done to investigate the potential nephroprotective effect of this class of drugs.

Abnormalities in the Thyroid Gland and Hypothalamic-Pituitary–Thyroid Axis

Abnormalities in the structure and function of the thyroid gland and in the metabolism and plasma concentrations of thyroid hormones are common in patients with CKD.[201] These derangements may be due to the uremic state per se, to nonthyroid disorders (chronic disease), or to concomitant disorders of the thyroid, the pituitary, or the hypothalamus. A detailed profile of the prevalent indices of thyroid status in CKD as compared to primary hypothyroidism and chronic nonthyroid illness is presented in Table 80.9.

Goiters, Thyroid Nodules, and Thyroid Carcinoma

Available data indicate that the prevalence of goiters is increased in CKD patients.[202,203] Ultrasound scanning shows an increase of thyroid volume in about 50% of hemodialysis patients.[203] Kaptein et al.[202] studied 306 CKD patients and compared them to 139 hospitalized control patients without renal disease. A goiter was present in 40% of the CKD patients and in 43% of those treated with dialysis, compared to 6.5% in the control group. The frequency of goiters was higher in patients treated for more than 1 year with hemodialysis (50%) than in those treated for a shorter time (39%).

80.9 Abnormalities of the Hypothalamic–Pituitary–Thyroid Axis in Patients with Chronic Kidney Disease, Chronic Nonthyroidal Nonkidney Illness, and Primary Hypothyroidism

	Free T_4	Free T_3	rT_3	TSH
Chronic kidney disease	N, ↓	↓	N	N
Chronic nonthyroidal nonkidney illness	N, ↓	↓	↑	N
Primary hypothyroidism	↓	↓	N	↑

N, normal; TSH, thyroid-stimulating hormone; T_4, thyroxine; T_3, triiodothyronine; rT_3, reverse triiodothyronine.

It has been suggested that in CKD, goiter formation is the result of increased plasma iodide concentrations.[201,204]

Thyroid nodules are more common in CKD patients than in the general population and were found in 55% of female hemodialysis patients compared with 21% of normal females.[205] We emphasize that it is necessary to exclude malignancy in CKD patients with solitary nodules.

The prevalence of thyroid carcinoma is increased in CKD patients. In a large sample of patients in the United States, the relative risk of thyroid malignancy was increased 2.9 times in females but not in males (1.2 times).[206] In Europe (the European Dialysis and Transplantation Association-European Renal Association [EDTA-ERA] registry), the frequency of thyroid cancer was increased by a factor of 4 to 8 in young female dialysis patients and by a factor of 2 in older dialysis patients.[207]

Thyroid Hormones

The plasma concentrations of both thyroxine (T_4) and triiodothyronine (T_3) are normal or reduced in CKD patients.[201,202,204] Plasma T_3 is more often and more markedly decreased than T_4.[201]

The reduced plasma T_3 concentration in CKD patients is the result of decreased peripheral conversion of T_4 to T_3 in several tissues. In contrast, the production of T_3 in the thyroid gland is normal. T_3 clearance rates are normal or decreased.[208] The impaired conversion of T_4 to T_3 may also be the result of malnutrition, because in CKD patients, a significant positive correlation was found between total plasma T_3 concentration and plasma albumin, as well as transferrin concentrations.[202] Chronic metabolic acidosis associated with CKD may contribute to this effect.[209]

In contrast to the other chronic nonthyroid diseases, reverse T_3 (rT_3) plasma concentration is normal in CKD patients.[210]

Although T_3 is the most active thyroid hormone, CKD patients with low plasma T_3 concentrations appear clinically euthyroid.[211] The expression of messenger RNA of T_3 receptors by mononuclear cells is increased in CKD patients compared with normal subjects.[212] This response of the receptor may help to maintain a euthyroid state despite low free T_3 concentrations.

In CKD, abnormal thyroid hormone indices do not indicate a state of hypothyroidism, but are a reflection of the state of chronic illness and/or malnutrition. Therefore, abnormal thyroid hormone indices (low T_3 and T_4 plasma concentrations) do not require therapy, which even carries a hazard. In CKD patients with low plasma T_3 concentration, it has been shown that triiodothyronine supplementation causes a negative protein balance.[213] The low T_3 state of CKD can be viewed as being protective, promoting the conservation of protein.

