CHAPTER

85 Dietary Factors in the Treatment of Chronic Kidney Disease

Sreedhar A. Mandayam • William E. Mitch • Joel D. Kopple

INTRODUCTION

Our goal is to provide the reader with an understanding of how chronic kidney disease (CKD) induces metabolic aberrations and how introducing nutritional factors can improve these metabolic problems. Achieving this goal requires knowledge about how the requirements of different nutrients change with the different stages of CKD. For example, diabetes is the most frequent cause of CKD and the incidence of diabetes is growing. In part, this is occurring because of the increasing prevalence of obesity. Clearly, both diabetes and obesity require the manipulation of the diet to improve health and to prevent adverse outcomes. In addition, diabetes and/or obesity is frequently accompanied by high blood pressure and diffuse vascular complications. If the salt intake of these individuals is not controlled, antihypertensive drugs tend to become ineffective.[1,2] There also are the consequences of progressively accumulating waste products leading to uremia (literally, urine in the blood). Because these waste products arise mainly from the metabolism of protein, it is not surprising that symptoms of CKD can be successfully reversed by controlling protein intake.[3–5] Besides ensuring that nutrient requirements are met, the nephrologist must understand how to monitor compliance and how to deal with the progressive loss of kidney function. As will be discussed, there remains uncertainty about the influence of dietary modification on the progression of CKD. Regardless, this is not the sole reason to manipulate the diet of a CKD patient.[6] Other reasons include correcting acidosis, preventing or ameliorating protein-energy wasting (PEW), suppressing uremic bone disease, combating hypertension, and reducing the accumulation of waste products and thereby mitigating uremic syndrome.[7,8] Ignoring these aspects of patient care hastens the need to begin dialysis. But several studies have demonstrated that initiating dialysis earlier (e.g., at glomerular filtration rates [GFR] of about 10 to 12 mL per minute) does not improve the mortality associated with CKD nor does it reduce the complications of CKD.[9–12] This makes it even more important to use dietary modification to prevent the complications of CKD.

Are there specific problems arising in CKD patients attributable to inadequate attention to nutritional principles? Among such problems, there is uremic bone disease. This complication has become more prominent, in part related to a recent and dramatic increase in phosphate additives to processed food.[13] In addition, hyperphosphatemia reduces the effectiveness of angiotensin-converting enzyme (ACE) inhibitors in slowing the loss of kidney function.[14] Likewise, adding sodium chloride to foods, particularly processed foods or fast foods, is a major contributor to increasing difficulties in managing hypertensive patients.[1,15] Another major diet-related problem is the accumulation of waste products when the dietary protein of a CKD patient is unrestricted.[8,16] For example, metabolic acidosis arises from the metabolism of amino acids in protein and acid excretion falls as function is lost.[7] This problem is raised because simply correcting the serum bicarbonate improves protein metabolism, calcium metabolism, and possibly, the progression of CKD.[17–22] Complicating dietary planning are the reports that the average intake of energy, calcium, and a number of vitamins may be inadequate in CKD patients. In short, attention to the diet of patients with CKD is not simply an intellectual exercise; it can produce rapid and sustained benefits as long as the adequacy of the diet is ensured.[6]

The need for and approaches to manipulation of the diet will depend on the degree of renal insufficiency. The most widely used classification of the degree of CKD was developed by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Committee and includes a level signifying an increase in the risk of progressive loss of kidney function (i.e., individuals with an estimated GFR [eGFR], of $<$60 mL/min/1.73 m^2). Notably, those with higher eGFR values can still develop complications of CKD.[23] The variables used in the equations that estimate GFR include age, serum creatinine, sex, and race and the interpretation of the eGFR level has several limitations. First, it was derived from individuals in the United States with established kidney disease but without severe PEW or morbid obesity. Second, there is evidence that the equations are inaccurate for other regions of the world, including Asia and Latin America.[24–26] Third, the boundaries

for the stages of renal insufficiency are somewhat arbitrary; it seems unlikely there is an absolute threshold identifying all patients who will develop progressive CKD. Fourth, certain activities can acutely reduce GFR (e.g., hypertension therapy with blockers of the renin–angiotensin system [RAS], a very low protein diet). In this case, the stage of CKD can change even though kidney damage has not occurred. Nonetheless, this system can identify patients for whom interventions, including dietary modification, could improve their overall health.

METABOLIC CHANGES IN CHRONIC KIDNEY DISEASE AND TOXINS IN OR DERIVED FROM NUTRIENTS

Although it is possible for one toxin or group of toxins to be responsible for specific signs and symptoms of uremia, the interaction of many toxins more commonly causes the problems of CKD. For example, it was reported that a combination of products of protein metabolism (urea, magnesium, acetoin, 2, 3-butylene-glycol, sulfate, creatinine, T-cresol, and guanidine) impairs oxidative metabolism in slices of the cerebral cortex. When studied at the same concentration but separately, however, none of the potential toxins exerted adverse effects on metabolism.[27] There are a large number of potential uremic toxins: in 2003, the European Uremic Toxin Work Group (EUTOX) identified 90 potential toxins that are accumulated in patients with CKD. Proving they are toxic has been difficult. Bergström [28] noted that the requirement for identifying a uremic toxin should include: (1) its chemical identity; (2) a concentration higher in tissues or plasma from uremic patients compared to levels in normal subjects; (3) a concentration should correlate with specific uremic signs or symptoms that are improved when the substance is removed; and (4) its toxicity in tissues, cells, etc. should be demonstrable at the concentration present in tissue or fluids from uremic patients. Few putative compounds have met these criteria.

Urea

There is some evidence that urea is toxic, but it is difficult to test for toxicity because the short half-life of urea makes it difficult to maintain a high level in blood and tissues. Nephrectomized dogs were treated with peritoneal dialysis and the serum urea nitrogen (SUN) level was raised to ~200 mg per deciliter by adding urea to the dialysate; the dogs developed weakness, anorexia, and decreased attentiveness.[29] Continued therapy led to vomiting, hemorrhagic diarrhea, hypothermia, and death. In humans undergoing maintenance hemodialysis (MHD), a similar strategy was used to increase the urea concentration in the dialysate: at serum urea nitrogen (SUN) levels of 140 to 200 mg per deciliter most patients developed malaise, lethargy, and some evidence of bleeding.[30] Consistent with the idea that urea is toxic at high levels is the recent report that urea can stimulate reactive oxygen species (ROS), leading to insulin resistance.[31] In patients with CKD, insulin resistance could lead to accelerated muscle wasting (see the following).

Urea toxicity could arise following its decomposition to ammonia or cyanate adducts. Cyanate can condense with NH_2-terminal amino groups and amides, altering the tertiary structure of proteins and, hence, interfering with enzyme activity. For example, a variety of lipids are carbamylated to form toxins, including 3-carboxy-4-methyl-5 propyl-2-furaproprionic carboxy-4methyl-5propyl-2furapropionic (CMPF) acid, a major cause of altered drug protein binding in uremia.[32,33] Still, the role of protein carbamylation in uremic toxicity is unsettled.[34] Finally, urea is converted to ammonia and carbon dioxide largely by bacterial ureases, but this does not raise blood ammonia substantially, at least in patients with normal hepatic function.[35] The kidney is another contributor to body ammonium levels but this function is markedly reduced or lost in kidney failure. Thus, hyperammonemia rarely occurs in kidney failure.

LOSS OF NONEXCRETORY KIDNEY FUNCTION AND TOXIC METABOLITES OF PROTEIN

At first glance, many of the manifestations of CKD appear to be due to small, water-soluble toxins that are cleared by hemodialysis or peritoneal dialysis because the removal of urea by dialysis reverses several uremic complications. Besides problems related to urea accumulation, the retention of salt leads to extracellular volume expansion, hypertension, cardiac dilatation, sympathetic nervous system activation, and inflammatory cytokine production. But, the removal of ions or small molecules is only part of the story. First, the loss of metabolic or endocrine functions of the kidney can cause certain complications of CKD. For example, loss of kidney-produced hormones, such as erythropoietin (EPO) or 1,25 hydroxyvitamin D3, can interfere with metabolic functions. Second, the ability to remove larger molecules (so-called middle molecules [0.5 to 3.0 kD] or larger polypeptides including many hormones and cytokines) is progressively diminished as CKD progresses. This interferes with normal cellular metabolism. A more easily understood example is the accumulation of unexcreted acid arising largely from metabolism of sulfur-containing and phosphate-containing proteins and lipids. Acid accumulation causes an increase in the breakdown of protein and essential amino acids. It also causes insulin resistance and abnormalities in endocrine function, including factors affecting bone metabolism.[17,36–39] Fortunately, these problems are largely prevented when metabolic acidosis is corrected.

Other potentially toxic metabolites of dietary protein can affect kidney function indirectly. For example, phenylalanine metabolites can accumulate when dietary protein is unrestricted; the phenylalanine metabolite, phenyl acetic acid, will inhibit the expression of inducible nitric oxide

synthase (iNOS) and, hence, may contribute to the development of atherosclerosis.[40]

Guanidino-Containing Compounds

Guanidino compounds are potent organic bases that accumulate in the sera and tissues of uremic patients.[41,42] Their production rises with excess protein intake. However, the production of guanidinosuccinic acid also increases in renal failure independent of protein intake, thus underscoring the metabolic complexities induced by CKD.[43,44] The controversy around the identification of uremic toxins such as guanidine compounds arises in part because of the difficulty measuring the plasma and tissue concentrations of guanidino compounds.[42] In uremic patients, plasma levels may be as high as 8 to 10 mM, but corresponding tissue levels have not been documented. Certain guanidino compounds can have neurotoxic effects: guanidine and methylguanidine are implicated in the development of peripheral neuropathy, and γ-guanidinobutyric acid, taurocyamine, homoarginine, and α-keto-δ-guanidinovaleric acid lower the seizure threshold of experimental animals.[45] The central nervous system excitatory effects of uremic guanidino compounds may reflect an inhibition of depolarization at γ-aminobutyric acid (GABA) receptors, selective activation of N-methyl-D-aspartate (NMDA) receptors by guanidinosuccinic acid, and an intrinsic depolarizing response.[46]

The Arginine Derivative Asymmetric Dimethylarginine

Asymmetric dimethylarginine (ADMA) derived from arginine can inhibit NOS, and its concentration rises in patients with CKD to decrease nitric oxide (NO) and impair vascular responses.[47,48] In experimental animals, ADMA is associated with concentration-dependent pressor and bradycardic responses and vasoconstriction.[49] In CKD patients, a decrease in the actions of NO because of a high ADMA level could aggravate hypertension and, possibly, the progression of renal failure.[50] Despite these intriguing reports, the influence of ADMA on cardiovascular disease is controversial.[48]

Products of Bacterial Metabolism

Uremic toxins can be produced by gut bacteria, and their absorption may be promoted by an increase in the permeability of the gastrointestinal mucosa.[51] The potential of these processes is great because of the huge mass of bacteria (there are more bacterial cells in the colon than in the rest of the human body). Specific uremia-associated problems include bacteria-produced nitrogen-containing waste products and aromatic compounds as well as aliphatic amines (e.g., phenols, indoles, aliphatic amines). With normal kidney function, these compounds do not accumulate because they are rapidly cleared by the kidneys. But, with CKD, some compounds (indoxyl sulfate, hippuric acid, p-cresol, and 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid) initiate toxic reactions in the brain or even contribute to progressive loss of kidney function.

Aromatic Amines

Tryptophan is touted as a major precursor of uremic toxins. It, along with aromatic amines, undergoes deamination and decarboxylation by gut bacteria, yielding metabolites such as indole, indoxyl, skatole, skatoxyl, indican, and indoleacetic acid. Their potential toxicity has been tested by feeding large amounts of the potential toxin and observing changes in organ functions. In the case of indoxyl sulfate, uremic rats were treated with a proprietary resin that absorbs it and other metabolites. The resin not only reduced plasma and urinary levels of indoxyl sulfate, but it also improved metabolism of the kidney and reduced the progression of renal failure.[52] In the United States, a randomized clinical trial of its effectiveness to retard the progression of CKD has shown promise with minimal toxic reactions.[53] This has led to plans for a more extensive trial. Aromatic amines could also exert toxicity by interfering with the binding of drugs to serum proteins yielding abnormal responses at doses used for normal adults. Aromatic amines could also serve as false neurotransmitters.[54] The infusion of phenol or p-cresol into dogs causes a variety of neurologic symptoms, whereas conjugated phenols can inhibit ATPases and ion transport systems to interfere with cellular metabolism.[55] p-Cresol can inactivate β-hydroxylase to interfere with the transformation of dopamine into norepinephrine to develop impaired macrophage function.[56,57]

Aliphatic Amines

Aliphatic amines such as monomethylamine are derived from the metabolism of creatinine. Alternatively, bacterial metabolism of choline or lecithin produces tertiary methylamines that can then be converted to form secondary methylamines.[58] Secondary methylamines accumulate in the blood, the cerebrospinal fluid, and brain tissue, but toxicity has not been demonstrated.

In summary, dietary protein is initially broken down into peptides and amino acids. These compounds in turn can be metabolized by bacteria in the gastrointestinal tract generating compounds that are absorbed. There is evidence that sufficiently high levels of these compounds could impair the function of different organs. However, it has been difficult to assign specific toxic reactions to these compounds because of: (1) difficulties in measuring their concentrations in specific tissues; and/or (2) toxic reactions that could be caused by direct interference with cell functions or through indirect actions that decrease organ function.

Nephrotoxic Compounds Derived from Dietary Protein

In 1905, Folin[59] pointed out that the principal metabolic response to a change in dietary protein intake is a parallel change in urinary urea excretion. This has been confirmed in normal adults and patients with CKD.[60,61] Many of the degradation products of dietary protein are excreted primarily by the kidney. Consequently, products arising from the metabolism of protein will accumulate in patients in direct

proportion to the amount of protein eaten and in inverse proportion to the degree of kidney failure. The accumulation of these compounds is in large part responsible for the symptoms and complications of CKD because decreasing dietary protein improves these symptoms.[3–6,62] Therefore, dietary counseling should be directed at reducing the SUN, but only following an assurance that adequate amounts of protein and energy are provided.

Illustrative examples of the principle that excess dietary protein participates in the generation of uremic toxicity are indoxyl sulfate and uric acid. Indoxyl sulfate arises from the metabolism of indoles such as dietary tryptophan.[52] Experimentally, indoxyl sulfate can accelerate kidney damage in models of glomerular sclerosis.[63] As indicated previously, a clinical trial was directed at assessing whether removing indoxyl sulfate by ingested activated charcoal will slow the progression of CKD.[64] Uric acid can contribute to the complications of CKD; a 12-year study of 47,150 previously normal men indicated that diets with high levels of meat or seafood were associated with an increased risk of gout.[65] This is relevant because Johnson and colleagues[30] have described an important association between an increase in uric acid and the development of hypertension. Untreated hypertensive adolescents were found to exhibit a correlation between systolic blood pressure and serum uric acid ($r = 0.8$).[66] In some of these adolescents, their hypertension was largely corrected by administering allopurinol. Notably, in CKD patients, serum uric acid does not rise to the level expected from the degree of lost kidney function because there is extensive metabolism of uric acid, presumably by bacteria in the gastrointestinal tract.[67] The degree to which dietary protein restriction modifies the serum uric acid of CKD patients has not been established, but there is the possibility that allopurinol treatment can help preserve renal function in patients with CKD.

MECHANISMS THAT REGULATE BODY PROTEIN STORES

Robust metabolic mechanisms act to maintain body protein mass following a change in protein intake. These act rapidly and precisely to adjust the rates of amino acid and protein metabolism. Specifically, when dietary protein falls, the major metabolic response is a suppression of the degradation of essential amino acids (EAAs). This response will help to maintain an adequate supply of EAAs for protein synthesis. The ability to decrease EAA degradation, however, is limited, reaching a minimum level when the amount of protein being eaten is at a level that is just adequate for achieving nitrogen balance (i.e., ~0.6 g protein per kilogram of ideal body weight per day). If dietary protein falls further, there also are adaptive responses that suppress protein degradation (protein synthesis may also increase but is less consistently found compared to a decrease in protein degradation). These responses limit the loss of protein stores and are active in normal adults or CKD patients as long as there are no complications such as acidemia or other catabolic illnesses.[68–70] Similar adaptive responses are also active in patients with the nephrotic syndrome.[71]

Protein Metabolism and Protein Stores

All intracellular and extracellular proteins are continually turning over, being degraded to their constituent amino acids and replaced by the synthesis of new proteins. The rapidity of the turnover of individual proteins varies widely, from minutes for some regulatory enzymes or transcription factors, to days or weeks for proteins like actin and myosin in skeletal muscle and months for hemoglobin in red blood cells. The rate of the degradation of proteins must be specific and highly regulated. Otherwise, countless cellular functions as well as the maintenance of protein stores (e.g., in muscle) would be jeopardized. Evidence that these processes are highly regulated includes the following: (1) The daily rates of protein turnover are enormous (3.7 to 4.7 g/kg/day) and therefore, even a small but sustained decrease in the synthesis of proteins or acceleration of protein degradation would result in marked loss of protein stores.[72] (2) Precise changes in the levels of proteins are required for the minute-to-minute regulation of transcriptional events or metabolic pathways. It is surprising, therefore, that the majority of intracellular proteins in all tissues is degraded by a single proteolytic system, the ATP-dependent, ubiquitin-proteasome system (UPS).[72] This specialized system exhibits remarkable specificity by individual proteins for degradation.