The Hypothalamic-Pituitary–Thyroid Axis

Despite a tendency to low plasma concentrations of T_4 and T_3, the plasma concentration of thyroid-stimulating hormone (TSH) is usually normal in CKD patients.[214] The normal plasma TSH concentration despite a low plasma concentration of the thyroid hormones suggests an abnormal regulation of the hypothalamic-pituitary–thyroid axis. The TSH response to TRH is usually blunted.[202,215] In CKD patients, the normal diurnal rhythm of TSH with a peak in the late evening or early morning is blunted,[216,217] and the nocturnal TSH surge is reduced.[216] The pattern of pulsatile TSH secretion is altered by the appearance of low-amplitude, high-frequency pulses.[217]

Primary Hypothyroidism and Hyperthyroidism

Primary hypothyroidism is two to three times more frequent in CKD patients than in the general population.[202] Risk factors are female sex, age greater than 50 years,[202] and increased iodine intake.[218] A recent study has shown a prevalence of subclinical hypothyroidism in 7% of patients with estimated GFR $\geq$ 90 mL/min/1.73 m^2 that increased to 17.9% in subjects with GFR $<$ 60 mL/min/1.73 m^2.[219]

It is very difficult to make the clinical diagnosis of hypothyroidism in CKD patients. The signs and symptoms of hypothyroidism, such as pallor, hypothermia, and asthenia, are also found in patients with advanced CKD and no hypothyroidism.[201] The only reliable procedure to diagnose hypothyroidism in renal failure is the finding of an elevated plasma concentration of TSH associated with clearly low plasma concentrations of T_4. Because heparin competes with T_4 at the binding site of the hormone-binding protein, causing an increase of plasma T_4 concentrations for at least 24 hours, blood for the determination of thyroid hormones should be sampled before heparin administration at the beginning of a dialysis session.[220]

The prevalence of hyperthyroidism in CKD is similar to that found in the general population, in areas with an inadequate intake of iodine.[221]

Abnormalities in the Vitamin D Metabolites

Vitamin D is first hydroxylated in the liver to 25-hydroxyvitamin D_3 (25[OH]D_3). The prevalence of 25-vitamin D_3 deficiency increases with the progression of CKD and approaches 80% in CKD stage 5 patients.[222] Moreover, in patients with nephrotic syndrome, the 25(OH)D_3 and vitamin D-binding protein is lost in the urine.[223] Similarly, 25(OH)D_3 is lost in the peritoneal fluid in CKD patients treated with peritoneal dialysis.[224] Therefore, both patients with nephrotic syndrome and CKD patients treated with peritoneal dialysis have a low 25(OH)D_3 plasma concentration. Although repletion with high-dose ergocalciferol (20,000 U per week during 9 months) is considered safe, it achieves the desired level in only about 50% of hemodialysis patients.[225] A small randomized trial found that 50,000 U of cholecalciferol weekly for 12 weeks was safe and effective in satisfying 25(OH)D_3 levels in stage 3 and 4 CKD patients.[226] In the general population, vitamin D deficiency has been linked to increased prevalence of hypertension, metabolic syndrome, insulin resistance, obesity, cardiovascular diseases (CVD), and albuminuria.[227]

25(OH)D_3 is transported to the kidneys for further hydroxylation, resulting in the production of the active

metabolite $1,25(OH)_2D_3$. It is known that with worsening renal function, there is progressive decline in the activity of 1α-hydroxylase, the enzyme critical in converting 25(OH) D_3 to 1,25-dihydroxyvitamin D_3 (calcitriol).[228] As a consequence, in anephric patients and in those in CKD stage 5, the blood levels of $1,25(OH)_2D_3$ are usually very low.[228] Moreover, patients with CKD display end-organ resistance to the action of $1,25(OH)_2D_3$. There is a decrease in the concentration of $1,25(OH)_2D_3$ receptors (VDR) in these patients.[229]

$1,25(OH)_2D_3$ exerts its action by binding to an intracellular VDR, which is located predominantly in the nucleus. The hormone–receptor complex interacts with DNA-responsive elements in target genes with the synthesis of proteins. The deficiency of $1,25(OH)_2D_3$ plays a paramount role in the genesis of many of the disturbances of divalent ions observed in patients with CKD. These abnormalities include secondary hyperparathyroidism, defective intestinal absorption of calcium, skeletal resistance to the calcemic action of PTH, defective mineralization of bone, growth retardation in children, and proximal myopathy.