The Ubiquitin-Proteasome System

The initial processes of protein degradation by the UPS involve a series of three enzymes that link ubiquitin (Ub) onto proteins.[72,73] The single E1 isoform (Ub-activating enzyme) uses ATP to activate Ub and then transfers Ub to one of 20 to 40 isoforms of the E2 Ub-carrier proteins (Fig. 85.1). These reactions provide some specificity for the degradation of substrate proteins; a specific E2 Ub-carrier conjugates with only some of the more than 1,000 different E3 enzymes. This third enzyme, an E3 Ub-protein ligase, is the key determinant of the specificity of proteolysis; a specific E3 Ub-ligase recognizes a specific protein substrate (or possibly specific classes of proteins) and transfers Ub to a lysine in the protein. This process is repeated until the initial Ub is increased to form a chain of four to five Ubs attached to the substrate protein. This poly-Ub chain is recognized by the 26S proteasome. It also uses ATP to degrade the substrate protein. The proteasome is a very large organelle consisting of >60 proteins that create a 20S, barrel-shaped particle with 19S regulatory particles at either or both of its ends. The 19S regulatory particles not only recognize polyubiquitin chains, but when ATP is present, the 26S proteasome also cleaves the poly-Ub chain from the doomed protein and unfolds the protein's tertiary structure. In the next step, the unfolded substrate protein is translocated through a tunnel-like structure into the 20S particle where it is degraded into peptides. The peptides are released into the cytoplasm and

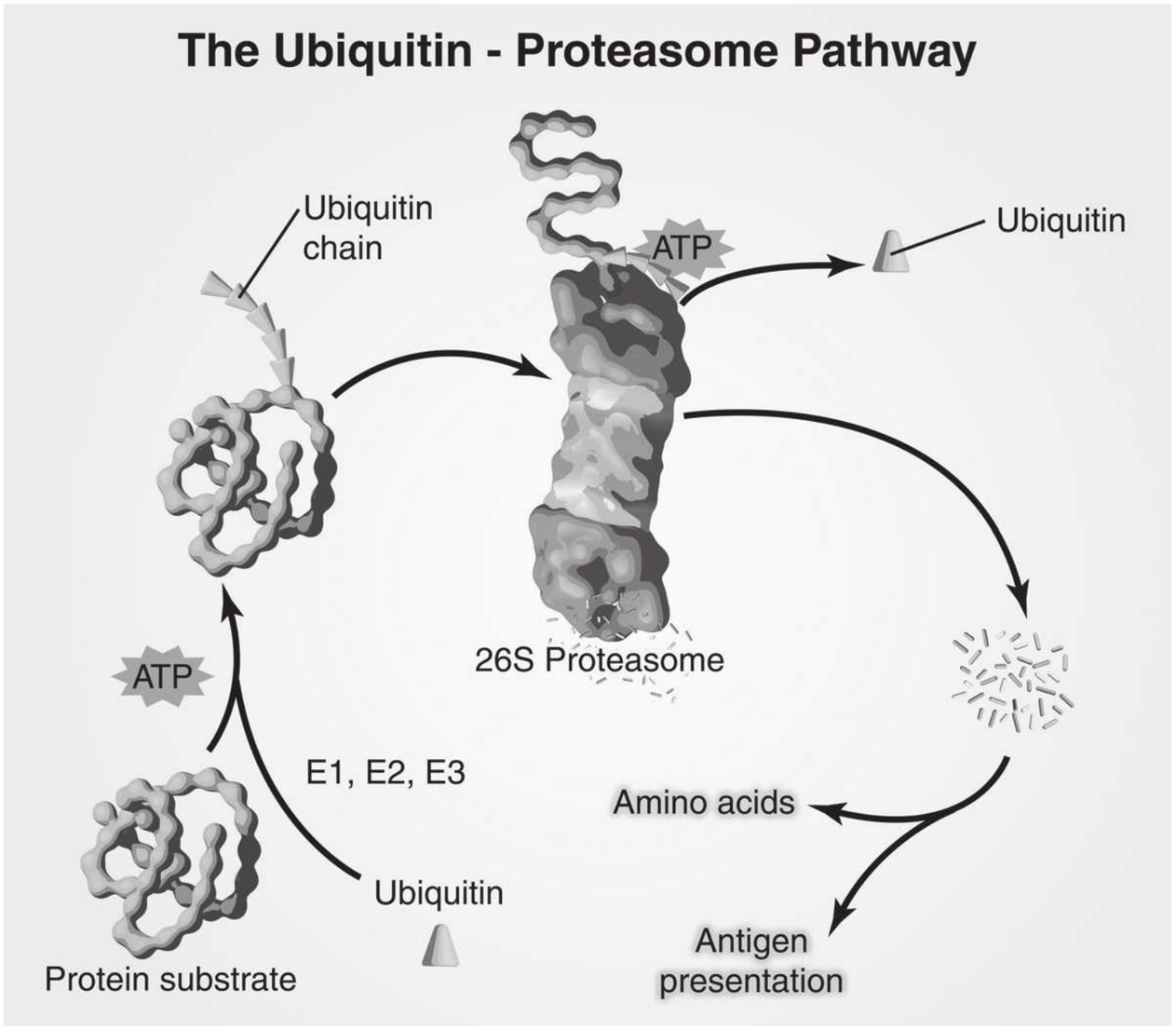


FIGURE 85.1 An illustration of the major components of the ubiquitin–proteasome system. (Lecker SH, Goldberg AL, Mitch WE. Protein degradation by the ubiquitin-proteasome pathway in normal and disease states. *J Am Soc Nephrol.* 2006;17:1807–1819.)

are converted to amino acids by peptidases.[73] The importance of these processes is underscored by the awarding of the 2004 Nobel Prize to Avram Hershko, Aaron Ciechanover, and Irwin Rose for discovering this system (http://nobelprize.org/chemistry/laureates/2004/).

Recent results have uncovered insights into the proteolytic processes that regulate muscle protein breakdown by the UPS and by mechanisms separate from the UPS. For example, in muscle wasting conditions, the expression of two E3 Ub-conjugating enzymes, Atrogin-1 (also known as MAFbx) and MuRF-1, are critical for the breakdown of muscle proteins.[73,74] In models of muscle wasting conditions, the expression of Atrogin-1 and MuRF-1 are increased 8- to 20-fold, serving as a sign that muscle protein breakdown is accelerated.[75,76] The signals that activate these E3 Ub-conjugating enzymes have been extensively studied and at least two transcription factors have been identified as regulators of Atrogin-1/MAFbx and MuRF-1 expression: the Forkhead transcription factors (FoxO) and the inflammatory transcription factor, nuclear factor-kappaB (NF-κB).[73,74]

At least five functions of the UPS have been identified as crucial for maintaining normal cellular functions: (1) It permits cells to adapt rapidly to physiologic changes because the UPS rapidly removes proteins to terminate an enzymatic or regulatory process. (2) The UPS can change gene expression by degrading transcription factors or cofactors/inhibitors that regulate transcription (e.g., the UPS degrades I-κB to activate NF-κB and accelerate inflammatory processes).[73] (3) The UPS eliminates misfolded or damaged proteins (e.g., the mutant transmembrane conductance regulator protein [CFTR] is selectively degraded by the UPS so it does not reach the epithelial cell surface in patients with cystic fibrosis). (4) The UPS presents antigen to the major histocompatibility complex, class I molecules, thereby participating in immunologic responses. (5) The UPS degrades cellular proteins (including muscle proteins), which are used in gluconeogenesis when energy intake is inadequate or in response to catabolic illnesses.

Chronic Kidney Disease Initiates Mechanisms That Cause a Loss of Muscle Protein

Epidemiologic evidence indicates that CKD is associated with a decrease in muscle and fat mass, which in turn is associated with an increased risk of morbidity and mortality.[77] The mechanisms causing protein wasting include CKD-induced acceleration of the degradation of proteins due to defective responses to insulin or insulin growth factor 1 (IGF-1) intracellular signaling. Other stimuli causing protein losses include the accumulation of acid (Table 85.1). In addition, an excess of angiotensin (Ang) II, impaired function of muscle precursor cells (i.e., satellite cells), and/or activation of the muscle protein, myostatin, which is synthesized in muscle and modulates muscle growth, stimulate the loss of protein stores. Although there is evidence that each of these factors controls muscle protein metabolism, it is likely that they often act together to cause a loss of muscle mass.

When is a loss of muscle mass suspected? Besides a loss of body weight, the principal evidence for subnormal protein stores has been hypoalbuminemia. The finding of hypoalbuminemia in CKD patients is generally presumed to be attributable to protein malnutrition.[78,79] However, malnutrition is defined as abnormalities related to an insufficient amount of protein, energy, or other nutrients in the diet or to an imbalance among dietary nutrients.[80] There are at least two reasons that the muscle wasting associated with CKD is not caused

85.1 Evidence That Metabolic Acidosis Induces Protein and Amino Acid Catabolism in Normal Infants and Children as Well as Chronic Kidney Disease Patients

Subjects Investigated	Measurements of Effectiveness	Outcome of Trial
Infants[226]	Low birth weight, acidotic infants were given $NaHCO_3$ or NaCl	$NaHCO_3$ supplement improved growth
Children[227] with CKD	Children with CKD had protein degradation measured	Protein loss was ~twofold higher when HCO_3 was <16 mM compared to >22.6 mM
Normal adults[228]	Induced acidosis and measured amino acid and protein metabolism	Acidosis increased amino acid and protein degradation
Normal adults[108]	Induced acidosis and measured nitrogen balance and albumin synthesis	Acidosis induced negative nitrogen balance and suppressed albumin synthesis
CKD[229]	Nitrogen balance before and after treatment of acidosis	$NaHCO_3$ improved nitrogen balance
CKD[22]	2 years $NaHCO_3$ therapy vs standard care	Slowed loss of creatinine clearance and improved nutritional status
CKD[17]	Essential amino acid and protein degradation before and after treatment of acidosis	$NaHCO_3$ suppressed amino acid and protein degradation
CKD[230]	Muscle protein degradation and degree of acidosis	Proteolysis was proportional to acidosis and blood cortisol
CKD[231]	Nitrogen balance before and after treatment of acidosis	$NaHCO_3$ reduced urea production and nitrogen balance
CKD[22]	Protein stores after $NaHCO_3$ treatment to slow progression	Serum proteins and weight improved
Hemodialysis[103]	Protein degradation before and after treatment of acidosis	$NaHCO_3$ decreased protein degradation
Hemodialysis[109]	Serum albumin before and after treatment of acidosis	$NaHCO_3$ increased serum albumin
CAPD[104]	Protein degradation before and after treatment of acidosis	$NaHCO_3$ decreased protein degradation
CAPD[106]	Weight and muscle gain before and after treatment of acidosis	Raising dialysis buffer increased weight and muscle mass

CKD, chronic kidney disease; CAPD, continuous ambulatory peritoneal dailysis.

by malnutrition per se: first, if protein malnutrition were the cause of defects in protein stores, then the abnormalities should be corrected by simply altering the diet. This hypothesis has been examined and found to be wanting: Ikizler et al.[81] measured rates of protein synthesis and degradation in fasting hemodialysis patients using labeled amino acid turnover techniques. They studied three protocols and in each instance measured protein metabolism before, during, and at 2 hours after completing dialysis.[82–83]. When dialysis was performed in fasting patients, protein degradation exceeded protein synthesis demonstrating that over days to weeks, these responses would produce a significant loss of body protein stores. In the second protocol, they tested the influence of intravenous parenteral nutrition (IDPN) given during hemodialysis.[82] IDPN did improve both protein synthesis and degradation measured during dialysis, but the increase in protein

degradation persisted at 2 hours following the completion of dialysis. In the third protocol, they tested the effects of an oral nutritional supplement versus IDPN. As before, protein balance improved with both supplements but at 2 hours after completing dialysis, protein balance was still negative.[83] Thus, abnormalities in protein metabolism were not eliminated by simply increasing the intake of protein and calories during dialysis. Others report similar conclusions: in a randomized, controlled trial of responses to IDPN, hemodialysis patients were compared to other hemodialysis patients who were not given a dietary supplement. After 2 years, the supplement had not improved mortality, body mass index, laboratory markers of nutritional status, or the rate of hospitalization.[84] Even though the excessive morbidity and mortality occurring in patients with CKD may not be corrected simply by changing the diet or correcting hypoalbuminemia, it is critical to plan the diet of CKD patients in order to ensure that they receive an adequate amount of protein and energy.[78,80] It is also necessary to avoid an excess of dietary protein because the accumulation of waste products will contribute to complications of CKD, especially in the nondialyzed patient with advanced CKD.[8]

What are the signals in CKD that enhance a loss of protein stores? Recent studies in rodent models of CKD have established that the accelerated muscle wasting involves cellular mechanisms that are similar to those causing muscle wasting in other catabolic conditions, such as cancer cachexia, starvation, insulin deficiency/resistance, or sepsis.[72,73] Common to each of these catabolic states is an acceleration of proteolysis via the UPS, which is presumably augmented by higher levels of messenger RNAs (mRNAs) encoding certain components of the UPS.[36] There are also increases or decreases in the expression of about 100 atrophy-related genes called atrogenes. The latter responses indicate that the mRNAs of atrophy-related genes in muscle wasting states are due to changes in gene transcription yielding a common transcriptional program that involves various growth-related genes in atrophying muscle.[85] The strongest evidence for the activation of the UPS in muscles of animals undergoing CKD-induced atrophy from catabolic diseases is that inhibitors of the proteasome block the increase in protein degradation in muscles isolated from rodent models of catabolic diseases.[36,86,87]

In CKD, abnormalities identified as signals that stimulate protein degradation in muscle include the development of metabolic acidosis, defects in insulin/IGF-1 intracellular signaling, or an increase in Ang II levels.[88–90] All three conditions cause muscle atrophy in rodents. Finally, CKD patients frequently have high circulating levels of inflammatory cytokines and this has been shown to cause accelerated muscle protein degradation at least in part by impairing insulin or IGF-1 signaling in muscles.[91,92]

Caspase-3 and Muscle Wasting in Chronic Kidney Disease

Muscle atrophy in catabolic conditions specifically affects contractile proteins, which comprise about two-thirds of the protein in muscle. Notably, the ubiquitin protease system (UPS) readily degrades major components of the myofibril (actin, myosin, troponin, or tropomyosin). But when these same proteins are present in complexes or in intact myofibrils, they are degraded very slowly by the UPS.[93] Therefore, other proteases must initially cleave proteins to break down the complex structure of muscle. The protease functioning in this fashion is caspase-3.[94] Notably, caspase-3 cleaves actomyosin in vitro, and it is stimulated in cultured muscle cells, where myofibrillar proteins are cleaved and subsequently degraded by the UPS. Caspase-3 activation produces a footprint of its activity, a 14kD C-terminal fragment of actin that is found in the insoluble fraction of muscle.[94] For example, accumulation of the 14-kD actin fragment is found in muscles of animals with accelerated protein degradation due to acidosis, diabetes, and Ang II–induced hypertension.[89,94,95] Likewise, the 14-kD actin fragment can be found in muscles of patients with CKD or other causes of muscle wasting. The level of the 14-kD actin fragment in muscle of CKD patients was found to decrease in response to an exercise program directed at increasing the patient's endurance. The level of the fragment was also highly correlated ($r = 0.78$) with the measured rate of protein degradation in muscles of patients undergoing hip replacement for osteoarthritis. Finally, the 14-kD actin fragment that was present in unburned muscle of patients who had a major burn injury to another area of the body was sharply increased.[96] Thus, the level of the 14-kD fragment seems to be closely related to the rate of protein degradation and is present in specific disorders characterized by muscle wasting. Additional testing will be needed to determine if this method could serve as a biomarker of accelerated muscle protein degradation in other conditions causing muscle wasting.

Signals Triggering Muscle Wasting in Chronic Kidney Disease or Other Catabolic States

CKD is associated with several complications that can trigger the UPS to degrade muscle protein, and there is evidence that these complications can function in concert to cause muscle wasting. Metabolic acidosis stimulates muscle protein breakdown by the UPS, but only when there is a concomitant increase in glucocorticoid production and development of insulin resistance.[97,98] Glucocorticoids are also required for the accelerated protein degradation that occurs in models of diabetes, high levels of Ang II, and sepsis.[90,99,100]

Impaired insulin/IGF-1 intracellular signaling is another stimulus for accelerated muscle protein breakdown. The mechanism involves the decreased activation of the phosphatidylinositol 3-kinase(PI3K)/Akt pathway.[89] Specifically, when insulin or IGF-1 signaling is low, PI3K activity falls, reducing the production of phosphadidylinositol-3,4,5 phosphate, the active product of PI3K. This results in decreased phosphorylation and activity of the serine/threonine kinase, Akt, leading to decreased phosphorylation of downstream kinases, gycogen synthase kinase 1 (GSK1) and mTOR/S6kinase, and suppression of protein synthesis.

Decreased PI3K/Akt signaling is a key step that stimulates protein degradation in muscle. Decreased PI3K/Akt signaling induces the expression of caspase-3 and the E3 Ub conjugating enzymes, Atrogin-1 and muscle ring finger protein 1 (MuRF-1), to enhance muscle protein degradation.[89] Expression of these E3 enzymes occurs because there is decreased phosphorylation of the Forkhead family of transcription factors (FoxO1, 3, 4). When these factors are not phosphorylated, they migrate into the nucleus to stimulate the transcription of Atrogin-1 and, potentially, other genes involved in muscle metabolism.[89,101,102] Insulin or IGF-1 blocks this process by stimulating the PI3K/Akt pathway to suppress the expression of Atrogin-1. Together, these results provide evidence that muscle wasting in response to the complications of CKD is due to a common signaling pathway that alters key enzymes modulating protein synthesis and degradation.

Are there methods for correcting the abnormalities in muscle protein metabolism that occur in CKD? In a mouse model of CKD, the mice were paired for SUN and weight and treated with either a humanized antibody or peptibody against myostatin or the diluent.[76] Peptibody treatment increased body and muscle weight while raising muscle protein synthesis and suppressing protein degradation. Interestingly, these beneficial responses were accompanied by an increase in the phosphorylation of Akt and a decrease in the circulating levels of tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6). These results suggest that methods could be developed to prevent muscle wasting in CKD patients.

This brief review of changes in muscle protein metabolism caused by progressive CKD emphasizes that activities of caspase-3 and the UPS participate in the turnover of the bulk of proteins in the body. Because the daily turnover of protein is high, even a small but persistent increase in protein breakdown would cause muscle wasting. Specific complications of kidney disease coordinate the activity of proteolytic systems (i.e., caspase-3 and the UPS) to degrade muscle proteins. These responses involve defects in insulin/IGF-1 intracellular signaling pathways and decreased PI3K/Akt signaling, which are initiated by metabolic acidosis or inflammation. In addition, glucocorticoids play a permissive role in stimulating muscle wasting. Understanding these regulatory mechanisms could blunt the muscle wasting that occurs in different catabolic conditions.

Factors Stimulating Loss of Muscle Mass in Chronic Kidney Disease

Abundant clinical evidence indicates that acidemia is an important cause of protein losses (Table 85.1). Reaich et al.[17] found that the rate of protein degradation in acidemic CKD patients is high, but when they were given sodium bicarbonate, protein degradation decreased by 28%. It increased again when the patients developed acidemia in response to eating an equimolar amount of sodium chloride. The stimulatory effect of metabolic acidosis on protein breakdown is also present in hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) patients.[103–105] At least in CAPD patients, increased muscle proteolysis was found to be related to activation of the UPS.[106,107] In normal adults, induction of metabolic acidemia not only increased insulin resistance but also caused negative nitrogen balance and reduced the rate of albumin synthesis.[38,108] Changes in albumin metabolism induced by metabolic acidemia also occur in hemodialysis patients; correcting their serum bicarbonate levels was found to increase serum albumin levels.[109] Despite these reports documenting the catabolic effects of metabolic acidemia, a cross-sectional analysis of dialysis patients suggested there is no relationship between acidemia and hypoalbuminemia, weight loss, etc.[110] There are several problems with this conclusion. First, a cause and effect relationship cannot be evaluated from results of a cross-sectional study.[111] Second, a single serum bicarbonate measurement is not sufficient to define the presence of acidemia, and there are technical problems with measuring serum bicarbonate: a delay in measuring the serum bicarbonate concentration allows for the escape of carbon dioxide, which lowers the bicarbonate artificially.[112] Third, there are many impaired hormonal responses in patients with metabolic acidemia, including the impaired function of growth hormone, the thyroid hormone, and the conversion of vitamin D to its most active form, 1, 25 (OH)2 cholecalciferol.[113–115] All of these could interact and impair the ability of CKD patients to maintain protein stores by indirect mechanisms.

SPECIFIC DIETARY CONSTITUENTS FOR PATIENTS WITH CHRONIC KIDNEY DISEASE

Energy Intake

In patients entering dialysis therapy, anthropometric abnormalities, including suboptimal body weight, could result from an inadequate energy intake.[116–118] Unfortunately, such caloric deficits are difficult to measure; estimates from the resting energy expenditure (REE) may underestimate or overestimate a patient's average activity. Moreover, indirect calorimetry measured during brief periods can yield erroneous conclusions when extrapolated to 24 hours. Estimates of energy intake based on dietary histories or questionnaires can lead to erroneous conclusions.[119,120]

The 1981 Food and Agricultural Organization (FAO)/World Health Organization (WHO)/United Nations (UN) recommended energy requirements based on 11,000 REE determinations made in healthy subjects.[121] But, the regression equations used to derive energy requirements had considerable variability. Extrapolating REE measurements to all activities with this degree of variability suggests caution is required in making decisions based on those types of measurements. Besides these issues, the individual can adapt to different calorie intakes: healthy adults eating an inadequate nutrient intake will decrease their REE value.[122] When normal adults ate diets with barely adequate amounts of EAA, their nitrogen balance improved when energy intake

increased.[123] Well-nourished adults achieve energy balance but only by decreasing their activity. With this adaptation, lean body mass can be lost.[118] Nonetheless, virtually all studies of REE by indirect calorimetry as well as studies based on nitrogen balances indicate that both CKD and maintenance dialysis patients have at least normal energy expenditures during resting or with a variety of activities. Patients with advanced kidney failure and those undergoing MHD or CPD usually have decreased daily physical activity. In normal sedentary adults, total daily physical activity is estimated to account for only about 15% to 25% of total daily energy expenditure. Thus, the reduced physical activity of advanced kidney failure or chronic dialysis patients generally does not result in a major reduction in daily energy expenditure in comparison to sedentary normal people without CKD.