The number of recent clinical studies suggest that $1,25(OH)_2D_3$ deficiency leads to increased mortality in CKD patients. The results of the small interventional studies suggest that treatment with calcitriol or other VDR agonists reduce the mortality among these patients. Kovesdy et al.[230] found in a single-center, nonrandomized, observational study of 520 males with CKD an association between calcitriol treatment and reduced mortality. Shoji et al. showed in a small observational study that patients taking alfacalcidol had a reduced risk of CVD death compared to patients who were not on vitamin D. Tentori et al.[231] published similar findings in a larger cohort treated with a VDR agonist. However, these studies are small, and more large studies are needed in this area.

The number of recent clinical studies suggest that $1,25(OH)_2D_3$ deficiency increases proteinuria in CKD patients. Recently, it was shown that low $25(OH)D_3$ and $1,25(OH)_2D_3$ were independently associated with increased albuminuria in CKD patients.[233] Moreover, Agarwal et al.[234] found an antiproteinuric effect of oral paricalcitol in CKD patients.[235] However, again, these studies are small, and more large studies are needed in this area.

The other abnormalities in the endocrine regulation of calcium and phosphate metabolism (among others, PTH and fibroblast growth factor-23) in CKD were discussed in other chapters of this text.

Alterations of the Renin–Angiotensin–Aldosterone System in Chronic Kidney Disease

The renin–angiotensin–aldosterone system (RAAS) is both an endocrine and a paracrine system, which plays a major role under physiologic and pathophysiologic conditions. The RAAS is involved in the regulation of blood pressure, control of volume, and sodium balance, as well as growth and remodeling of cardiovascular and renal tissues under pathologic conditions, to name only a few. Space does not permit giving an exhaustive overview, and we restrict the discussion to problems where measurement of the components of the system provides guidance to the clinician.

Plasma Renin Activity

In CKD patients suffering from primary renal disease, the activity of the renin-angiotensin system is inappropriately high. Weidmann et al.[236] documented that in hemodialysis patients, plasma renin activity (PRA) is higher at any given level of exchangeable body sodium than in normal subjects. These observations demonstrate that sodium retention and hypervolemia do not adequately suppress renin secretion, indicating disruption of the negative feedback between volume state and renin secretion. In renal disease, an important mechanism that accounts for increased and unregulated renin secretion is luminal narrowing of preglomerular vessels because of vascular sclerosis. Consequently, the "baroreceptor" in the juxtaglomerular apparatus will measure falsely low perfusion pressures, which is analogous to the kidney with a Goldblatt clip of the renal artery. Renin will, therefore, be secreted even when blood pressure is high and exchangeable sodium is increased. Normally, PRA decreases asymptotically with increasing blood pressure. In contrast, in patients with renal disease, renin secretion is not adequately suppressed by high blood pressure values, and PRA remains inappropriately high.

In CKD patients, the basal values of PRA, as measured in peripheral blood, vary. These variations are most likely due to variable degrees of renal ischemia in different renal diseases, to variable disruption of the negative feedback-control system between body fluid volume and renin secretion, and to nonstandardized conditions of examination. Weidmann and Maxwell[237] reported that PRA is highest in patients with nephrotic syndrome. On the other hand, in some patients with renal disease, particularly diabetic nephropathy, obstructive uropathy, or interstitial nephritis, hyporeninemic hypoaldosteronism with low PRA values is seen rather frequently.[238] It should also be mentioned that hypertensive CKD patients are treated with medications that may affect renin secretion, thus contributing to the variability of PRA. After hemodialysis, PRA may increase dramatically as a result of ultrafiltration and hypovolemia.[239]