Energy Requirements of Chronic Kidney Disease Patients

Unfortunately, there have been few evaluations of the energy requirements of CKD patients or their responses to a reduced-calorie intake. In one landmark study, the energy expenditure of normal subjects, CKD patients, and hemodialysis patients during rest and exercise revealed no differences among the three groups.[124] Notably, when calorie intake was reduced, energy expenditure did not fall, indicating that CKD patients do not develop a special ability to adapt to a low-calorie intake. Thus, an inadequate energy intake when coupled to dietary protein restriction could cause negative nitrogen balance (i.e., a loss of protein stores).[8] Most studies of energy expenditure in CKD and MHD patients support the thesis that energy expenditure is normal, but one group of investigators reported that energy expenditure on both dialysis and nondialysis days was 7% higher in hemodialysis patients compared to normal adults.[124,125] If, indeed, uremia increases energy expenditure, impaired energy use (e.g. insulin resistance) could cause a loss of lean body mass. This is relevant because patients with serum creatinine values >2.4 mg per deciliter or those who are obese or those with metabolic acidosis can develop insulin resistance and impaired energy use.[2,38,126,127] Fortunately, a low protein diet can actually improve insulin resistance.[3,5,128,129] Regarding this conclusion, energy intake in patients with moderate renal insufficiency in the MDRD study was below 30 to 35 kcal/kg/day yet the loss of body mass was infrequent and only a few patients were withdrawn from the trial because of nutritional considerations.[130] On the other hand, the MDRD study used dietary interviews and diaries to estimate energy intake, methods that can give erroneous results, particularly in CKD or MHD patients.[119,120] Regardless, if a patient is losing weight and there is a history of a low energy intake, additional calories are needed. Intake from such a supplement must be monitored closely because it may lead to an increase in body fat rather than larger stores of protein.[131]

The contribution of a low energy intake to nutritional deficiencies in CKD patients is unclear: CKD outpatients who were eating 16 to 20 g per day of protein plus a supplement of EAA had no change in nitrogen balance when their energy intake was varied between 22 and 50 kcal/kg/day.[132] On the other hand, Kopple et. al.[133] fed six CKD patients a constant, minimal protein intake of 0.55 to 0.60 g/kg/day and measured nitrogen balance while calorie intake was varied from 15 to 45 kcal/kg/day. They concluded that the dietary energy requirement for nitrogen equilibrium for CKD patients who are eating low protein diets should be 35 kcal/kg/day in order to maximize dietary protein use. If CKD patients are at or below their ideal body weight, we believe their energy intake should be 35 kcal/kg/day.[134] For overweight patients, energy intake should be restricted to reduce obesity because obesity causes insulin resistance and impairs the use of protein and calories.[2,120, 131]

Protein Requirements

Nitrogen balance (Bn) is a measurable index of changes in body protein stores and serves as the gold standard for assessing dietary protein requirements. A neutral or positive Bn indicates that the body's protein stores are maintained or increased. For healthy adults engaging in moderate physical activity and eating sufficient calories, the World Health Organization (WHO) used Bn values to conclude that the average requirement for protein of mixed biologic value is approximately 0.6 g of protein per kilogram of body weight per day. This average dietary protein requirement plus 2 standard deviations was assigned as the "safe level of intake," or 0.75 g/kg/d; this value should meet the protein requirements of 97.5% or more of healthy adults.[121] There are two caveats: first, not all normal adults will require this amount of dietary protein, but some will need more than 0.75 g/kg/day. Second, for CKD patients, an increase in dietary protein will increase the production of urea and other waste products. If these compounds are not excreted, uremia will develop.[72,135] Adaptive metabolic responses are activated when dietary protein is restricted (see previous). The presumed origin of these metabolic responses is a decrease in plasma insulin leading to the conversion of body protein stores (principally, skeletal muscle) into amino acids, which are converted to glucose in the liver. Insulin is likely to be one of the most potent mediators of these changes in protein turnover because it suppresses protein degradation in normal or diabetic subjects.[136,137] This could explain why diabetic patients (including those with insulin resistance) being treated by hemodialysis are at increased risk of developing an accelerated loss of lean body mass.[138] Because insulin resistance can be present in patients with serum creatinine levels as low as 2.4 mg per deciliter and because metabolic acidosis can cause insulin resistance, insulin-initiated mechanisms could be a key factor regulating whole body protein metabolism.[38,127] In summary, healthy adults successfully adapt to dietary protein restriction by: (1) suppressing the catabolism of EAA and, possibly, NEAA; and (2) suppressing protein degradation while stimulating protein synthesis. A principal mediator of these changes is likely to be insulin.

Protein Requirements for Chronic Kidney Disease Patients

Patients with advanced CKD that is uncomplicated by metabolic acidemia or inflammation, etc. are remarkably efficient at adapting to dietary protein restriction.[68] In response to the limitation of dietary protein from 1.0 to 0.6 g/kg/day, they reduce amino acid oxidation and protein degradation as well as normal adults. The same adaptive responses occur if the diet is restricted to only 0.3 g/kg/day plus a supplement of essential amino acids or their nitrogen-free analogs (ketoacids). These diets are associated with the maintenance of indices of adequate nutrition during more than 1 year of observation.[69,70] Clinically, it must be recognized that compensatory responses will not fully compensate for an inadequate diet and the diet will cause loss of lean mass. Moreover, diabetic patients may not activate adaptive changes to dietary protein restriction as efficiently as do normal adults or CKD patients. Finally, if CKD is complicated by acidemia or inflammatory or chronic illnesses, patients may not be able to activate an adaptive response to dietary restriction.

Protein Requirements for Nephrotic Patients

Patients who are excreting more than 3 to 5 g of protein per day could be at increased risk for protein wasting because their protein intake may not meet minimal requirements. This does not mean that prescribing an excess of protein will improve protein stores. Unfortunately, a high protein diet actually raises the degree of proteinuria in CKD patients.[139,140] This problem is emphasized because patients eating a well-designed low-protein diet can experience a decrease in proteinuria and an increase in serum albumin concentrations compared to patients fed excessive amounts of protein (see the following). The other problem is that feeding a high protein diet increases the likelihood of developing complications of CKD. The other reason to emphasize this problem is the consensus that the degree of proteinuria is closely related to the risk for progressive kidney and cardiovascular diseases.[141] The other factor to consider regarding dietary protein prescriptions for nephrotic patients is that it can activate the same adaptive responses as CKD patients or normal subjects.[71] This ability leads to neutral Bn of nephrotic patients fed 0.8 or 1.6 g/kg/day (plus 1 g of dietary protein for each gram of proteinuria) and 35 kcal/kg/day of energy. There is evidence that even less dietary protein ($<$0.6 g/kg/day) may not increase the risk of protein wasting in patients with the nephrotic syndrome.[142] In summary, patients with uncomplicated CKD, including those with nephrotic range proteinuria, activate normal compensatory responses to dietary protein restriction by suppressing EAA oxidation and reducing protein degradation. These responses lead to the preservation of lean body mass during long-term dietary therapy. When nephrotic patients excrete $\geq$10 g of protein per day, there are no clear guidelines for manipulating their dietary protein and calories.

Dietary Sodium and Chloride

Normal adults maintain an extracellular fluid volume that changes by $<$1 L (1 kg of body weight) and only have minimal changes in blood pressure despite wide variations in daily salt intake. But, if blood pressure rises when sodium chloride intake increases, a patient is labeled salt sensitive and salt balance occurs only slowly. Notably, salt sensitivity can precede established hypertension and it constitutes a cardiovascular risk factor, complicates antihypertensive therapy, contributes to a progressive loss of kidney function in patients with CKD, exacerbates proteinuria, and diminishes the antiproteinuric responses of patients with kidney disease.[143,144] For these reasons, regulating sodium chloride intake is essential for the treatment of patients who have or who are at risk for high blood pressure, for those with kidney disease, and/or for those with cardiovascular risk factors. Treatment with diuretics generally fails in patients who have no dietary guidelines for salt intake because salt intake can cancel the effectiveness of diuretics.[145] Unfortunately, regulating sodium chloride intake is difficult because salt is added to so many foods; it is estimated that, generally, $>$80% of daily sodium intake is already an integral part of foods.[146,147]

A sodium intake of 2 g per day or 84 mEq per day is widely recommended for patients with hypertension or cardiovascular and kidney diseases. It is important to specify this amount because a no-added-salt diet contains about 4 g of sodium or 168 mEq.[1,148] This level of salt intake exacerbates blood pressure and edema in many CKD patients. Fortunately, a diet of 2 g of sodium per day can be achieved with skilled diet planning.

Salt-sensitive patients with CKD and hypertension can be detected by determining if their blood pressure rises $>$10% when a low salt diet is switched to a high salt diet. The frequency of salt-sensitive individuals (with the exception of some patients with primary interstitial kidney disease) increases with age, especially when renal function is declining.[147,149,150] Salt restriction is especially important in the treatment of hypertensive CKD patients because antihypertensive agents, with the possible exception of calcium channel blockers, are less effective when sodium intake is unrestricted.[151] Because it is an achievable goal, the ideal sodium intake for hypertensive patients is 2 g per day. A decrease in dietary salt can transiently reduce GFR but this usually reverses within a week. Because most dietary salt is already in foods, especially in prepared or fast foods, it is difficult to predict salt intake. Because $\sim$95% of sodium ingested is excreted by the kidneys, the sodium content of a 24-hour urine sample is the best indicator of sodium intake. With fever, strenuous exercise, or diarrhea, and especially in patients with an ileostomy, there can be significant extrarenal sodium losses. To monitor salt intake, CKD patients should weigh themselves daily and record their weight; if weight is declining, it is most likely due to a loss of extracellular salt and water, and contrariwise, if weight is increasing, it is most likely due to an accumulation

of salt and water. In such cases, the diet should be reviewed to determine the source of the unwanted salt. Monitoring body weight is emphasized because sodium excretion fluctuates widely during the day, and a "spot" urine for measurement of the sodium/creatinine ratio does not provide reliable insights into the assessment of dietary salt. Fortunately, even patients accustomed to a high sodium chloride intake experience salt cravings, and they should be reassured that the craving will disappear after a few weeks.[146,152]

In summary, a cornerstone of designing diets for CKD patients is to establish appropriate goals for blood pressure and sodium intake. Home blood pressure recording or ambulatory 24-hour blood pressure recordings are the most reliable in assessing the effectiveness of therapy. Compliance with dietary salt restriction must be monitored by 24-hour urine collections for sodium content. Fortunately, this same collection can be used to determine creatinine clearance and to estimate protein intake from urea excretion (see the following) and the presence of microalbuminuria and other minerals. If sodium excretion is excessive and blood pressure increases, education by the nutritionist and repeated measurements of 24-hour urine sodium collections will make dietary planning easier.

Dietary Potassium

Guidelines from the Institute of Medicine recommend a potassium intake of 4.7 g per day.[153] Fortunately, the ability to excrete this amount of potassium is usually retained until renal insufficiency is very advanced.[154] The ability to eliminate potassium is maintained by increased potassium excretion by both the gut and kidney, making the design of diets to restrict both dietary salt and potassium possible.[154] If hyperkalemia is present, a search is needed to determine if there is acidemia, defects in aldosterone actions, or if treatment has been changed to include nonsteroidal anti-inflammatory drugs (NSAIDs) or blockers of the renin-angiotensin-aldosterone system (RAAS). If these changes are required, dietary potassium must be restricted. The diet is limited to ~1.5 g per day; compliance is monitored from the 24-hour urinary excretion of potassium.

It is fortunate that the ability to excrete potassium is maintained because diets rich in potassium (e.g., fruits and vegetables) reduce the likelihood of developing chronic diseases, such as coronary heart disease and diabetes. Moreover, clinically important reductions in blood pressure have been documented to occur when adults with normal blood pressure or mild hypertension consume a potassium-rich diet. For example, in the DASH (Dietary Approaches to Stop Hypertension) Study,[155] potassium was increased in the diet but a potassium supplement was not supplied. Adults with systolic blood pressures <160 mm Hg and diastolic blood pressure 80 to 95 mm Hg were fed a standard Western diet high in saturated fat and low in fruits and vegetables and calcium. They were then randomly assigned to the same diet, which included a diet rich in fruits and vegetables versus a combined diet rich in fruits, vegetables, and with low-fat dairy products. This last diet had a reduced content of saturated and total fat. For all three groups, sodium intake and body weight were maintained at constant and at similar levels. Systolic and diastolic blood pressures decreased with the fruit and vegetable diet, and a more pronounced reduction in systolic and diastolic pressures occurred with the combination of high fruit and vegetable, and low-fat dairy product diet (−11.4 and −5.5 mm Hg, respectively). The changes in blood pressures were substantially greater in African American participants as compared to Caucasians.[156] This study did not address the effects of these diets in CKD patients but may be applicable because of the adaptations in potassium excretion.

Regarding CKD patients, the National Kidney Foundation's expert panel[157] recommended the restriction of dietary potassium in adults with CKD at stage 4 (estimated GFR <30 mL/min/1.73 m^2). The regulation of the serum potassium concentration at the desired level is complicated because patients with advanced CKD generally have low values of total body potassium, even when the serum potassium is high.[158] More studies are needed to determine the usefulness and dangers of increasing (or limiting) dietary potassium in patients with CKD.

VITAMINS AND TRACE ELEMENTS IN RENAL DISEASE

Micronutrients, vitamins, and trace elements are required for energy production, organ function, and cell growth and protection (e.g., from oxygen free radicals). Consequently, they should be included when planning diets for CKD patients.[159] Besides an insufficient intake, losses of protein-bound elements with proteinuria, decreased intestinal absorption of micronutrients, cellular metabolic changes or circulating inhibitors, and medicines that antagonize some vitamins can cause micronutrient deficiency syndromes. Unfortunately, there is very little information concerning the minimum requirements or the recommended daily allowances (RDA) for these nutrients in CKD patients. For CKD patients, supplements of water-soluble vitamins are routinely prescribed because meat and diary products are routinely restricted in their diets and there can be benefits of a daily supplemental vitamin. The long-term administration of vitamin B6 and folate can improve responses to EPO.[160] Vitamin B1 (thiamine) losses can occur with diuretic therapy or hemodialysis, potentially causing problems when the diet is restricted. However, there are no long-term evaluations detailing the incidence of thiamine deficiency even though some of its cardiovascular and neurologic symptoms can mimic complications of advanced CKD. For MHD patients, the average concentrations of folate, niacin, and vitamins B1, B6, B12, and C in whole blood and erythrocytes are often normal, presumably because the diet protein requirement of 1 g/kg/day is being eaten.[161] However, low or borderline low levels of certain vitamins, particularly vitamins B6 and C, folic acid, and 25-hydroxycholecalciferol and 1,25-dihydroxycholecalciferol, are often reported.[162] The need for some vitamins is

increased in kidney failure, so we recommend that a supplement containing the RDA for water-soluble vitamins be prescribed for CKD, hemodialysis, and CAPD patients.

Riboflavin is necessary for normal energy use because it is used to maintain levels of the coenzymes flavin mononucleotide and flavin adenine dinucleotide. Riboflavin is present in meat and dairy products and its deficiency can produce sore throats, stomatitis, or glossitis, which may be mistaken for uremic symptoms. Folic acid is found in fruits and vegetables, but cooking can destroy it, and hence, it could become deficient in patients with restricted diets. Because folic acid is required for adequate EPO treatment and for the synthesis of nucleic acids and for methyl group transfer reactions and because it may decrease homocysteine production, it should be provided as a supplement. Vitamin B6 (pyridoxine) is necessary for many metabolic reactions involving amino acids via transaminase-catalyzed reactions. It is contained in meats, vegetables, and cereals. A deficiency can produce symptoms of a peripheral neuropathy or altered immune function, or host resistance may develop. Because these problems could complicate advanced uremia, a daily pyridoxine HCl supplement providing 5 mg per day for stage 4 and 5 CKD patients and 10 mg per day for MHD and CPD patients is recommended. Vitamin B12 is required for the transfer of methyl groups among metabolic compounds and for the synthesis of nucleic acids. Its major sources are meat and diary products. A deficiency state is unusual because this vitamin is stored in the liver. Also, little vitamin B12 is removed during hemodialysis because its molecular weight is rather high (1,355 Da), and it is largely protein bound in plasma. A daily supplement containing the RDA is recommended even though the likelihood of CKD, MHD, or CPD patients developing a deficiency state is low.[159]

Vitamin C or ascorbic acid protects against antioxidant reactions and is involved in the hydroxylation of proline during collagen formation. It also is contained in meat, dairy products, and most vegetables so a deficiency state is unusual. Unfortunately, dialysis readily removes vitamin C, so a deficiency state can develop in patients eating an inadequate diet. Since high doses of vitamin C are metabolized to oxalate which can precipitate in soft tissues (including the kidney), vitamin C supplements should contain only the RDA amount.

The remaining water soluble vitamins, including biotin, niacin, and pantothenic acid, have been less well studied. Biotin functions as a coenzyme in bicarbonate-dependent carboxylation reactions and is produced by intestinal microorganisms. Consequently, a deficiency state is unusual. Niacin (nicotinic acid) is used as a nicotinamide adenine dinucleotide phosphate coenzyme. It is synthesized from the essential amino acid, tryptophan; a deficiency produces diarrhea, dermatitis, or increased triglycerides. Pantothenic acid is involved in the function of coenzyme A and, hence, in the metabolism of fatty acids, steroid hormones, and cholesterol. Although there is minimal information about the efficacy and consequences of these vitamins in renal disease, a supplement of the RDA of these vitamins appears to be quite safe, and we also recommend supplements, but only at amounts equivalent to the RDA.

In summary, patients eating restricted diets are at risk for developing vitamin-deficiency syndromes. Even MHD and chronic peritoneal dialysis (CPD) patients who are urged to eat generous amounts of protein and energy are at risk for ingesting less than the RDA of vitamins established for normal subjects and the daily requirements at least for vitamin B6 and folate appear to be increased in these patients.[163] We conclude that CKD as well as chronic dialysis patients should have a water-soluble vitamin supplement because it may prevent certain problems from developing and probably does little harm. Because hyperoxaluria and possibly peripheral neuropathy can occur with high doses of vitamin C and pyridoxine, respectively, megavitamin therapy should be avoided.[164]

The requirements for fat-soluble vitamins in patients with CKD have not been established, and there are reasons to suspect that some of these vitamins may even cause complications of CKD. We recommend that fat-soluble vitamins should be given only when there is a well-defined indication. Because many multivitamin preparations contain fat-soluble vitamins, these preparations should be avoided unless there is evidence for a deficiency condition. Notably, plasma vitamin A (retinol) levels are usually increased in CKD patients because the level of retinol-binding protein is high, making it likely that tissue levels are normal or increased.[159] Supplemental vitamin A can contribute to anemia, dry skin, pruritus, bone resorption, and hepatic dysfunction in uremic patients.[165]

The requirements for vitamin E, another fat-soluble vitamin, are not established. Vitamin E has been given in experimental models of CKD, providing some reduction in the degree of renal injury in rats with experimental immunoglobulin A (IgA) nephropathy or glomerulosclerosis following a subtotal nephrectomy or diabetes.[166] Although plasma vitamin E levels are generally reported to be normal in uremic patients, the question of supplementing vitamin E to suppress lipid peroxidation/oxidant stress has not been settled. Vitamin E may reduce the rate of progression of carotid artery stenosis in MHD patients with a history of vascular disease. Other studies have not confirmed a beneficial effect of vitamin E on atherosclerosis in patients with CKD. Another factor to be considered is that vitamin E supplements may be hazardous. The Heart Outcomes Prevention Evaluation (HOPE) Study was carried out in older people who were at a high risk for adverse cardiovascular events; there was no restriction to the presence or absence of CKD. Patients treated with daily vitamin E (400 IU) developed a delayed and significantly increased risk for heart failure and hospitalization for heart failure.[167] The RDA for vitamin E is 15 mg per day, and lower doses of vitamin E could be given to CKD or maintenance dialysis patients. Indeed, some multivitamins contain quantities of vitamin E that are less than the RDA and are provided largely to ensure that the daily vitamin E intake meets the RDA. Although vitamin E might reduce oxidant stress, it is controversial whether routine vitamin E supplements should be given to CKD patients.

The vitamin D analogs, 25-hydroxycholecalciferol and 1,25-dihydroxycholecalciferol, are bound to an alphalike globulin and may be lost in the urine in nephrotic patients.[168] This can lead to decreased ionized and total calcium, and bone disease in some patients and patients with the nephrotic syndrome should have regular surveillance of vitamin D levels. Recommendations for supplemental vitamin D are discussed in Chapter 73.

The need to supplement most trace element supplements for CKD and maintenance dialysis patients is not clear. The controversy arises because of difficulties in determining if body stores are insufficient, adequate, or excessive. A deficiency may not be reversed solely if only more trace elements are supplied.[159] Aluminum has been studied extensively because aluminum-containing antacids have been used to control serum phosphorus and, in the past, dialysates were contaminated with aluminum. Aluminum accumulation can cause bone disease, especially osteomalacia, a progressive dementia, proximal muscle weakness, impaired immune function, and anemia.[169,170] Aluminum retention also can reduce serum iron stores, contributing to resistance to erythropoetin (EPO) therapy.[171] Plasma and leukocyte zinc levels are reportedly decreased and may be associated with endocrine abnormalities such as high plasma prolactin levels.[172] In patients with advanced CKD, the urinary excretion of zinc or fecal zinc may be decreased.[173] Some reports indicate that dysgeusia, poor food intake, and impaired sexual function, which are common problems of uremic patients, may be improved by giving patients zinc supplements.[174] Other studies, however, have not confirmed these results.[175] A zinc supplement has been reported to increase B-lymphocyte counts, granulocyte motility, and taste and sexual dysfunction.[159]

The finding that serum selenium is low in dialysis patients has raised the question of supplementing selenium because selenium participates in the defense against oxidative damage of tissues, which may be increased with kidney failure.[176] The relationship among other trace elements and the occurrence of beneficial or adverse reactions has not been well studied in CKD patients. Hence, with the possible exception of the nephrotic syndrome, we do not recommend routinely giving supplements of trace elements unless there is documentation that trace element intake is low or a deficiency is present. This may be the case for iron, zinc, and selenium. The exception would be patients who are receiving long-term parenteral or enteral nutrition without supplements of trace elements; these individuals should routinely be given trace elements. Finally, the appearance of skin rashes, neurologic abnormalities, or other unexplained problems in maintenance dialysis patients should prompt a search for excessive concentrations of trace elements in the dialysate.

Assessment of Dietary Compliance

The classic report of Folin[59] pointed out that urea excretion is the principal change in urinary nitrogen that occurs when dietary protein changes. This has been repeatedly confirmed and provides a firm foundation for assessing compliance with low-protein diets.[60,61,177] The rate of urea production exceeds the steady-state rate of urea excretion in both normal and uremic subjects because there is an extrarenal clearance of urea. This extrarenal removal of urea is due to its degradation by bacterial ureases present in the gastrointestinal tract.[178–180] In the past, it was believed that urea degradation to ammonia contributes substantially to amino acid synthesis in the liver and, hence, improves the nutritional status of uremic patients.[181] This is incorrect; the ammonia nitrogen is simply used to synthesize urea by reincorporating it into urea.[179,180] Fortunately, the rate of net urea production closely parallels dietary nitrogen[60,177] and net production (i.e., urea appearance [UNA]) is easily calculated because the concentration of urea is equal throughout body water.[154,179] Because water represents ~60% of body weight in nonedematous patients, changes in the urea nitrogen pool can be calculated by multiplying 60% of nonedematous body weight in kilograms by the SUN concentration in grams per liter. The UNA is calculated as the change in the urea nitrogen pool (positive or negative) plus urinary urea nitrogen excretion. If the SUN and weight are stable, urea nitrogen accumulation is zero and UNA equals the excretion rate (Table 85.2).

Nonurea Nitrogen

Unlike urea nitrogen, nonurea nitrogen excretion (i.e., the nitrogen excreted in feces and in urinary uric acid, creatinine, and unmeasured nitrogenous products) does not vary greatly over a large range of dietary protein.[60,61] The nonurea nitrogen excretion averages 0.031 g of nitrogen per kilogram of ideal body weight per day (Fig. 85.2). This average value was derived from patients with ≤ 5 g per day of proteinuria; if proteinuria exceeds 5 g per day, then protein in the diet should be increased by the amount of protein lost in the urine. There is no significant correlation between nonurea nitrogen excretion and dietary protein in patients eating low-protein diet.[61,117] This finding is important because a value of nonurea nitrogen excretion depending on weight provides a method for assessing compliance with protein-restricted diets. We examined results of over 70 nitrogen balance measurements and found no significant correlation between dietary nitrogen and either fecal nitrogen or nonurea nitrogen excretion, at least in CKD patients eating protein-restricted diets.[61] This distinction is important because independence of nonurea nitrogen excretion from dietary protein yields a method of assessing compliance with protein-restricted diets. Compliance is assessed by converting the prescribed protein intake to its nitrogen equivalent by multiplying dietary protein by 0.16 (protein is 16% nitrogen). If nitrogen balance is assumed to be zero, then nitrogen intake equals the sum of UNA (Table 85.2) plus 0.031 g/kg/day of nitrogen.[60] Therefore, the patient is compliant if the intake equals the output. However, when intake is greater or less than nitrogen output, then the assistance of a skilled dietician is needed. The caveat is that this method cannot be used reliably if a patient is receiving total parenteral nutrition or eating completely digestible foods (e.g., astronauts). In summary, total nitrogen

85.2 Estimating Compliance with Dietary Protein Using Urea Turnover

1. A 70-year-old man with a urea clearance of 10 mL/minute weighs 70 kg. He is taught a diet containing 0.8 g protein/kg/day in order to meet the daily allowance of protein recommended by the World Health Organization. His serum urea nitrogen (SUN) and weight are stable. A 24-hour urine collection contains 6 g of urea nitrogen.

   Because protein is 16% nitrogen, he is eating 9 g of nitrogen daily. His non-urea nitrogen excretion is 70 kg × 0.031 g of nitrogen/kg/day or 2.17 g of nitrogen per day and his total nitrogen excretion is 6 + 2.2 = 8.8 indicating that he is compliant with the prescribed diet.
2. A 60-year-old woman with stage V CKD is admitted to the hospital for plastic surgery. She has been taught a diet that contains 40 g of protein/kg/day (~6.4 g of nitrogen per day because protein is 16% nitrogen). She is excreting 4 g urea nitrogen per day, but on the 2nd day of admission, her SUN rises from 50 to 60 mg/dL.

   Her non-urea nitrogen excretion is estimated as 60 × 0.031 g of nitrogen/kg/day or 1.9 g of nitrogen/day. Thus, her total excretion is 9.5 g of nitrogen/day. (Total nitrogen excretion = 4 g urinary urea nitrogen + 1.9 g non-urea nitrogen + the accumulation of 3.6 g urea nitrogen [36 L as estimated body water × 0.1 g urea nitrogen per liter of body water.]) Her nitrogen excretion substantially exceeds her prescribed intake so a nutrition/dietician consult and a stool sample for blood are obtained.

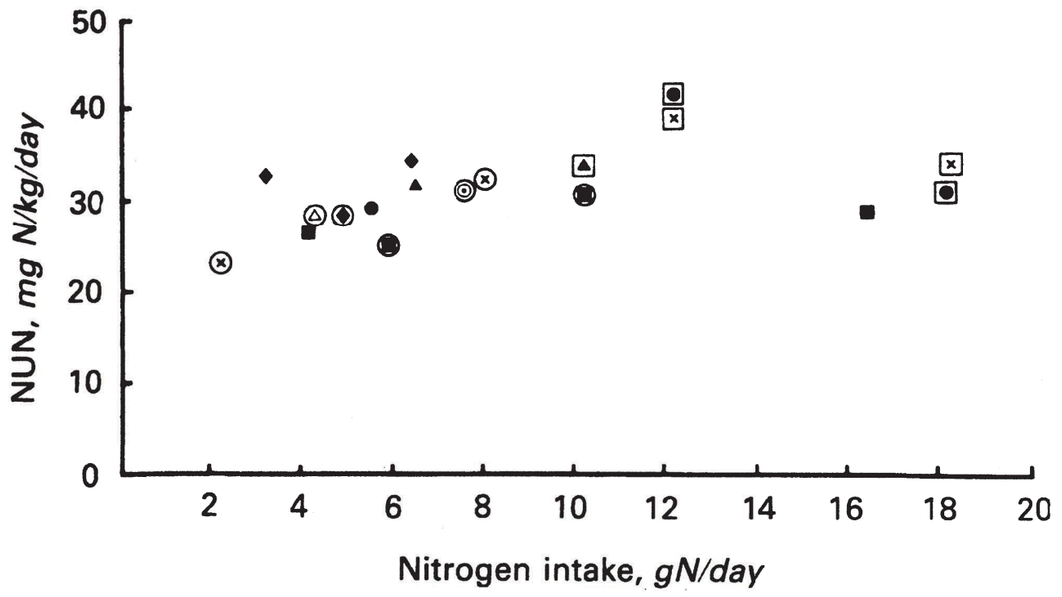


FIGURE 85.2 Calculated values of total nonurea nitrogen (NUN) excretion in normal subjects (*solid symbols*) and patients with chronic renal failure. The average value for patients not being treated by dialysis is 0.031 g of nitrogen per kilogram per day. (From Maroni BJ, Steinman T, Mitch WE. A method for estimating nitrogen intake of patients with chronic renal failure. *Kidney Int*. 1985;27:58.)

excretion is calculated from weight, SUN, and urea nitrogen excretion. It is compared to the prescribed protein intake and if the values are different by more than 20%, then reasons for noncompliance or the reasons for a negative nitrogen balance should be investigated.[182] Another equation that takes into account unmeasured losses of nitrogen through respiration, sweat, exfoliated skin, flatus, and sputa is

$$\text{Dietary nitrogen intake in grams per day} = 1.20\ \text{UNA (g/day)} + 1.74.$$

Multiplying the amount of dietary nitrogen intake by 6.25 estimates the protein intake.

Another potential use of the calculated dietary protein is to evaluate a patient's calorie intake. First, the ratio of dietary protein to calories can be estimated from the patient's dietary history. Second, the protein intake calculated from urea nitrogen excretion as just outlined is divided by the calculated protein intake yielding the calorie intake. This type of analysis should be used regularly in patients treated with restricted diets because calorie intake must be sufficient to use protein in the diet efficiently to maintain body protein stores. The importance of using these calculations regularly is highlighted by the report that CKD patients frequently underreport their calorie intake, especially if they are obese.[183]

Other methods of assessing protein intake, including dietary histories, were exhaustively reviewed by Bingham[184]: interview methods are less accurate and, over time, patients learn the appropriate responses to questions about dietary habits. Examples of this problem have been reported by Kloppenburg et al.[120] and Molitch et al.[183] They evaluated food records and anthropometric and oxygen consumption data of dialysis patients and CKD patients. They found that energy intake was grossly underestimated when assessed by diet records. In summary, dietary compliance can and should be calculated from the measured urea nitrogen excretion and the nonurea nitrogen excretion.

DIETARY PROTEIN RESTRICTION AND THE PROGRESSION OF RENAL INSUFFICIENCY

Several conditions related to a loss of kidney function have been identified from studies of experimental kidney damage (Table 85.3). Regarding responses in the patient, beneficial effects of dietary restriction on the progression of CKD were reported in the late 1970s, but the reports were criticized because they relied on changes in the serum creatinine or creatinine clearance to assess progression. There also were difficulties in the study design (including the lack of randomization and retrospective analyses). The Modification of Diet in Renal Disease (MDRD) Study,[185] an intention-to-treat analysis of the largest trial of dietary protein restriction and progression, led

85.3 Experimental Renal Diseases Improved by Dietary Protein Restriction

Remnant kidney
Nephrotoxic serum nephritis
Doxorubicin nephrosis
DOCA salt hypertension
Spontaneous hypertension with reduced renal mass
Salt-sensitive hypertension with glomerulonephritis
Diabetes mellitus
Spontaneous glomerular sclerosis of aging
Antitubular basement membrane nephritis

DOCA, deoxy-cortisone acetate.

to the conclusion that there was no benefit of protein-restricted diets on progression. There were notable problems with this interpretation but there are other reasons to manipulate the diet of CKD patients, namely to prevent complications of CKD.

Randomized Controlled Trials in Nondiabetic Chronic Kidney Diseases

Clinical trials that satisfy "high quality" requirements[186] include the report of the Northern Italian Cooperative Study Group, which analyzed results from 456 patients categorized according to the National Kidney Foundation (NKF) definition as stage III to IV CKD patients.[187] The patients were examined over at least 2 years following their random assignment to diets containing either 0.6 g of protein per kilogram per day (low-protein diet [LPD]) or 1g/kg/day (control group) plus at least 30 kcal/kg/day. The actual protein intake was determined from the urea nitrogen excretion,[60,61] and unfortunately, varied minimally. The average protein intake was 0.9 g/kg/day for the control group and 0.78 g/kg/day for the LPD group with substantial overlap in the amounts of protein eaten. Thus, the study did not test the hypothesis that eating a low protein diet will slow the loss of kidney function. Because dietary protein differed by 0.12 g/kg/day, it is not surprising that there was only a borderline difference in the primary outcome of renal survival, defined as the start of dialysis or the doubling of serum creatinine between control and LPD groups; slightly fewer patients assigned to the LPD group reached the end point (P = .059).

The MDRD study evaluated different levels of protein intake and two levels of blood pressure control in a 2 × 2 design.[185] GFR was measured as the urinary clearance of ^{125}I-iothalamate to determine how rapidly renal function was lost. In Study A (stages III to IV CKD), 585 patients were randomly assigned to a standard diet of >1 g of protein per kilogram per day or a diet containing 0.6 g of protein per kilogram per day and there were targeted mean arterial blood pressures of 105 or 92 mm Hg. In Study B, 255 stage IV CKD were randomly assigned to diets of 0.6 g of protein per kilogram per day or 0.3 g of protein per kilogram per day supplemented with a ketoacid/essential amino acid mixture, very low protein-keto acid (VLP-KA); the same blood pressure goals were sought. Actual protein intakes based on urea nitrogen excretion[60,61] were 1.11 and 0.73 g of protein per kilogram per day, respectively, in Study A and 0.69 and 0.46 g of protein per kilogram per day (plus the supplement in the VLP-KA group), respectively, in Study B. The analysis revealed no statistical difference in the rate of loss of GFR between the two groups in Study A. Results of Study B showed a trend toward a slowing of the loss of GFR for the VLP-KA diet patients (P <.07), but the difference was not statistically significant.

There are a number of caveats in the interpretation of this study: (1) In Study A, there was an initial, rapid decrease in GFR in CKD patients assigned to the restricted, 0.6 g/kg/day of protein intake. This response has been ascribed to a physiologic reduction in glomerular hemodynamics.[188] Subsequently, the loss of GFR was slower in CKD patients prescribed the LPD versus those assigned to the control diet (1.11 g of protein per kilogram per day). Thus, if the physiologic response is disregarded because it does not represent kidney damage, the rate of loss of GFR from the end of the initial 4 months until the last measurements yields a significantly lower value in patients assigned to the protein-restricted group. There also was a significant improvement in kidney survival (P = .009). (2) ACE inhibitors were prescribed to some patients in both Study A and B, which can influence the rate of loss of kidney function.[141] (3) The trial may have been discontinued prematurely.[182] For example, in the U.S. National Institutes of Health (NIH)-sponsored Diabetes Control and Complications (DCCT) Trial of the risks and benefits of strict blood glucose control, there was no protective effect of the intervention on the progression of kidney disease initially. But, after 4 years of strict glucose control, the development of microalbuminuria or macroalbuminuria was significantly depressed with strict glucose control. (4) Secondary analyses of the MDRD trial, although less robust for assessing efficacy, did identify the slowing of progression in those patients who had a measured decrease in dietary protein.[189,190] A low protein diet reduced the rate of loss of GFR in Study B patients (P = .011). There also was a reduction in the frequency of renal death (death or initiation of dialysis; P = .001). Specifically, for every 0.2 g/kg/day reduction of dietary protein, there was a 1.15 mL/minute/year reduction in the rate of loss of GFR and a 49% reduction in the frequency of renal deaths. (5) The inclusion of results from these patients with polycystic kidney disease had no benefit of restricting dietary protein or controlling blood pressure. Because polycystic kidney disease patients constituted ~25% of patients enrolled in the MDRD study, including them could have biased the interpretation of the results.[185] Based on an intention-to-treat analysis, restricting dietary protein in the MDRD study did not produce a statistically significant slowing of the rate of loss of GFR.

In an 18-month study, Williams et al.[191] compared three dietary interventions in 95 patients with stage IV to V CKD: (1) 0.6 g of protein per kilogram per day and 800 mg of phosphate intake; (2) 1,000 mg of phosphate per day plus phosphate binders; and (3) unrestricted dietary protein and phosphate. Dietary compliance was estimated from diet records and urea

excretion, yielding levels of 0.7, 1.02, and 1.14 g of protein per kilogram per day plus 815, 1,000, and 1,400 mg of phosphorus per day, respectively. Rates of progression were measured by creatinine clearances. There were no differences in the decrease in creatinine clearance over time among the three groups nor were there differences in the numbers of patients who died or began dialysis therapy. Criticisms, however, are that changes in creatinine clearance may not accurately represent changes in GFR. In addition, differences in actual protein intakes were minimal and the number of CKD patients studied was small.

Cianciaruso et al.[192] studied patients with stage IV to V CKD during 18 months of observation following assignment to 0.55 or 0.8 g of protein per kilogram per day. They randomly assigned 212 patients to receive the lower protein intake and 211 CKD patients to receive the higher level of dietary protein. Based on estimates from urea excretion,[60] the protein-restricted group ate 0.72 g compared to 0.92 g of protein per kilogram per day of the high protein diet patients ($P < .05$). The authors found no alteration in body composition or nutritional indices (principally, serum albumin) in either group. Based on an intention-to-treat analysis, 13 patients in the 0.92 g of protein per kilogram per day group versus 9 assigned to the 0.55 g of protein per kilogram per day died or were started on maintenance dialysis during the study.

Munford[193] evaluated if a very low protein intake supplemented with ketoacids might affect the efficiency of EPO therapy in 20 patients who were examined over 2 years. Patients were randomly assigned to 0.49 g/kg/day plus a supplement of ketoacids/amino acids or 0.79 g/kg/day. For the VLPD-KA group, only two had to begin dialysis compared to seven subjects assigned to the higher dietary protein group ($P < .05$). There also was an improvement in EPO responsiveness.

Ihle and colleagues,[194] studied 72 Australian patients with stage IV to V CKD. The patients were randomly assigned to a diet of unlimited protein or 0.4 g of protein per kilogram per day and were observed for 18 months (Fig. 85.3). Based on urea excretion,[60] the dietary protein-restricted group ate 0.69 g of protein per kilogram per day versus 0.8 g of protein per kilogram per day for the control group. The GFR (^{51}Cr-EDTA clearance) progressively declined, but only in patients eating the unlimited diet. The number of patients who had to begin dialysis was also lower in the protein-restricted group ($P < .05$). The authors did note that patients in the protein-restricted group lost weight, but otherwise there were no abnormalities in other anthropometric measures or in serum albumin.[194]

Jungers et al.[195] reported the outcomes of dietary protein manipulation in only 19 stage V CKD patients. Ten patients were randomly assigned to a VLPD-KA regimen, whereas nine were assigned to a conventional low protein diet of 0.6 g of protein per kilogram per day. Unfortunately, the actual amount of dietary protein eaten in the two groups differed by only 0.2 g/kg/day. This factor and the small number of patients limits the interpretation of the results.