It should be mentioned that PRA in the circulation does not adequately reflect the activity of local tissue RAAS systems. The paradox that drugs, which block the RAAS, are highly effective and renoprotective (e.g., in patients with diabetic nephropathy as documented by the Lewis trial[240] and the IDNT[241] or RENAAL trials[242]) is explained by the activation of local renin systems in proximal tubular epithelial cells, in podocytes, in mesangial cells, among others, despite low PRA in the circulation.[243]

The importance of the RAAS in CKD is illustrated by the fact that in CKD patients, blockade of the system reduces progression,[240–242] lowers elevated blood pressure,[244] and induces partial regression of cardiovascular structural abnormalities, such as left ventricular hypertrophy (LVH).[245]

In CKD patients, a treatment blockade of the RAAS carries an increased risk of hyperkalemia.[246]

Aldosterone

In early experimental studies, it was shown in subtotally nephrectomized rats that after adrenalectomy, less proteinuria and structural lesions were seen.[247] Conversely, DOCA salt administration caused malignant nephrosclerosis.[248] The pathogenetic role of aldosterone in CKD was shown in the model of subtotal nephrectomy: despite a RAAS blockade with the administration of an angiotensin converting enzyme inhibitor (ACEI) and the ARB administration of aldosterone, increased proteinuria as well as glomerular lesions and also increased heart weight occurred, thus documenting the adverse effects of aldosterone on the kidney and the heart.[249] More remarkably, the administration of spironolactone even caused a regression of the established glomerulosclerosis in the subtotal nephrectomy model.[250] Xue et al.[251] documented local synthase and aldosterone production in the cortex of adrenalectomized diabetic rats. In a model of diabetic nephropathy, spironolactone ameliorated signs of inflammation,[252] thus underlining the importance of the anti-inflammatory effect of mineralocorticoid receptor blockade. It is important that aldosterone induces target organ damage in the kidney and the heart only in a high salt environment,[253] thus identifying salt as a permissive factor.

The important role of aldosterone in CKD is also supported by numerous clinical observations. Plasma aldosterone concentrations were elevated in patients when GFR was < 70 mL per minute,[254] and a correlation between plasma aldosterone concentration and the rate of progression was noted by Walker[255] and Ruggenenti et al.[256]

The first proposal to use spironolactone to reduce proteinuria despite a RAAS blockade in CKD patients was made by Chrysostomou and Becker.[257] Eight patients with proteinuria > 1 g per 24 hours despite ACEI treatment were given 25 mg spironolactone. Proteinuria decreased from an average of 3.81 to 1.75 g per 24 hours without a significant change in blood pressure or creatinine clearance. Meanwhile, this finding has been confirmed in numerous studies. In a meta-analysis, Bomback et al.[258] found that proteinuria was decreased by 15% to 54% in proteinuric patients on an RAAS blockade, which was accompanied by a decrease in GFR. A meta-analysis by Navaneethan et al.[259] also showed a significant reduction of proteinuria, but this did not translate into a reduction in GFR. Whether this reflects reversal of hyperfiltration or whether observation times were not sufficient is currently unclear.

Abnormalities in the Cardiac Natriuretic Peptides

Cardiomyocytes produce and secrete a pulsatile family of related peptide hormones named cardiac natriuretic hormones, which have potent diuretic, natriuretic, and vascular smooth muscle relaxing effects.[260] Cardiac natriuretic hormones include the atrial natriuretic peptide (ANP), the brain natriuretic peptide (BNP), and their related peptides. ANP is released by atrial myocytes in response to stretches associated with increased atrial pressure, whereas the ventricular production and release of this peptide are triggered only in the presence of ventricular hypertrophy. BNP is produced by ventricular myocytes and its generation rate is increased in heart failure and left ventricular hypertrophy. Therefore, the plasma concentration of cardiac natriuretic hormones is increased in diseases characterized by expanded fluid volume, including renal failure, liver cirrhosis, and heart failure.[261]

In CKD patients, plasma concentrations of ANP and BNP are elevated.[262–264] Moreover, in these patients, the pulsatile secretion of ANP and BNP is preserved with abnormally high amplitude.[265] In the predialysis phase of CKD, there is a significant correlation between plasma ANP and serum creatinine concentrations.[264] The causes of high plasma concentrations of ANP and BNP in advanced CKD are multifactorial and depend on: (1) an increase in intravascular filling and atrial distension,[263] (2) concomitant heart failure, and (3) diminished renal clearance.[266,267] Indeed, the removal of fluid by ultrafiltration during dialysis therapy is associated with a decrease in the plasma ANP and BNP concentrations.[268]