Malvy et al.[196] studied 50 stage IV to V CKD patients by randomly assigning them to a VLPD-KA diet or a diet of 0.65 g of protein per kilogram per day. The time until a patient's creatinine clearance decreased below 5 mL/min/1.73 m^2 or until dialysis was required was measured. There was no significant difference in renal survival between the two diets, but the study was underpowered to test the hypothesis adequately. Patients in the VLPD-KA group lost 2.7 kg, including loss of both fat and lean body mass; this was not found in patients prescribed the 0.65 g of protein per kilogram diet. Interpreting these results is difficult because no patients were studied while eating an unrestricted diet. Still, the time for patients to reach a GFR of 15 mL/min/1.73 m^2 or less averaged 9 months for those assigned to the LPD regimen but 21 months for VLPD-KA patients. It was concluded that delaying the need for dialysis can be accomplished by dietary manipulation.

Mircescu et al.[197] assessed the clinical course of 53 stage IV to V CKD patients for 60 weeks. Twenty-six patients were randomly assigned to a diet of 0.6 g of protein per kilogram per day and 27 were assigned to a VLPD-KA diet yielding average protein intakes of 0.59 ± 0.08 g and 0.32 ± 0.07 g of protein per kilogram per day respectively. There were no deaths in either group, but 7 of the 26 patients assigned to the 0.6 g of protein per kilogram per day diet reached end-stage renal disease versus only 1 of the 27 assigned to the VLPD-KA diet ($P = .06$). Other responses to the VLPD-KA diet included a 24% decrease in serum phosphorus ($P < .05$). There were no changes in nutritional status of either group and no significant differences in the loss of GFR from serum creatinine (eGFR), but no conclusion about progression was reached as the number of patients studied was too few to examine this question rigorously (the authors estimated that approximately 100 patients per group would be required to identify significant differences in the number of renal deaths associated with the VLPD-KA diet).

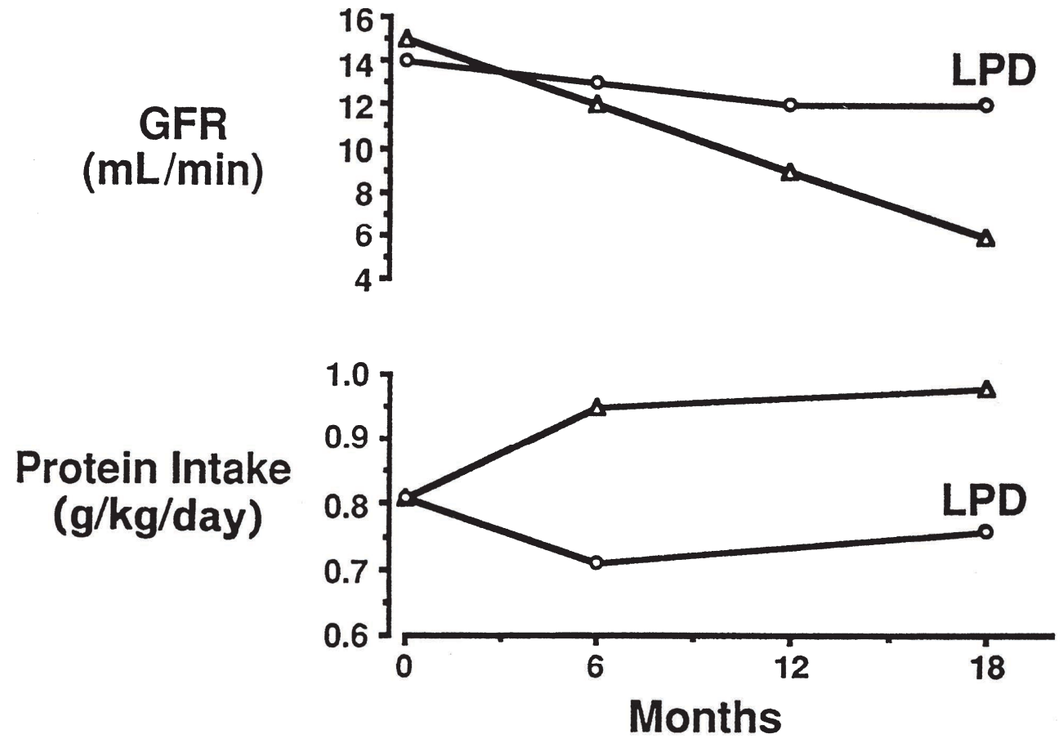


FIGURE 85.3 Changes in glomerular filtration rate (GFR) measured as the plasma clearance of 51 chromium ethylene diaminetetraacetic acid (51Cr-EDTA) in patients prescribed a protein-restricted diet (*open circles*) or an unrestricted diet (*open triangles*). The calculated level of dietary protein based on urea excretion[120] is also shown. The low-protein regimen significantly reduced the decline in GFR. *LPD,* low protein diet. (Figure was drawn from the results of Ihle BU et al.[194] and is reproduced with permission from Mitch WE, Klahr S. *Nutrition and the Kidney*. [2nd ed.]. Boston: Little, Brown, 1993, 254.)

Rosman et al.[198,199] studied the influence of dietary protein restriction in 228 stage III and stage IV to V CKD patients during 2 or 4 years. The control group ate an unrestricted diet, whereas patients assigned to the dietary protein-restricted diets ate different levels of protein: stage III CKD patients were instructed in a diet consisting of 0.6 g of protein per kilogram per day and stage IV to V CKD patients ate a diet of 0.4 g of protein per kilogram per day. After 2 years, the authors found decreased proteinuria and a significant slowing of the progression of kidney failure but only in male patients; patients with polycystic kidney disease had no beneficial responses. After 4 years, there was a survival benefit (i.e., the percentage of patients requiring dialysis) for patients treated by restricting dietary protein (60% versus 30%, $P < .025$).[199] It was concluded that compliance with the diets was fairly good and did not cause signs of malnutrition.

Brunori et al.[200] examined elderly Italian patients with stage V CKD by randomly assigning patients to treatment with a protein-restricted diet or chronic dialysis therapy. Results in the 56 patients treated with the VLPD-KA diet were compared to 56 patients assigned to dialysis. The survival rate was 83.7% and 87.3% in the dialysis and low protein diet, respectively ($P = .6$). Patients assigned to dialysis had a 50% higher degree of hospitalization. Based on an intention-to-treat analysis, the authors found a continuous benefit of the protein-restricted diet over time. The authors concluded that those randomly assigned to the VLPD-KA diet had no difference in life span compared to those treated by hemodialysis. The VLPD group had fewer hospitalizations.

Acidosis and Progression of CKD

Recent results have rekindled interest in a mechanism proposed to explain the loss of kidney function in CKD, namely that acidosis contributes to the loss of function. As noted earlier, the development of metabolic acidosis depends on the amount of protein ingested plus the limited ability to excrete acid and, therefore, dietary factors will influence the degree of acidosis. Nath et al.[201] proposed that acidosis could activate complement, leading to kidney damage. In 2009, CKD outpatients were evaluated and it was concluded that those with serum bicarbonate values $\leq$ 22 mM had a significantly greater likelihood of progressive loss of eGFR compared to patients with values $\geq$ 27 mM.[202] Another group reported that the administration of sodium citrate to patients with albuminuria and stage II CKD reduced the production of endothelin and the likelihood of decreasing eGFR.[203] They expanded these studies and performed a randomized clinical trial of administration of sodium bicarbonate to patients with stage II CKD and hypertension.[204] Over a 5-year period, patients treated with sodium bicarbonate had slowing of the loss of eGFR compared to patients treated with equivalent amounts of NaCl. In another randomized clinical trial, deBrito-Ashurst and colleagues[22] demonstrated that the administration of sodium bicarbonate slowed the loss of kidney function and improved nutritional indices (e.g., serum albumin).

Randomized, Controlled Trials in Diabetic Kidney Disease

Clinical trials of the influence of dietary restriction in diabetic, CKD patients generally have been too brief to identify differences in renal deaths compared to patients assigned to unrestricted diets. Consequently, surrogate analyses including a reduction in the degree of microalbuminuria or proteinuria, and/or changes in creatinine clearance or serum creatinine (converted to eGFR using the standard MDRD equation) have been examined to determine the efficacy of protein-restricted diets on the progression of CKD or changes in nutritional factors. In many of the early trials, a confounding factor was the unregulated prescription of ACE inhibitors, which can change the progression. For these reasons, the influence of dietary protein restriction in slowing the progression of diabetic nephropathy is unsettled.

Zeller et al.[205] compared diets containing 1 g of protein per kilogram per day with 0.6 g of protein per kilogram per day in 36 type 1 diabetic CKD patients during an average of 35 months. Changes in creatinine clearance and GFR (iothalamate clearance) were assessed, as were actual protein intakes based on urea excretion. The groups averaged 1.08 g versus 0.72 g of protein per kilogram per day, respectively. The low protein regimen significantly ($P < .02$) reduced the rate of decrease in GFR in patients who initially had eGFR values >45 mL per minute compared to results with the control diet. The nutritional status was not compromised by the low protein diet.

Hansen et al.[206] analyzed results from the longest randomized trial of patients with type 1 diabetes and CKD. The groups were prescribed their usual protein intake or a diet containing 0.6 g of protein per kilogram per day over 4 years. Average protein intakes were 1.02 g/kg/day versus 0.89 g/kg/day, a minimal difference. Not surprisingly, the degree of proteinuria in the two groups was not different. However, the frequency of renal deaths (i.e., progression to end-stage renal disease) was 36% lower in patients consuming the protein-restricted diet. When renal deaths were analyzed, adjusting for cardiovascular disease by the Cox analysis, the benefits of the low protein diet were even more significant ($P = .01$).

Meta-Analyses of Reports of Progression of Chronic Kidney Disease with Low Protein Diets

A meta-analysis provides an alternative approach that is based on analyzing the combined results from all methodologically acceptable clinical trials with the goal of increasing the number of participants available for analyses. The analyses can identify responses in each original study even though that study was sufficiently underpowered to examine the significance of the outcome.[207] Outcomes from large randomized trials are considered to be level one evidence versus evidence from meta-analyses, which are considered to be equal to outcomes derived from small randomized trials. After searching the literature to collect trials, including searches of international databases and often including

results from non–English-based journals, a set of rigorous criteria have been established to select or reject reports that are not randomized, controlled trials so that biased results could be minimized.[208] The most frequent outcome in meta-analyses of the influence of dietary protein manipulation is renal death, signified by a patient's death, the need to start dialysis,[209–211] the rate of decline in kidney function,[208] or changes in the degree of proteinuria.[212]

Kasiske et al.[208] studied results from >1,900 patients and found that the protein-restriction reduced the loss of GFR by only 0.53 mL/minute/year (P <.05). Although this result can be considered positive in terms of a renal protective effect of the diets, it was concluded that the results were not very important clinically.

Fouque et al.[186] performed a meta-analysis of 10 randomized controlled trials directed at evaluating whether low protein diets slow the loss of kidney function in nondiabetic CKD patients. Renal death was the outcome and the baseline characteristics of the patients in terms of gender and the causes of kidney diseases were equally distributed between the control and the diet-restricted groups. The outcomes of 1,002 patients assigned to dietary protein restriction were compared to the outcomes of 998 patients who had been assigned to higher protein intakes (Fig. 85.4). In the low

Analysis 1.1. Comparison I Low protein versus higher protein diets, Outcome I Renal death.

Review: Low protein diets for chronic kidney disease in nondiabetic adults

Comparison: Low protein versus higher protein diets

Outcome: Renal death

Study or subgroup	Low protein n/N	Higher protein n/N	Risk Ratio M-H, Random, 95% Cl	Weight	Risk Ratio M-H, Random, 95% Cl
1 0.6 g/kg/d versus higher protein diet					
Locatelli 1991	21/230	32/236		15.7%	0.67 [0.40, 1.13]
MDRD 1994	18/291	27/294		12.9%	0.67 [0.38, 1.20]
Williams 1991	12/33	11/32		9.8%	1.06 [0.55, 2.04]
Subtotal (95% CI)	**554**	**562**		**38.3%**	**0.76 [0.54, 1.05]**
Total events: 51 (Low protein), 70 (Higher protein)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.37$, df = 2 (P = 0.50); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.65 (P = 0.099)					
2 0.3–0.6 g/kg/d versus higher/free protein diets					
Cianciaruso 2008	9/212	13/211		6.2%	0.69 [0.30, 1.58]
di lorio 2003	2/10	7/10		2.5%	0.29 [0.08, 1.05]
Ihle 1989	4/34	13/38		4.1 %	0.34 [0.12, 0.95]
Jungers 1987	5/10	7/9		8.4 %	0.64 [0.32, 1.31]
Malvy 1999	11/25	17/25		15.8%	0.65 [0.39, 1.09]
Mirescu 2007	1/27	7/26		1.0%	0.14 [0.02, 1.04]
Rosman 1989	30/130	34/117		23.7 %	0.79 [0.52, 1.21]
Subtotal (95% CI)	**448**	**436**		**61.7%**	**0.63 [0.48, 0.83]**
Total events: 62 (Low protein), 98 (Higher protein)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.27$, df = 6 (P = 0.39); $I^2 = 4\%$					
Test for overall effect: Z = 3.31 (P = 0.00092)					
Total (95% CI)	**1002**	**998**		**100.0%**	**0.68 [0.55, 0.84]**
Total events: 113 (Low protein), 168 (Higher protein)					
Heterogeneity: $Tau^2 = 0.0$, $Chi^2 = 8.20$, df = 9 (P = 0.51); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.68 (P = 0.00024)					

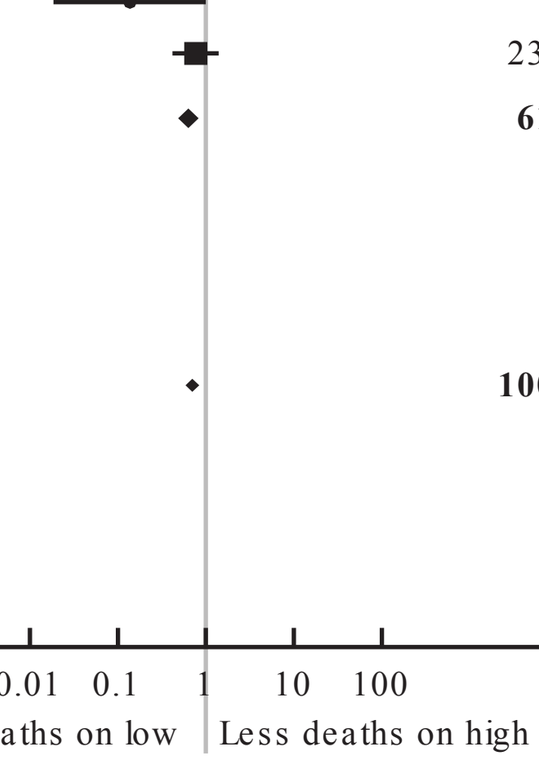


FIGURE 85.4 A representation of the results of a meta-analysis of low protein diets in patients with chronic kidney disease. *M-H,* meta-analysis for harm; *MDRD,* modification of diet in renal disease; *CI,* confidence interval. (From Fouque D, Laville M. Low protein diets for chronic renal failure in non-diabetic adults. *Cochrane Database of Systematic Reviews*. Issue 3, Art. No.: CD001892. Copyright Cochrane Collaboration; reproduced with permission.)

protein groups, 113 renal deaths occurred versus 168 patients in the control group, leading to a 0.68 odds ratio for renal death in the low protein group compared to the control group (the 95% confidence interval was 0.55 to 0.84; P = .0002). The authors concluded that eating low protein diets can result in a 32% reduction in death or the need to start dialysis therapy when results were compared to eating unlimited amounts of protein.[186]

The number needed to treat (NNT) is a tool for comparing the outcomes of a treatment in different studies, especially when risks of events are quite different between studies.[213] NNT indicates the number of patients that would have to be treated for 1 year to spare one major event (e.g., renal death). The NNT for a low protein diet varied from 2 to 56 for each study.[186] The variation was high because patients had different degrees of renal insufficiency at the start of the trials and the outcomes are confounded because the absolute risk of renal death would be greater in those CKD patients with more impaired kidney function.[195,196] Importantly, this level of NNT is acceptable for analyses of primary and secondary prevention outcomes in part because a low protein diet is far less expensive than dialysis or transplant therapy. In addition, these NNTs compare favorably with examples such as the well-accepted reduction in mortality with statin therapy, in the 4S trial (NNT = 30) or in the WOSCOPS study (NNT = 111).[214]

The discrepancy between the meta-analysis of Kasiske et al.[208] and other investigators may be related to the types of outcomes. Renal death, including the commencement of chronic dialysis therapy, was reported to be significantly and importantly reduced with low protein diets. The finding that renal death was delayed with low protein diets may be due to the slowing of the rate of loss of GFR or to the fact that low protein diets, by generating fewer uremic toxins, may maintain a healthier state for patients with stage 5 CKD. Consequently, physicians may delay the initiation of chronic dialysis therapy until a lower GFR is reached when compared to patients eating less well-controlled diets. It should be emphasized that none of these meta-analyses limited an examination of patients who were highly adherent to their prescribed low protein diets. It is possible that the benefits of low protein diets for these patients would be greater.

Conclusions about a benefit of low protein diets in patients with diabetic nephropathy yield opposing views. Pedrini et al.[210] reported that outcomes based on the combined criteria of microalbuminuria and a decline in renal function improved by 44% (P <.001) in patients assigned to low protein diets. More recently, Pan et al.[212] analyzed eight randomized trials with results from 519 patients: 253 in the low protein diet group and 266 in the control group. Changes in GFR or creatinine clearance, HbA1c levels, proteinuria, and serum albumin levels were recorded. No definitive differences in death or dialysis were uncovered with the two diets. Notably, however, the difference in dietary protein was minimal, at 0.36 g/kg/day (1.27 versus 0.91 g of protein per kilogram per day; P = .04). Proteinuria did decrease (P = .003), and glycosylated hemoglobin improved in seven of eight studies (a mean reduction of 0.31%; P = .005). Limitations of this review were the inclusion of results from patients with type I and II diabetes and from patients with early renal disease (e.g., isolated microalbuminuria but no renal insufficiency or only those with macroalbuminuria [>1 g per day]). In addition, four trials lasted only 12 months. Finally, the total number of patients (about 500) might not have been sufficient to detect statistical differences for all measures.

Regardless, this analysis confirms that reducing protein intake in patients with diabetes and CKD improves insulin sensitivity, decreases HbA1c, and reduces proteinuria, two independent factors associated with renal protection.

In summary, the meta-analysis technique indicates that there can be clear benefits for CKD patients eating low protein diets, including a reduced risk of renal death or a substantial delay until dialysis is required. This conclusion stands in sharp contrast to the suggestion by some that dialysis should be started early. Notably, tests of the efficacy of early dialysis have revealed that it does not improve mortality and certainly is more costly.[5,9,10,215] It is controversial whether dietary restriction will slow the loss of kidney function. But, there are other reasons to assess the diets of CKD patients: a well-planned diet can avoid some of the complications of CKD and delay the time until dialysis or transplantation becomes necessary.

Nutritional Impact and Safety of Modified Diets in Chronic Kidney Disease

A critical issue in the evaluation of outcomes with long-term dietary modification is whether a low protein diet is nutritionally sound and safe for patients with CKD. The MDRD Study enrolled 840 patients with different stages of CKD, providing the largest number of patients to address this question.[185] Patients were examined for an average of 2.2 years and a large number of measurements of nutritional status (e.g., body weight and anthropometrics, serum proteins, dietary adherence) were gathered. Based on urea excretion,[60] the average protein intakes of the different groups were significantly different. Kopple et al.[130] concluded there was some decrease in the estimated protein intake of subjects as their renal insufficiency advanced. There also was a decrease in energy intake, but this conclusion is not solid because the reliability of estimating calorie intake from dietary diaries can be problematic.[119,120] Notably, only 2 of the 840 participants had to stop the trial because of concerns about the nutritional status. Assignment to the low protein diet was associated with a small loss of body weight and arm muscle area (an index of muscle mass), but there was a small increase in serum albumin.

In contrast to these rather positive outcomes from the MDRD study, Menon et al.[216] reported that their analysis of results from the U.S. Renal Data System (USRDS) revealed a problem. They gathered data from the USRDS about patients

entering dialysis or receiving a transplant and all-cause mortality during the almost 10 years of the study, including the 2.2 years of the actual MDRD study. This led them to conclude that patients assigned to the VLPD-ketoacid diet had an associated increased risk of death. No information was provided about the compliance of the patients during the MDRD study nor were dietary factors examined following the end of the MDRD study. There was no information about other illnesses, dialysis-related factors, or treatments occurring after the end of the MDRD study. It was speculated that there could have been persistent restriction of dietary protein after beginning dialysis, or possibly, an accumulation of an unidentified toxin that somehow influenced the survival. Regarding the former, one group reported that patients trained in low protein diets had a delay of 3 months before their dietary protein was raised after the initiation of dialysis therapy.[217] In contrast, other investigators found no delay in increasing protein intake after dialysis therapy begins.[218] Regarding the possibility that the increased risk of death was related to an accumulation of an unidentified toxin, no such substance was looked for or identified. Importantly, the ketoacid supplements were discontinued at the end of the MDRD study, making it unlikely that nutritional or toxic responses occurring years later were due to ingestion of the ketoacid supplements. Other problems with the Menon et al.[216] analysis have been detailed.[219]

Results compiled by Chauveau and colleagues[5] provide a markedly different outcome. They detailed the long-term survival of 220 stage IV to V CKD patients who had been treated with 0.3 g of protein per kilogram per/day plus a mixture of ketoacids for an average of 33 months (4 to 230 months) before starting dialysis or being transplanted.[5] The authors analyzed the survival of these patients and compared it to a larger cohort of patients who were not treated with a low protein diet but who were treated concurrently by the same investigators. At 1 year after beginning dialysis, the authors concluded that the survival of dialysis patients was 97%, and after 5 years, it was 60%. For the kidney transplant patients, the survival at 5 and 10 years was 97% and 95%, respectively. When compared to the survival of U.S. patients, these results are excellent.[220] On the other hand, results achieved by Chauveau et al.[5] were compared to retrospective control patients who may not have received the same intensity of care as did patients assigned to a more complicated dietary regimen. Because the number of patients treated by Chauveau et al.[5] and those analyzed by Menon et al.[216] are similar, these widely disparate results are unexplained. A notable difference in the reports is that details of treatment and outcomes are provided in the report of Chauveau et al.[5] but not by the Menon et al.[216] publication. The Menon et al.[216] manuscript, however, does compare patients who were randomly assigned to different treatment regimens and who were followed very closely for the first 2 years of a 10-year period. We conclude that low protein diets, including the VLPD-KA regimen, are probably not harmful and do not increase mortality in patients, including in those who progress to a stage requiring dialysis or transplantation.

Conclusions

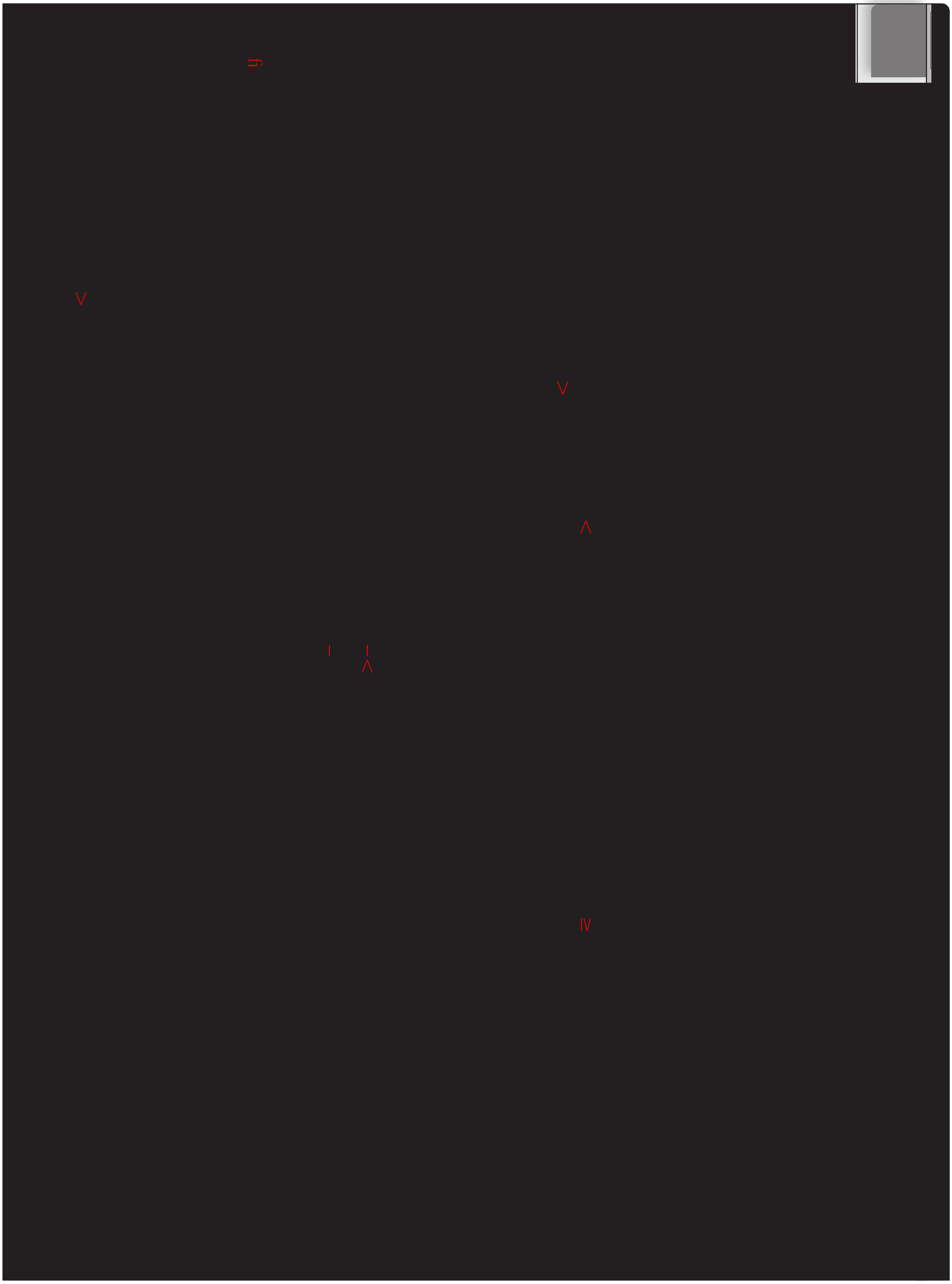
Patients with CKD can respond to dietary manipulation to reduce the signs and symptoms of uremia. The regimen is nutritionally safe as long as there is no complicating factor such as acidosis, infection, etc. Consequently, dietary manipulation should be included in a treatment program that includes monitoring protein and energy intake in collaboration with a dietician.[60,221] We suggest that such a regimen be implemented for patients with stages III to V CKD, if not earlier. The observation that protein intake may voluntarily decrease as renal insufficiency progresses should not be a signal to raise dietary protein because this will simply increase the degree of uremia (including hyperphosphatemia, metabolic acidosis, aggravate hypertension, etc.) and will not raise serum protein above what a well-designed low protein diet will achieve.[3,222,223] A well-designed protein-restricted diet may increase serum albumin.[6] Regarding benefits on the progression of CKD, a low protein diet could delay the need for dialysis by ameliorating uremic symptoms while maintaining nutritional status. In addition, adherence to a well-designed diet could prove valuable in correcting complications of CKD. For example, the effectiveness of ACE inhibitors in slowing progressive CKD is blunted by increased serum phosphorus, a problem that should be avoided by dietary manipulation.[14] There is strong evidence for the long-term safety of this approach.[224,225] Clearly, successful implementation of dietary therapy requires the motivation of both the patient and the physician. The principal, if not the only disadvantage of such therapy (assuming that it is successful in eliminating uremic symptoms), is the dietary restriction it entails, but it is reasonable to expect that dialysis therapy will be significantly delayed.

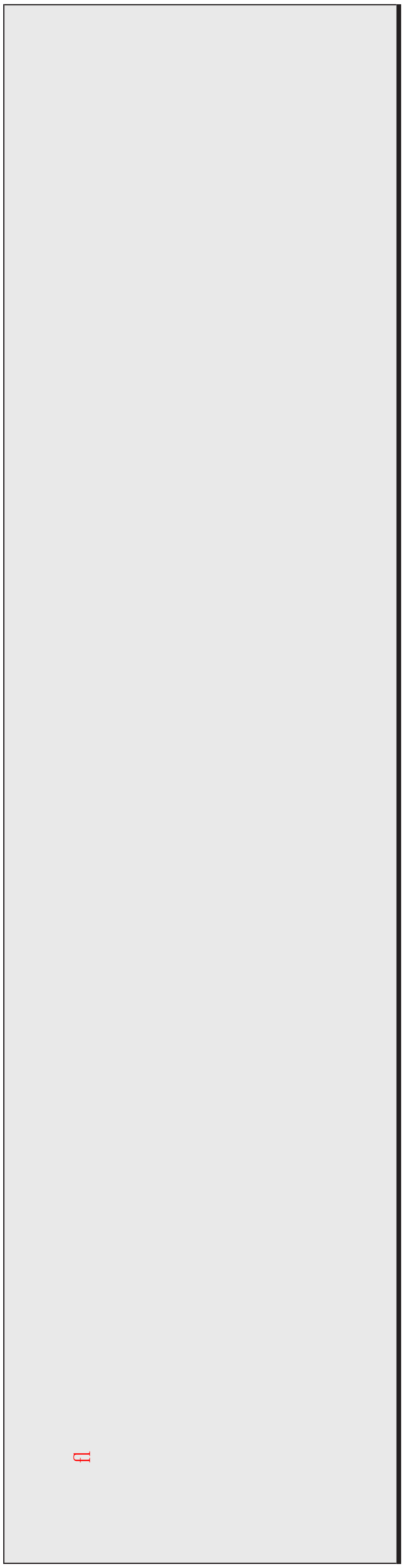
Dietary Protein Requirements for Dialysis and Transplant Patients

Maintenance hemodialysis (MHD) patients have increased dietary protein requirements due to losses of amino acids, peptides, and proteins by the dialysis procedure.[232,233] Hemodialysis also stimulates protein catabolism by engendering an inflammatory, catabolic response (Table 85.4).[234] Nitrogen balance results suggest that most maintenance hemodialysis patients require about 1 g of protein per kilogram per day to maintain both protein balance (Bn) and normal total body protein mass.[235] The National Kidney Foundation K/DOQI Clinical Practice Guidelines on Nutrition in Chronic Renal Failure recommend 1.2 g of protein per kilogram of body weight per day.[236] To ensure an adequate intake of essential amino acids, at least half of the dietary protein should be of high biologic value. There are currently no data concerning dietary protein requirements for patients undergoing MHD five or more times per week.

Chronic Peritoneal Dialysis (CPD)

Blumenkrantz and coworkers[237] studied protein and mineral balances in eight clinically stable men who underwent





13 metabolic balance studies of 14 to 33 days' duration in a clinical research center. Patients were fed diets with an average of 0.98 or 1.44 g of protein per kilogram per day (SD) and total energy intake (diet plus dialysate) was 41.3 ± 1.9 or 42.1 ± 1.2 kcal/kg/day with the low and high protein diets, respectively (Fig. 85.5). Bn results adjusted for changes in body urea nitrogen but not for unmeasured losses was +0.35 ± 0.83 g per day with the 1.0 g per kilogram protein diet and +2.94 ± 0.54 g per day with the higher protein intake (P = NS). When nitrogen balances are adjusted by subtracting about 1 g per day for unmeasured losses through skin, respiration, flatus, and blood sampling, Bn was negative with the low protein diet but still positive with the higher protein diet. There was a curvilinear relationship between dietary protein intake and nitrogen balance in the 13 studies.[237] Based on the these reports, we recommend prescribing 1.2 to 1.3 g of protein per kilogram per day to CAPD and automated peritoneal dialysis (APD) patients as recommended by the NKF K/DOQI Clinical Practice Guidelines on Nutrition in CRF for clinically stable CPD patients.[238] As with MHD patients, at least 50% of the dietary protein should be of high biologic value. Protein depleted patients may become anabolic with intakes as high as 1.5 g of protein per kilogram per day. In most CAPD and APD patients, there may be a need to increase the number or volume of dialysate exchanges or at least the volume of dialysate outflow.

Other nitrogen balance studies[239] in MHD or CPD patients have not included either the total nitrogen intake and/or outputs or the duration of these studies was too short to interpret the results rigorously. Patients classified as high peritoneal transporters. by the peritoneal equilibration test tend to lose more protein and amino acids into peritoneal dialysate versus low transporter patients. The high transporters also have, on average, lower serum albumin levels.[240] Dietary protein intakes of 1.2 to 1.3 g per kilogram per day should provide sufficient amounts of protein and amino acids to compensate for the increased peritoneal losses if the synthetic function for serum proteins is normal.

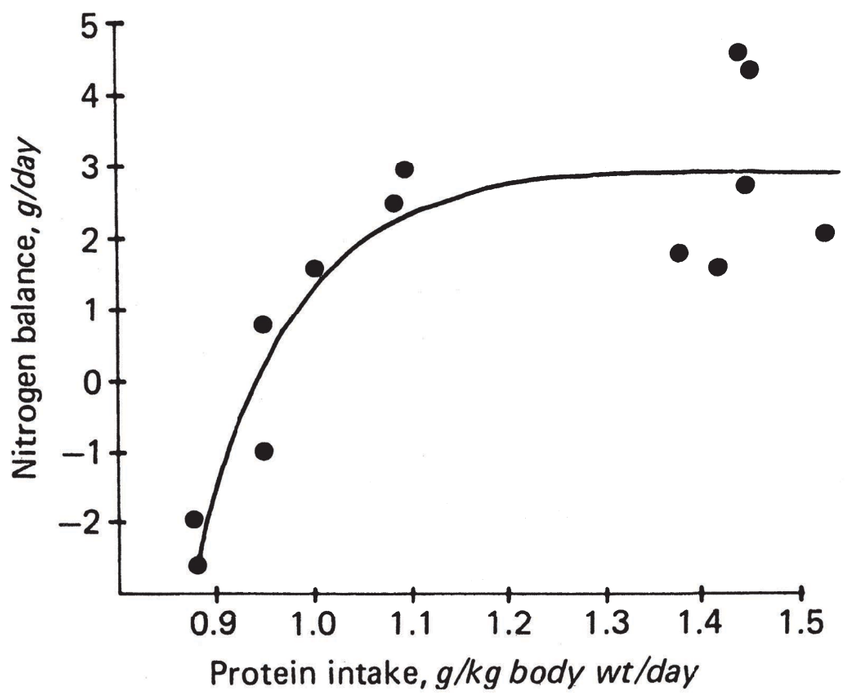


FIGURE 85.5 The relationship between dietary protein intake and nitrogen balance measured in 13 studies in 8 men undergoing CAPD. Each *circle* represents the mean balance data observed in an individual patient fed a constant diet for 14 to 33 days in a clinical research unit. The *curved line* represents the calculated relationship between nitrogen balance and protein intake. (From: Blumenkrantz MJ, Kopple JD, Moran JK, et al. Metabolic balance studies and dietary protein requirements in patients undergoing continuous ambulatory peritoneal dialysis. *Kidney Int*. 1982;21:849, with permission,)

Some nephrologists describe MHD or CPD patients who have dietary protein intakes of about 0.9 to 1.0 g per kilogram per day and do not appear protein depleted and lead physically active, rehabilitated lives. These observations have raised questions as to whether the foregoing recommended dietary protein intake may be excessive for maintenance dialysis (MD) patients. First, the number of MHD or CPD patients who have undergone careful nitrogen balance or other studies of their dietary protein requirements is small, and conclusions concerning their dietary protein needs therefore are imprecise; this is particularly true for MHD. Moreover, some MD patients who appear to be doing well will have evidence for protein depletion. Epidemiologic studies have associated protein depletion, even in mild forms, with increased mortality.[241]

The concept of dietary allowances presupposes that in order to ensure a sufficient nutrient intake for virtually all individuals (i.e., about 97%) in a population, the recommended allowance must be greater than the actual requirement for a large proportion of that population.[242] This reasoning is similar to that used by the WHO and the U.S. National Academy of Sciences when they recommended dietary protein intakes for normal adults. Thus, if the recommended protein allowance is 1.2 to 1.3 g/kg/day, many patients will tolerate lower protein intakes without developing protein depletion. At present, no known method identifies which patients can safely ingest lower levels of protein. To be safe, unless the patient can be shown to maintain a healthy nutritional status, he/she should be prescribed the recommended dietary allowance. Subtle forms of protein losses are particularly difficult to detect and a normal serum albumin concentration for patients may indeed be > 4.0 g/dL to be reassured of desirable clinical outcomes.[243]

Energy

Most studies indicate that energy expenditure measured by indirect calorimetry appears to be normal during resting and sitting or with defined exercise or after ingestion of a standard meal for nondialyzed CKD patients or those treated by MHD or CAPD.[235,244–246] In two studies of nondialyzed CRF or MHD and CPD patients, resting energy expenditure was increased.[247] What is most impressive about the foregoing studies is that there is no report of decreased energy expenditure in CKD, MHD, or CPD patients. Nitrogen Bn measurements indicate that in nondialyzed stage V CKD patients ingesting 0.55 to 0.60 g of protein per kilogram per day the amount of energy intake necessary to ensure neutral or positive nitrogen Bn is approximately 35 kcal/kg/day.[235] In clinically stable MHD patients ingesting 1.13 ± 0.02 (SEM) g

of protein per kilogram per day, Bn and anthropometric measurements indicate that close to 38 kcal/kg/day may be necessary to maintain body mass.[246] Virtually every study of stage IV and V CKD patients or MHD and CPD patients indicates that their mean energy intakes are below this level, averaging 24 to 27 kcal/kg/day.[248] Children with chronic renal failure (CRF) also have low energy intakes.[249] Many patients undergoing CPD tend to gain body fat and weight, probably due to the glucose uptake from the dialysate and the subsequent rise in insulin.

The NKF K/DOQI Clinical Practice Guidelines for Nutrition in CRF recommend that the energy intake for stage III CKD patients and for MHD and CPD patients should be 35 kcal/kg/day for individuals <60 years of age and 30 to 35 kcal/kg/day for those >60 years old (Table 85.4).[238] This intake includes energy derived from the diet plus glucose taken up from dialysate in MHD or CPD patients. The recommended energy intake is somewhat lower for individuals >60 years of age because they tend to be more sedentary and have less muscle mass. These recommendations are rather similar to those for normal individuals engaged in light-to-moderate activity as put forth in the RDAs by the Food and Nutrition Board, National Academy of Sciences.[242] Patients with an edema-free body weight greater than 120% of desirable body weight may be treated with lower calorie intakes. Some patients, particularly those with more mild renal insufficiency or younger or middle-aged women, may become obese on this energy intake or may refuse to ingest the recommended calories to avoid obesity and may require a lower energy prescription. It is important to monitor dietary intake and to treat inadequate intakes, even in clinically stable healthy appearing adults with advanced CKD or MHD or CPD patients. To remedy this problem, the dietician can recommend high-calorie foods that are low in protein and sodium and that can be prepared easily.