The measurement of ANP and BNP plasma concentration was used as a biochemical marker of volume overload in the CKD patient for the improved identification of "dry weight."[269] The use of ANP and BNP to improve the definition of dry weight has yielded variable results, however.[269] The weight of evidence indicates that measurements of ANP and BNP plasma concentration add little to the clinical examination.[269] This is because of (1) a wide variability in results, (2) a lack of correlation with measures of extracellular volume, (3) an inability to detect volume depletion (no differences between normovolemia and hypovolemia), and (4) often, the presence of cardiac dysfunction as a confounder.

Results of recent studies suggest that, in general, the estimation of plasma concentrations of cardiac natriuretic hormones (BNP and N-terminal proBNP) could be useful for a differential diagnosis of heart failure.[270] Moreover, a number of studies in heart failure showed a prognostic relevance of plasma concentrations of cardiac natriuretic hormones.[270] In CKD patients, most studies indicate that the upward adjustment of diagnostic cut points preserves the usefulness of BNP and N-terminal proBNP for the differential diagnosis of heart failure.[271]

Left ventricular hypertrophy and left ventricular dysfunction are considered predictors of cardiovascular and total mortality in dialysis patients. Mallamaci et al.[272] found that measuring the plasma concentrations of cardiac natriuretic hormones, particularly BNP, may be useful in identifying dialysis patients with left ventricular hypertrophy or for excluding systolic dysfunction.

In CKD stage 5d patients, it was found that both BNP and ANP plasma concentrations are strongly related to left

atrial volume (LAV) and predict LAV changes over time.[273] Moreover, in a prospective study of a cohort of dialysis patients without overt heart failure, Zoccali et al.[274] found that high plasma concentrations of cardiac natriuretic peptides, particularly BNP, were strong predictors of cardiovascular mortality. The prognostic value of concentrations of cardiac natriuretic peptides in hemodialysis patients was confirmed by several recent studies.[275–277]

Abnormalities in Gastrointestinal Hormones

Elevated plasma gastrin concentrations have been reported in CKD patients.[278–280] Hypergastrinemia in CKD is due predominantly to "big" gastrin (G34). Plasma concentrations of "little" gastrin (G17) are normal in CKD patients.[279] G34 is biologically 6 to 8 times less active than G17. Postprandial gastrin release in CKD patients in the first 30 minutes was similar to that in normal subjects, but the peak values were attained later and the response was more prolonged.[280] Because the kidney is the main site of gastrin biodegradation,[281] hypergastrinemia in uremic patients is regarded mainly as the consequence of reduced renal degradation of this hormone.

Ghrelin is a gut peptide that stimulates the production of GH from the pituitary gland.[282] Ghrelin and synthetic ghrelin analogs increase food intake by an action exerted at the level of the hypothalamus. They activate cells in the arcuate nucleus that include the orexigenic NPY neurons.[282] The two major forms of circulating ghrelin are acylated (< 10%) and des-acyl ghrelin.[282] Acylated ghrelin promotes food intake, whereas des-acyl ghrelin induces negative energy balance.[282] Elevated plasma ghrelin levels were observed in CKD stage 5d patients.[283] However, only plasma des-acyl ghrelin levels were elevated in CKD. It is suggested that in elevated des-acyl ghrelin levels, plasma concentration is involved in anorexia in CKD patients.[284] Increased total ghrelin levels in CKD are due to the decreased degradation of ghrelin in the kidney.[284] The results of two small interventional clinical studies suggest that ghrelin treatment in uremia results in an improved nutritional status. A single subcutaneous injection of ghrelin enhanced short-term (3 days) food intake.[285] A subsequent report from the same group indicated that the daily administration of synthetic ghrelin stimulated food intake over a period of 7 days.[286] Importantly, energy expenditure was unchanged and there was no subsequent compensatory reduction in energy intake in these patients. Results of these two preliminary studies on ghrelin have renewed hope for the successful treatment of uremic PEW.