Lipids

There are several mechanisms that produce abnormal serum lipids and lipoproteins in CKD patients.[250] Stage IV and V CKD patients and patients undergoing MHD and CPD frequently have a high incidence of increased serum triglyceride levels, low-density lipoprotein (LDL), very low LDL (VLDL), and serum lipoprotein (a) (Lp[a]); their serum level of high density lipoprotein (HDL) cholesterol is often low. CPD patients often have higher serum total cholesterol, triglycerides, LDL cholesterol, and apolipoprotein B levels than do MHD patients.[250] Qualitative changes in the apolipoprotein concentrations also occur; among these is an increase in small density LDL (sd LDL).[250,251] Elevated serum triglyceride levels in uremia appear to be caused primarily by the impaired catabolism of triglyceride-rich lipoproteins.[250] Reduced catabolism leads to increased quantities of apoB-containing triglyceride-rich lipoproteins in IDL and VLDL and reduced concentrations of HDL. The key alteration in the apolipoprotein levels appears to be a decreased ratio of apoA-1 to apoC-Ill.[250] Activities of plasma and hepatic lipoprotein lipase and lecithin cholesterol acyltransferase (LCAT) are reduced,[250] and it is often difficult to provide sufficient energy without resorting to a large intake of purified sugars because of other dietary restrictions. CPD, with its attendant glucose load from the dialysate, appears to promote a further increase in serum triglycerides and cholesterol. Patients with the nephrotic syndrome usually have hypertriglyceridemia with an increase in serum total cholesterol and LDL cholesterol. LDLs, intermediate density lipoproteins (IDLs), VLDLs, and LP(a) are increased,[252] and serum HDL tends to be low. Serum phospholipids and apoproteins B, C-II, C-III, and E are increased, whereas apoproteins A-I and A-II are normal. Elevated serum cholesterol is caused by increased hepatic synthesis of lipoproteins and cholesterol and reduction in LDL receptor activity, playing an important role in the clearance of IDLs. These changes are aggravated by urinary albumin losses. Decreased activity of lipoprotein lipase contributes to the elevated serum triglyceride levels. There also is an elevation in plasma cholesterol ester transfer protein (CETP) and decreased catabolism of LDL apolipoprotein, at least by the more typical receptor pathway.

Renal transplant recipients may have high serum total and LDL cholesterol values plus increased LDL and IDL lipoproteins. Increased serum total cholesterol, LDL cholesterol, and triglycerides are more likely to be present in transplant recipients with chronic rejection and to correlate with a decrease in kidney function.[253] Therapy with glucocorticoids, cyclosporine A, sirolimus, tacrolimus, diuretics, or certain antihypertensives plus kidney failure, fasting hyperinsulinemia, and obesity are commonly present in renal transplant recipients and can add to the serum lipid disorders.

Because alterations in lipid metabolism and serum lipids may contribute to the high incidence of atherosclerosis and cardiovascular cerebrovascular and peripheral vascular disease in CKD patients, attention has been directed at reducing serum triglycerides and LDL cholesterol and increasing HDL cholesterol. Treatment strategies to correct abnormal lipid levels and the risk of cardiac and vascular disease should involve three components: nutrient intake, medicines, and exercise. The statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are beneficial in the general population in terms of reducing coronary artery disease at least in certain groups of high risk coronary heart disease patients.[254] Besides the lowering of LDL cholesterol, statins may slightly increase serum HDL cholesterol and may have anti-inflammatory, antithrombotic, and fibrinolytic effects to increase nitric oxide biosynthesis and bioavailability, to decrease synthesis of certain proinflammatory cytokines, to improve impaired endothelial function, and to protect against progressive renal injury in animals.[254] Statins will decrease LDL cholesterol in CKD patients, including patients with the nephrotic syndrome or treated by MHD or following kidney transplantation.[314,315] In the general population, higher doses of statins may be more protective against adverse cardiovascular events.

Unfortunately, in diabetic or nondiabetic MHD patients, statins do not exert benefits from cholesterol lowering[255,256]; adverse cardiovascular events and all-cause mortality were not reduced. On the other hand, statins may reduce adverse cardiovascular events and slow the rate of progression of CKD in patients with mild-to-advanced CKD.[257] We recommend a dietary plan similar to that of the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) for all patients with CKD, including MHD and CPD patients, patients with the nephrotic syndrome, and renal transplant recipients, especially if their serum LDL levels are >100 mg per deciliter.[258] Because these patients are at a high risk for cardiovascular, cerebrovascular, and peripheral vascular diseases, we prefer to set a target LDL cholesterol of 70 mg per deciliter. The diet should provide ≤ 25% to 35% of total calories from fat with polyunsaturated fatty acids providing up to 10% of total calories, monounsaturated fatty acids providing up to 20% of total calories, saturated fatty acids providing less than 7% of total calories, and a cholesterol content of 200 mg per day or lower. Carbohydrate intake should be 50% to 60% of total calories and should be derived predominantly from foods rich in complex carbohydrates. Fiber intake should be 20 to 30 g per day.[258] Because this diet may be less palatable, energy intake should be monitored to ensure that it remains adequate (see the subsequent text). Patients should not become obese (i.e., body mass index [BMI] should be <28 kg per square meter). It is recognized that most individuals will not be able to adhere exactly to this diet. But, even an incomplete modification of the diet to lower the serum cholesterol could reduce the risk of adverse vascular events.[259]

Omega-3 fatty acids (e.g., eicosapentaenoic acid and docosahexaenoic acid are found in fish oil) and can lower serum triglycerides and exert variable effects on serum LDL and HDL cholesterol.[260] Fish oil also decreases platelet aggregation and appears to exert anti-inflammatory effects, whereas omega-3 fatty acids may enhance immune function. Low fat diets and lipid-lowering medicines retard the rate of progression of renal failure in animal models,[261] and in humans, some suggest that omega-3 fatty acids may lower the progression of renal failure in renal transplant patients as well as the progression of IgA nephropathy.[262,263]

The fibric acid derivative, fenofibrate, reportedly reduces the progression to albuminuria in type 2 diabetic patients.[264] Fenofibrate may be tried cautiously in patients with high levels of triglycerides because statins or fibric acid derivatives can induce a number of side effects, including myopathy. The combined use of a statin and a fibrate is likely to cause a severe myopathy and both should not be used unless careful and repeated monitoring is available. The reports of patients with CKD being treated with carnitine for hypertriglyceridemia are divided between those that show a lowering of serum triglycerides versus others showing minimal benefit or even a rise in serum triglycerides.[236] Sevelamer HCl acts to bind phosphate in the gastrointestinal tract but also lowers serum LDL cholesterol and increases serum HDL cholesterol. For CPD patients with severe, resistant hypertriglyceridemia, L-carnitine may be given at 500 to 1,000 mg per day. For such patients being treated by MHD, 10- to 20-mg L-carnitine per kilogram thrice weekly could be administered at the end of each dialysis treatment to examine efficacy.

Intensive dietary and lifestyle counseling of diabetic patients may significantly reduce or prevent the magnitude of albuminuria, the rate of progression of CKD, adverse cardiovascular events, and stroke.[265,266] We recommend a TLC NCEP diet for CKD patients or for MHD or kidney transplant recipients. To correct hypertriglyceridemia, we increase dietary lipid intake to <40% of total calories but only when fasting serum triglycerides are very high (i.e., ≥ 500 mg per deciliter). In addition, the dietary carbohydrates should mainly be composed of complex carbohydrates. Occasionally, it may be necessary to add a medicine such as ezetimibe to reduce intestinal cholesterol absorption, a statin or other cholesterol-lowering medicines, plus dietary manipulation to reach acceptable serum LDL cholesterol levels.[267]

Oxidant and Carbonyl Stress, Homocysteine

Antioxidants or antioxidant precursors, such as vitamins E and C or selenium, have been proposed as a method of reducing oxidant stress. Supplemental selenium should be taken with caution as it accumulates because of decreased excretion by the damaged kidney.[268] The body selenium burden is difficult to assess because selenium is protein bound and binding properties are altered in uremia. One glass per day of alcohol (e.g., red wine), statins, and regular exercise reportedly reduce oxidant stress.

Plasma homocysteine is increased in nondialyzed CKD patients and in about 90% of MHD and CPD patients.[269] The mechanism for this increase is unclear but may involve impaired remethylation of homocysteine back to methionine.[270] In the general population, elevated plasma homocysteine is associated with cardiovascular disease through three suggested biochemical mechanisms[271]: homocysteine oxidation generates hydrogen peroxide, it decreases methylation reactions from the accumulation of S-adenosylhomocysteine, and it acylates proteins by homocysteine thiolactone. In MHD, there can be a positive association between an increase in plasma homocysteine and adverse cardiovascular events, but other studies conclude that there is a negative association between these factors. In one large, controlled trial of CKD and MHD patients, large doses of a folic acid, pyridoxine HCl, and vitamin B12 did reduce plasma homocysteine levels but did not improve cardiovascular events or all-cause mortality.[269] To date, the treatment of MHD patients to reduce high plasma homocysteine does not improve their outcome.

Carnitine

Carnitine is a naturally occurring compound that is essential for life because it facilitates the transfer of long chain (>10 carbon) fatty acids into muscle mitochondria.[272] This activity is considered necessary for normal skeletal and cardiac

muscle function. Patients undergoing maintenance dialysis, and particularly maintenance hemodialysis, but not patients with advanced CRF, display low serum free carnitine and, in some but not all studies, low skeletal muscle free and total carnitine levels.[236,272] In patients with stage IV or V CKD plus MHD patients, muscle acyl-carnitines (fatty acid-carnitine compounds) are increased, and serum total carnitine (i.e., acylcarnitines plus free carnitine) is normal or elevated.[273] Randomized clinical trials in patients with CKD and MHD or CAPD patients suggest that L-carnitine may provide such clinical benefits as increased physical exercise capacity, increased hematocrit, reduced interdialytic symptoms of skeletal muscle cramps or hypertension, or improvement in overall global sense of well-being or the improvement of various symptoms often found in CKD patients.[236] L-carnitine is also reported to improve nitrogen balance in CAPD patients.[277] The most promising of proposed applications is the treatment of EPO-resistant anemia. Until more definitive studies are available, it seems reasonable to use L-carnitine for MHD or CPD patients who satisfy any of the following conditions: (1) disabling skeletal muscle weakness or cardiomyopathy; (2) muscle cramps or hypotension during hemodialysis treatment; (3) severe malaise; or (4) anemia refractory to EPO therapy. The patient could be given a 3- to 6-month trial of L-carnitine (or 9 months for refractory anemia). The optimal carnitine dose is not defined and a dose of 20 mg per kilogram at the end of each hemodialysis is reasonable.[236]

Magnesium

In CKD or MHD patients, about 40% to 50% of ingested magnesium is absorbed from the intestinal tract.[237,275] Because the absorbed magnesium is excreted primarily by the kidney, hypermagnesemia may occur in kidney failure patients. Magnesium commonly accrues in bone and may play a causal role in renal osteodystrophy.[276] If the patient takes high magnesium substances (e.g., magnesium antacids or laxatives), serum magnesium will increase and the substance should be stopped. A magnesium content of about 1 mEq per liter in the hemodialysate, 0.50 to 0.75 mEq per liter in peritoneal dialysate, plus a dietary magnesium intake of 200 to 300 mg per day will maintain serum magnesium at normal or only slightly elevated levels.[237]

Fiber

Studies in normal adults suggest that a high dietary fiber intake may lower the incidence of constipation, irritable bowel syndrome, diverticulitis, and neoplasia of the colon and, possibly, improve glucose tolerance. In patients with CKD, a high dietary fiber intake may reduce the SUN by enhancing its fecal excretion.[277] Consequently, CKD or MHD patients should have a dietary fiber intake of 20 to 30 g per day.

PRIORITIZING DIETARY GOALS

The number and magnitude of the changes in the dietary intake for stage III to V CKD including MD patients are so great that if they were all presented to the patient at one time, the patient could become demoralized and lose his or her motivation to comply with the diet. We recommend prioritizing goals by emphasizing the importance of controlling the protein, phosphorus, sodium, energy, potassium, and magnesium intake and the need to take calcium and vitamin supplements for stage IV to V CKD patients. Unless the patient has a lipid disorder or other risk factors for adverse cardiovascular events, the adherence to these dietary guidelines are not as strongly emphasized, at least initially. Statins or fibric acid derivatives are usually better tolerated than dietary modifications and their use may enable patients to focus on other pressing aspects of dietary modification. If the patient has complied well with the other elements of dietary therapy but has a lipid disorder that can benefit from dietary therapy or wishes to modify fat, carbohydrate, or fiber intake, then other modifications can be adjusted by encouraging the patient to participate actively in designing the diet.

Adjusted Edema-Free Body Weight

Because the recommended nutrient intakes are often based on body weight, a reference weight should be used in prescribing the diet for individuals with kidney disease. The National Kidney Foundation Clinical Practice Guidelines on Nutrition in CKD published the following statement[236]: "The body weight to be used for assessing or prescribing protein or energy intake is the adjusted edema-free body weight or aBWef. For MHD patients, the weight should be obtained postdialysis, but for PD patients, it should be obtained following drainage of the dialysate." The aBWef is used for CKD and MHD plus CPD patients, who have BWef $<95\%$ or $>115\%$ of the median standard weight of the National Health and Nutrition Examination Survey II (NHANES II) data.[278,279] For patients between these levels, the actual BWef is used. The guideline also notes: "for DEXA measurements of total body fat and fat-free mass, the actual edema-free body weight obtained at the time of the DXA measurement should be used. For anthropometric calculations, the postdialysis (for MHD) or postdrain (for CPD) actual edema-free body weight should be used." The aBWef is calculated as follows[236]:

$$\text{aBWef} = \text{BW} + [(\text{SBW} - \text{BWef}) \times 0.25]$$

where BWef is the actual edema-free body weight and SBW is the standard body weight from the NHANES II data.

NUTRITIONAL THERAPY FOR ACUTE KIDNEY INJURY

Patients with acute kidney injury (AKI) have varying degrees of alterations in their metabolic and nutritional status. Patients without catabolism from underlying illnesses are usually not oliguric and the cause of their AKI is typically an isolated event, such as the administration of radiocontrast drugs or aminoglycoside nephrotoxicity. Patients with AKI requiring more complex attention have evidence of increased

net protein breakdown (synthesis minus degradation) and disordered fluid, electrolyte, and/or acid–base status. There is often an excess total body water, azotemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, and a large anion gap metabolic acidosis. Rarely, AKI patients will have net protein degradation that is massive, with net losses as high as 200 to 250 g per day.[280] Patients are more likely to be catabolic when the AKI is associated with shock, sepsis, or rhabdomyolysis. The patients with net protein catabolism may accelerate the increase in plasma concentrations of potassium, phosphorus, nitrogenous metabolites, and non–nitrogen-containing acids. For these reasons, PEW is prevalent in AKI patients and is associated with increased morbidity and mortality.[281]

Results of animal studies indicate that acute uremia causes disorders in amino acid and protein metabolism. The UNA rises rapidly in rats with AKI versus events in control animals. There is increased uptake of several amino acids by livers of acutely uremic rats leading to increased urea synthesis. These animals have enhanced protein degradation and reduced protein synthesis in skeletal muscle.[282,283] Insulin treatment suppresses muscle protein degradation and increases protein synthesis. The insulin responses of the animal with AKI are impaired because of insulin resistance in muscle; this also occurs in patients with AKI.[280] In addition, acidemia contributes to protein catabolism (see previous). These responses can be attributed to AKI alone and when they are complicated with sepsis, hypoxia or trauma catabolism increases substantially. The mechanisms for the catabolic effect responses to AKI include: (1) products of metabolism may be toxic when their concentration rises due to impaired removal by the damaged kidney. (2) Alterations in catabolic hormones in plasma can promote wasting because the infusion of cortisone, epinephrine, and glucagon causes a sustained increase in glucose production, increased protein catabolism, increased energy expenditure, and negative Bn.[284] In addition, hypercatabolic illnesses are often associated with the release of catabolic cytokines or microbial toxins, elevated acute phase reactants, plus increased oxidants and elevated counterregulatory hormone levels (e.g., parathyroid hormone). (3) Acidemia increases the catabolism of amino acids and proteins. (4) There may be increased protease activities in plasma, which degrade proteins, or other changes (e.g., increased myostatin). Other potential causes for PEW in AKI arise because patients are unable to eat adequately due to anorexia or vomiting or impaired gastrointestinal function. Secondly, an underlying medical disorder can stimulate catabolism. Third, there can be losses of nutrients in draining fistulas or with dialysis, and the hemodialysis procedure may stimulate catabolism.

Nutritional Therapy for Acute Kidney Injury

If parenteral nutrition is required for the nutritional support of AKI patients, the nine EAA (including histidine) are used more efficiently for nitrogen or protein conservation compared to mixtures of EAA and nonessential amino acids (NEAA).[280] In addition, the small amount of EAA can decrease the rate of rise of potassium, phosphorus, and magnesium and can decrease the SUN and other potentially toxic products of protein and amino acid metabolism.[285] However, to maintain neutral or near-neutral nitrogen balance or to minimize net protein catabolism, particularly in hypercatabolic AKI patients, parenteral nutrition with larger amounts of EAA and NEAA may be necessary.

Effect of Continuous Venovenous Hemofiltration/Continuous Venovenous Hemodiafiltration on the Nutritional Management of Patients with Acute Kidney Injury

Continuous venovenous hemofiltration (CVVH), CVVHD (CVVH with concurrent hemodialysis), or CVVHDF (continuous venovenous hemodiafiltration) are used for very ill patients with AKI, CKD, or other causes of fluid or nitrogen intolerance (e.g., liver or heart failure). These dialysislike procedures, CVVH/CVVHD/CVVHDF, are performed while requiring only low blood and (for CVVHD) dialysate flow rates; they are usually administered throughout the 24 hours. These procedures offer potential advantages, including: (1) large quantities of water, electrolytes, and metabolites may be removed each day compared to standard 4-hour hemodialysis; (2) the removal of water and electrolytes is slow and, hence, causes less hypotension; (3) it is safe to administer greater amounts of amino acids and other nutrients because of the increased removal of fluid from the patient; (4) the daily clearances of molecules may avoid hemodialysis. These advantages have increased the use of CVVH/CVVHD/CVVHDF but it should be pointed out that these procedures have not improved the mortality or complications for AKI patients when compared to standard hemodialysis therapy. Finally, there is sustained low-efficiency dialysis (SLED) or hemodialysis carried out with low blood and dialysate flow rates similar to the advantages of CVVH/CVVHD/CVVHDF.