The plasma concentrations of other gastrointestinal hormones, such as cholecystokinin,[287] gastric inhibitory peptide,[288] pancreatic polypeptide,[289] secretin,[290] gastrin releasing peptide,[290] and motilin,[278] are elevated in CKD patients. Both normal[279] and markedly elevated[291] plasma concentrations of vasoactive intestinal polypeptide (VIP) were found in CKD patients. The pathophysiologic importance of these findings remains to be elucidated.

Abnormalities in the Hormones of Adipose Tissue

The adipose tissue is an important endocrine organ producing biologically active substances with local and/or systemic action. An incomplete list comprises plasminogen activator inhibitor type-1 (PAI-1), transforming growth factor β (TGF-β), tissue factor (TF), complement factors (e.g., adipsin), adipocyte complement–related protein, TNF-α, acylation stimulating protein (ASP), angiotensinogen (Ang), prostaglandin (PGI–2α), IGF-1, macrophage inhibitory factor (MIF), sex hormones, glucocorticoids, Ang II, visfatin, omentin, leptin, adiponectin, and resistin.[292]

Leptin

Leptin is a protein that is predominantly produced by adipocytes. It is encoded by the ob gene. It is presumed that leptin is involved in the regulation of appetite, food intake and energy expenditure, sexual maturation and fertility, hematopoiesis, and activity of the hypothalamic-pituitary-gonadal axis. Obese individuals have high plasma leptin concentrations.

Patients with advanced CKD have elevated plasma leptin concentrations compared to body mass index (BMI) and sex-matched healthy individuals.[293] Leptin concentrations are normalized by a successful kidney transplantation.[294] Interestingly, the influence of impaired kidney function on the plasma leptin concentration is less pronounced in noninflammatory acute renal failure than in CKD, suggesting the participation of the other factors influencing leptin secretion in this state.[295]

It was shown that the decreased leptin clearance by insufficient kidneys leads to its accumulation in the circulation.[296,297] Results of kinetic studies suggest that the renal metabolism of leptin involves an active uptake of leptin by the renal tissue.[298] Cumin et al.[299] studied changes of plasma leptin concentration in Zucker obese rats subjected to a bilateral nephrectomy or a bilateral ureteral ligation. A bilateral ureteral ligation reduced glomerular filtration by increasing tubular pressure. Following the bilateral nephrectomy in these experiments, plasma leptin concentrations increased by 300%, a value much higher than only the 50% increase after a bilateral ureteral ligation. Results of this elegant experimental study suggest that leptin elimination is only partly dependent on glomerular filtration.[299] Therefore, renal elimination is not necessarily affected by the disease in direct proportion to changes in glomerular filtration.

The increased plasma leptin concentration in CKD is not due to oversecretion of this protein. It was shown that leptin gene expression in adipocytes in CKD patients is lower than in healthy individuals.[300] Leptin plasma concentrations are not reduced by low-flux dialysis membranes, whereas high-flux dialysis membranes decrease leptin levels.[301] CAPD patients are characterized by higher plasma leptin concentrations than hemodialysis patients.[302]

There is growing evidence that leptin, originally considered exclusively as an anorexigenic hormone, exerts actions in the periphery outside of the central nervous system.

Indeed, leptin receptors are found in many tissues. It was initially thought that hyperleptinemia was an adequate explanation for anorexia in CKD patients.[303] However, subsequent studies addressing the relation between nutritional status and plasma leptin concentration in CKD yielded conflicting results.[304,305] Therefore, the role of high plasma leptin concentration in anorexia and malnutrition in CKD patients is not proved. Leptin stimulates the proliferation and the differentiation of hematopoietic stem cells.[306] It is likely that the effects of leptin and erythropoietin are synergistic. It deserves consideration whether high plasma leptin concentrations in CKD patients counteract the development of anemia when a plasma erythropoietin concentration is relatively decreased.

Leptin may also participate in CKD progression. It was shown in rats that leptin infusion led to the increase of glomerular TGF-β and collagen intravenous (IV) expression and to the enhancement of proteinuria.[307]

Apart from this, leptin likely plays a pathophysiologic role in hypertension, cardiovascular diseases, and endothelial dysfunction.[308] Leptin receptors are highly expressed in carotid plaques while they correlate with macrophage density. Leptin may contribute to the development of hypertension mainly through increased sympathetic nervous activation both centrally and at the kidney; endothelial dysfunction through the regulation of blood vessel tonus and imbalance between endothelial nitric oxide synthase (eNOS) expression and intracellular L-arginine; and atherogenesis through the stimulation of platelet aggregation, inflammation, endothelial dysfunction, neointimal hyperplasia, and vascular smooth muscle cell (VSMC) proliferation and migration.[308] Whether the hyperleptinemia seen in CKD contributes to the uremic cardiovascular risk is unexplored.

Adiponectin

Adiponectin is one of the protein hormones secreted by adipocytes, which circulate in the bloodstream in relatively high concentrations (almost 0.01% of total plasma protein) with presumed antiatherogenic and insulin-sensitizing properties. Within the circulation, adiponectin is present as a wide range of multimers: from trimers (low molecular weight [LMW]), hexamers (medium molecular weight [MMW]), to dodecamers or 18-mers (high molecular weight [HMW]). It was demonstrated that HMW is the most active form of adiponectin to improve insulin sensitivity. In hemodialysis and peritoneal dialysis CKD patients, plasma adiponectin concentrations are approximately 3 times higher than in healthy subjects.[309] Impaired kidney function does not affect the relative proportion of plasma fractions of adiponectin (i.e., HMW, MMW, or LMW adiponectin).[309] Also, the expression of receptors for adiponectin in CKD patients is preserved and similar to those observed in healthy subjects.[310] The increased plasma adiponectin concentration in CKD patients is due to the disturbances of its renal biodegradation and elimination. The kidney is the main organ participating in the biodegradation and elimination of adiponectin from circulation. Thus, as expected, successful kidney transplantation is accompanied by a prompt reduction of plasma adiponectin concentration.[311] Another piece of evidence is provided by the inverse relationship between plasma adiponectin concentration and GFR in apparently healthy individuals,[312] mild or moderate CKD,[313] and kidney transplant patients.[314] Iwashima et al.[309] showed a gradual increase of plasma adiponectin concentration in parallel to the stages of CKD. An additional argument supporting renal elimination of adiponectin is the lower concentration of this protein in plasma samples from renal veins than in samples from the aorta.[315] The increased plasma adiponectin concentration in CKD patients cannot be explained by its oversecretion by adipose tissue. The expression of adiponectin gene (ApM1) in adipocytes is even decreased in patients with advanced CKD.[316] A possible cause of lower adiponectin gene expression in CKD patients is the frequently coexisting microinflammation, increased oxidative stress in these subjects, and increased sympathetic nervous activity.[317]

It has been shown that in hemodialyzed patients, similarly to subjects with normal kidney function, lower plasma adiponectin concentrations are associated with cardiovascular complications, such as coronary artery disease or peripheral arterial occlusive disease.[318,319] Similarly, plasma adiponectin concentrations in peritoneal dialysis patients with carotid artery plaque were lower than in those without.[320] Moreover, in hemodialyzed patients, an inverse relationship was found between plasma adiponectin concentrations and intima-media thickness of the common carotid artery, which is an early marker of atherosclerotic changes.[321] Even in interlobular kidney arteries, the presence and complexity of arteriosclerotic lesions was negatively related to plasma adiponectin concentration as demonstrated by Iwasa et al.[322] in kidney biopsies of patients with immunoglobulin A (IgA) nephropathy.

Zoccali et al.[323] showed that low plasma adiponectin concentrations are a new risk factor for cardiovascular morbidity in hemodialysis patients. This observation was confirmed in peritoneal dialysis patients[324] and in mild-to-moderate CKD.[313] However, more recent studies[325–327] show contradictory results.

Animal experiments suggest that adiponectin normalizes albuminuria and improves podocyte foot process effacement. Therefore, it could be hypothesized that a high plasma adiponectin concentration slows CKD progression. However, current clinical evidence suggests that high, not low, adiponectin is associated with CKD progression at least in patients with diabetic kidney disease.[325,328]

Trying to reconcile the previously described contradictions, it has been proposed that increased adiponectin may be a reflection of a reparatory response to the microvascular insults in CKD.[308]

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