Amino acid losses during CWH/CWHD/SLED are influenced by the permeability characteristics of the filter membrane, the ultrafiltration and dialysate flow rates, and the amount of amino acids infused.[286] Approximately 4 to 7 g per day of amino acids are removed with CVVH[286] and this loss represents about 8.9 ± 1.2 (SEM)% and 12.1 ± 2.2% of the daily quantity of amino acids infused into the AKI patient. Amino acid losses with CVVH generally average about 6% to 12% of the daily amino acids infused; this level can be higher when the rate of amino acid infusion rises because the amount removed depends on the plasma concentration. Calcium and magnesium losses during CVVH or CVVHD average 2,800 and 600 mg per day, respectively, and losses of zinc average about 1.20 mg per day.[287] Although the infusion of large quantities of amino acids during CVVH/CVVHD/CVVHDF/SLED will improve the nitrogen Bn, it is not clear that there is a net accrual of protein stores. The infused amino acids might simply increase intracellular and extracel-

lular amino acid levels to produce positive intake but do not improve protein synthesis or suppress protein degradation in AKI patients. Still, results of nonrandomized and randomized prospective clinical trials of AKI patients treated with enteral or parenteral nutrition indicate that Bn is directly related to the intake of protein or amino acids.[288] Regarding actual amounts, about 1.5 g of protein or amino acids per kilogram per day seemed to maintain nitrogen Bn in severely catabolic patients. There also was a greater probability of survival for AKI patients who had an improvement in Bn after adjusting for age, sex, and APACHE II score.[288] This association did not extend to protein or amino acid intake and survival. Possible reasons why intake alone did not improve survival are (1) the degree of protein catabolism was not reduced by increasing amino acid/protein intake; (2) the ability to achieve positive Bn may only identify survivors; and (3) perhaps greater amounts of amino acids would improve survival. Regardless, these results must be interpreted cautiously with regard to the differences in characteristics of the patients, the small number of patients, and the need to include unmeasured nitrogen losses (e.g., respiration/skin losses) in assessing Bn.[289]

Enteral Versus Parenteral Nutrition

Patients with AKI and superimposed illnesses should always be given oral nutrition if feasible. The substitution of liquid formula diets, elemental diets, or tube or enterostomy feeding should be attempted if dietary intake is minimal. For patients requiring feeding by enteric tube or gastrostomy, liquid protein-based or elemental diets can be tried to increase protein and energy intake. It is always prudent to assess what other constituents make up the diet because increasing phosphate intake, etc. can be countereffective. There are reviews of techniques used to achieve enteral feeding and the complications arising when using chemically defined diets and tube feeding.[290] Most of the principles will be applicable to patients with kidney failure. Notably, enteral feeding is extensively used for pediatric patients, particularly infants with CKD.

Patients with AKI requiring enteral nutrition frequently have high residual volumes in the stomach, signifying impaired gastric emptying or nasogastric tube obstruction.[291] Despite these problems, enteral feeding is a safe and effective way to provide nutrition for adults with AKI if attention is given to the rate of delivery and the need to increase intake when there are disruptions due to medical and surgical care.

Peripheral vein parenteral nutrition can be an alternative to total parenteral nutrition (TPN). This is suggested because TPN requires central venous catheters, thus increasing the risks of complications.[291] Like TPN, peripheral parenteral nutrition requires careful monitoring because there are complications. For example, the osmolality of the infusate must be restricted to $\leq$ 600 mOsmol to prevent thrombophlebitis, and the needles should be changed every 24 to 72 hours to prevent infections. The large quantity of fluid infused in order to provide adequate calories and amino acids represents another problem for patients with limited kidney function. The costs of peripheral parenteral nutrition are similar to those of TPN due to the expenses of administering fluids in order to achieve nutritional requirements. Because the risks of peripheral venous parenteral nutrition are lower, some patients with AKI may be treated with peripheral nutrition as an adjunct to their oral or enteric feeding. For example, a solution containing an 8.5% to 10% amino acid solution plus a 20% lipid emulsion could be used to meet part of the total nutritional requirements in conjunction with the higher osmolality fluids (e.g., carbohydrates) being given by the enteral route.

Why Benefits of Nutritional Therapy Have Not Been Unequivocally Demonstrated

Notwithstanding earlier reports,[285,288] it has not been demonstrated that treatment with amino acids and other nutrients improves either the rate or incidence of recovery of kidney function or the nutritional status. Intuitively, nutritional therapy could benefit patients with AKI and, at least in patients with AKI who have survived for >2 weeks but still have difficulty in meeting nutritional requirements, oral or parenteral nutritional support should improve nutritional status. Why has it been difficult to demonstrate the benefits of nutritional therapy? First, the clinical course of patients with AKI is variable and complex, so large numbers of patients are required for randomized prospective evaluations of nutritional therapy. Second, some of the published comparisons were retrospective or inadequately controlled, leading to unintentional biases. Third, the optimal composition of nutrients in the enteral or parenteral solutions is not defined and the lack of outcome benefits for AKI patients could simply reflect the inadequacy of the nutritional formulations. Fourth, the paucity of randomized, controlled trials with AKI patients have relied on morbidity, mortality, or subsequent quality of life as the key outcome measures. These outcomes may actually reflect the presence of other illnesses, not just the presence of AKI. Fifth, no prospective controlled comparisons have assessed the clinical course of AKI patients with nutritional therapy versus those without nutritional therapy.

Recommended Nutritional Support for Patients with Acute Kidney Injury

The therapeutic approach in Tables 85.4 and 85.5 represents our analysis of published reports and personal experience. Based on the diversity of the clinical status of patients with AKI, the prescription for intakes of nutrients will depend on the patient's nutritional status, estimates of protein catabolic rates, residual GFR, and the indications for initiating intermittent dialysis therapy, SLED, or CVVH/CVVHD/CVVHDF. The malnourished or hypercatabolic patient might receive an excess of nutrients provided during intermittent hemodialysis, SLED, or CVVH/CVVHD/CVVHDF. On the other hand, patients with residual kidney function might also receive excess nutrients because he or she has less of a risk for developing fluid and electrolyte disorders or the accumulation of metabolic waste products. For those with minimal urine flow but

who are not very catabolic, water/mineral intake can be limited and calories with small amounts of amino acids—and especially EAA—may be given to decrease the need for dialysis. In general, the fluid intake (including water present in wet foods) should equal the fluid output from urine and other sources (e.g., nasogastric aspirate, fistula drainage) plus about 400 mL per day. This will take into account endogenous water production from metabolism and insensible water losses (e.g., from respiration and skin). If the patient is catabolic and in negative calorie and Bn, fluid intake should be restricted to allow for a loss of 0.2 to 0.5 kg per day. The intake of sodium and other minerals should be restricted to prevent their accumulation as judged by body weight, blood pressure, and the changes in the concentrations of sodium, potassium, phosphorus, etc. Insulin should be used to maintain normal plasma glucose concentrations and because it may improve mortality as was demonstrated in nonuremic patients with catabolic illnesses.[292] Because of the large glucose loads associated with enteral or parenteral feeding, hyperglycemia is common and insulin should be used to keep plasma glucose concentrations at 80 to 100 mg per deciliter.[293] The use of other hormones is less certain. For example, recombinant human growth hormone (rhGH) can improve Bn in patients with acute catabolic stress or with chronic illnesses, but trials of rhGH in critically ill patients indicate that the hormone can increase mortality in severely ill patients.[294]

The following discussion of specific nutrient intakes for patients with AKI can be used with oral, enteral, or intravenous nutrition. Information from TPN is emphasized because it is frequently used for more catabolic patients with AKI and it requires special attention to avoid complications. As noted earlier, the preferred route of feeding is total enteral nutrition (TEN) because it is associated with reduced morbidity.[295] This may reflect better preservation of the mass and physiology of the intestines and elements of host resistance.

Nitrogen Intake

The intake of nitrogen as protein or amino acids should be tailored to the clinical condition and dialysis needs of the patient. The intake is restricted for patients who have low values of urea production (i.e., 4 to 5 g of nitrogen per day but not severe protein malnutrition). These patients are expected to recover kidney function within weeks (Tables 85.4 and 85.5). Because the dialysis procedure causes catabolism (see previous), protein and amino acid intakes are restricted to avoid dialysis or reduce its frequency. For example, EAA with or without arginine may be given at 0.30 to 0.50 g per kilogram aBWef per day. More than 40 g per day of the nine EAAs should not be given in order to avoid serious amino acid imbalances. For patients who can eat, low protein feedings of 0.10 to 0.30 g/kg/day plus 10 to 20 g per day of EAA can be used to avoid rapid accumulation of nitrogenous waste products. Fortunately, these regimens will usually maintain neutral or mildly negative Bn and will reduce the need for dialysis. For patients with residual function (e.g., GFR of 5 to 10 mL per minute) but minimal catabolism, he or she can be treated as a patient with stage III to V CKD. The prescription would be a diet of 0.60 g per kilogram aBWef per day, primarily high biologic value protein or about 0.28 g of protein per kilogram per day supplemented with 6 to 10 g per day of EAA or a mixture of ketoacids and EAA. If the patient requires parenteral nutrition, the prescription is 0.60 g per kilogram aBWef per day of EAA and NEAA intravenously. If there is catabolism and/or a UNA >5 g of nitrogen per day, and the AKI is predicted to last for more than 2 weeks, the prescribed intake should be 1.0 to 1.2 g per kilogram per day for patients undergoing regular hemodialysis 3 times weekly and 1.2 to 1.5 g per kilogram per day for patients requiring standard hemodialysis more than 3 times weekly and approximately 1.5 to 2.5 g per kilogram per day in patients treated by SLED or CVVH/CVVHD/CVVHDF (Table 85.5). It should be noted that the UNA (and hence, the SUN) will invariably rise and this change plus the fluids given to meet these requirements generally increase dialysis needs.

Energy

The energy requirements for patients with AKI are determined by the same factors that affect patients without kidney failure and include weight, age, sex, associated diseases, and physical activity. When energy expenditure rises, it is largely but not entirely due to sepsis or other catabolic illnesses.[247] It is not known whether AKI per se changes energy expenditure. However, AKI treated by CVVH/CVVHD reduces energy expenditure in patients but whether this is hazardous is unknown.[296] Based on the principle that energy intake should rise when nitrogen intake is low, coupled with the need to provide large amounts of protein/amino acids in catabolic patients, the prescription for energy requirements are high and this complicates the provision of TPN and even enteral nutrition. Because patients with AKI provided with higher energy intakes had an improvement in survival, it is important to ensure that their energy requirements are satisfied.[280] A standard method for assessing energy needs is the Harris-Benedict equations that estimate basal energy expenditure (BEE) from age, sex, body weight, and height.

The Harris-Benedict equations are as follows[297]:

For men: BEE – 66.5 + (13.8 × weight [kg]) + (5.0 × height [cm]) – (6.8 × age [years])

For women: BEE – 655.1 + (9.6 × weight [kg]) + (1.8 height [cm]) – (4.7 × age [years])

The calculated BEE is then multiplied by an adjustment factor for the increase in energy expenditure associated with different clinical conditions (Table 85.6). Finally, the BEE is increased by 25% to adjust for individual variability, physical activity, and the potential needs associated with a low nitrogen intake and AKI. For these reasons, the BEE calculated for patients with AKI is

Energy requirements = Estimated BEE × Adjustment for illness × 1.25

85.5 Composition of Solutions for Total Parenteral Nutrition in Patients with Acute Kidney Injury[a]

			Vitamins	
Essential and nonessential Free crystalline amino acids[b] (4.25–5.0%)	42.5–50	g/L	Vitamin A[f] Vitamin D Vitamin K Vitamin E[g] Niacin	2,000 IU/day see text 7.5 mg/week 10 IU/day 20 mg/day
Essential amino acids (5%)[b]	12.5–25	g/L	Thiamine HC1 (B_1) Riboflavin (B_2)	2 mg/day 2 mg/day
Dextrose (D-glucose)[c]	350	g/L	Pantothenic acid (B_3)	10 mg/day
Lipid emulsion	10% or 20%	in 500 mL	Pyridoxine HC1	10 mg/day
Energy (approximately)	1,140	kcal/L	Ascorbic acid (C) Biotin	60 mg/day 200 mg/day
Electrolytes[d]			Folic acid[g]	1 mg/day
Sodium[e]	40–50	mmol/L	Vitamin B_{12}	3 μg/day
Chloride[e]	25–35	mmol/L		
Potassium	<35	mmol/day		
Acetate	35–40	mmol/day		
Calcium	5	mmol/day		
Phosphorus	8	mmol/day		
Magnesium	4	mmol/day		
Iron	2	mmol/day		
Other trace elements	See text			

[a]The nutrients listed are present in each bottle containing 50 mL of 8.5% to 10% crystalline amino acids or 250 to 500 mL of 5% essential amino acids and 500 mL of 70% D-glucose. The vitamins and trace elements are an exception because they are added to only one bottle per day. For those doses of nutrients that are expressed as concentrations rather than as quantities per day, the dose refers to the quantity present in each liter of dextrose and amino acids, with or without lipids. The patient's fluid status and serum electrolytes and glucose values must be monitored closely. The composition and volume of the infusate may be modified according to the nutritional status of the patient (see text).

[b]For patients who are more catabolic (e.g., UNA >5 g/day), who are undergoing regular dialysis treatments (particularly for 2 or more weeks), or who are very wasted, essential and nonessential amino acids should be infused; about 1.0 to 1.2 g/kg/day for hemodialysis patients and 1.0 to 1.3 g/kg/day for intermittent peritoneal dialysis, CAPD, or APD patients (see text). 1.5 to 2.5 g/kg/day of essential and nonessential amino acids may be given to patients undergoing CVVH/CVVHD/CVVHDF or SLED. For patients who are not very wasted, who are less catabolic, who are not undergoing regular dialysis therapy, and who will not be receiving TPN for more than 2 or 3 weeks, 21 to 40 g per day of the nine essential amino acids may be infused. See text for a discussion of the formulations of amino acids.

[c]70% D-glucose is added as necessary to obtain an energy intake of 30 to 35 kcal/kg/day (see text); lower energy intakes may be used in very obese patients. For the higher levels of energy intake (i.e., 45 kcal/kg/day), additional 70% D-glucose may be added to the solutions. Generally, lipids are infused each day to provide 20%–30% of total calories in order to balance the sources of calories and to prevent essential fatty acid deficiency. For patients who are septic or at high risk for sepsis, about 10%–20% of calories may be given as lipids. The lipids probably should be infused over 12 to 24 hours to reduce the hyperlipidemia that occurs with the intravenous infusion of lipid emulsions and to avoid impairment of the reticuloendothelial system. The lipids may be infused through a separate line or mixed with the amino acid and dextrose solutions and infused soon after mixing (see text). Usually a 20% lipid emulsion (250–500 mL) is used to reduce the water load. The approximate calorie values are dextrose monohydrate, 3.4 kcal/g and amino acids, 3.5 kcal/g.

[d]When adding electrolytes, the amounts intrinsically present in the amino acid solution should be taken into account.

[e]Refers to the final concentrations of electrolytes after any additional 70% dextrose or other solutions have been added.

[f]About 600/xg/day of retinol activity equivalents (RAE) (see text) should be given orally or parenterally and not in the TPN solution because of chemical antagonisms.

[g]May need to be increased with use of lipid emulsions.

APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemofiltration with concurrent dialysis; CVVHDF, continuous venovenous hemodiafiltration; SLED, slow, low-efficiency dialysis; TPN, total parenteral nutrition; UNA, urea nitrogen appearance.

85.6 Adjustment Factors for Estimating Energy Expenditure During Illness

Type of Stress	Fraction of Normal Basal Energy Expenditure
Malnutrition (chronic, severe)	0.70–1.00
Nondialyzed chronic renal failure	1.00
Maintenance hemodialysis	1.05
Elective surgery	
Early (1–4 days)	1.00
Late (18–21 days)	0.95
Peritonitis	1.15
Soft tissue trauma	1.15
Fractures	1.20–1.25
Infections	
Mild	1.00
Moderate	1.20–1.40
Severe	1.40–1.60
Burns (percent of body surface)	
0%–20%	1.00–1.50
20%–40%	1.50–1.85
40%–100%	1.85–2.05

The basal energy expenditure values during the normal healthy state may be multiplied by these approximate factors to estimate resting energy expenditure during acute or chronic illness.
Adapted from Wilmore DW. The metabolic management of the critically ill. New York. Plenum, 1977; and Monteon FJ, Laidlaw SA, Shaib JK, et al. Energy expenditure in patients with chronic renal failure. 1986; Kidney Int. 30:741.

The Harris-Benedict equations reportedly overestimate the resting metabolic rate by 10% to 15%,[298] especially in patients with low values of BEE. The WHO equations, compiled from about 11,000 measurements in adults of both genders, all ages, and a wide variety of ethnic groups and body mass indices, are[299]

$$RMR = 15.4 \times \text{weight (kg)} - 27.0 \times \text{height (m)} + 717$$

Men: 30 to 60: $RMR = 4.6 \times \text{weight (kg)} + 16.0 \times \text{height (m)} + 901$

Women: 18 to 30: $RMR = 13.3 \times \text{weight (kg)} + 334.0 \times \text{height (m)} + 35$

30 to 60: $RMR = 8.7 \times \text{weight (kg)} - 25.0 \times \text{height (m)} + 865$

Where RMR is resting metabolic rate (in kilocalories per day). Indirect calorimetry can be used to estimate energy expenditure and, if multiplied by 1.25 as in the previous equation, the BEE for patients with AKI requiring nutritional support is between 30 and 35 kcal per kilogram aBWef per day. The higher energy intake (i.e., 35 kcal/kg/day) is generally used for patients with higher UNAs who are severely ill and not obese. Using these methods, a rising UNA despite an appropriate amino acid intake could theoretically be corrected by raising energy intake to 35 kcal/kg/day. Larger energy intakes have not been shown to improve patient outcomes and they generate more carbon dioxide from the metabolism of infused carbohydrates and fat, compromising blood gasses if pulmonary function is impaired. A very high-energy intake also can cause obesity and fatty liver. Because AKI patients may not tolerate a large water intake, glucose is usually administered in a 70% solution yielding energy from glucose monohydrate at 3.4 kcal per gram or, for 70% dextrose, about 2.38 kcal per milliliter. Amino acids provide about 3.5 kcal per gram and they can be given simultaneously with carbohydrates (see Table 85.5).

Lipids are commonly given from the onset of TPN, but the optimal amount of fat required is controversial because of the impaired lipid clearance of AKI.[300] Although 25 g per day will prevent essential fatty acid deficiencies, 30% to 40% of calories as lipid emulsions are used to meet energy needs. It has been suggested that lipid emulsions can transiently lower host resistance by inhibiting the function of the reticuloendothelial system.[300] A prudent approach is to infuse lipid emulsions over 12 to 24 hours to minimize high levels of plasma lipids and to interfere with the reticuloendothelial system.[300] Nonseptic patients may be given up to 20% to 30% of calories as lipid emulsions, but those who are septic should not receive intravenous lipids to avoid impaired function of the reticuloendothelial system. Alternatively, the provision of omega-3 fatty acids may enhance immune function and host resistance.[301]

Minerals

Recommendations for mineral intakes are tentative and should be modified according to a patient's clinical status (Table 85.5). If a serum electrolyte concentration rises, the rate of its infusion should be adjusted. But, parenteral nutrition can rapidly lower potassium and phosphorus (and potentially others), related in part to the action of insulin. Alternatively, the low concentration may signal the need for administering a supplement. Note that calcium and magnesium deficiencies may occur during CVVH/CVVHD/CVVHDF treatment.[302] With the exception of iron and possibly zinc, copper, and selenium, supplements of trace elements are probably not needed for AKI patients unless the nutritional support will be extended for 2 to 3 weeks. Low values of plasma selenium can occur with the multiple organ dysfunction syndrome and, in a prospective trial, patients given 535 μg per day of sodium selenite had less morbidity and a reduced need for CVVHD.[303] Nutritional requirements

for other trace elements for AKI patients receiving TEN or TPN have not been established.

Vitamins

Requirements for vitamins are not defined for patients with AKI and tentative recommendations for patients receiving parenteral nutrition are listed in Table 85.5. We recommend that AKI patients receive water-soluble vitamins to make up for poor intake and dialysate losses (see previous). During CWH/CVVHD, water-soluble vitamins are lost and require supplements. AKI can also affect the fat-soluble vitamins, A, E, 25-OH vitamin D3, and l,25-(OH)2 vitamin D,3 and vitamin K. Vitamin D should be used for specified conditions and vitamin A should be given only for demonstrated deficiency because serum vitamin A levels are increased in CKD patients and supplements may cause toxicity. Vitamin E may be beneficial for CKD patients but requirements are poorly established (see Table 85.5). Vitamin K deficiency can occur because of poor appetite and antibiotic treatment of AKI patients (antibiotics suppress vitamin K–producing intestinal bacteria).[304] Vitamin K is given routinely to patients receiving parenteral nutrition (Table 85.5). Regarding water-soluble vitamins, 10 mg per day of pyridoxine hydrochloride and only 60 to 100 mg of ascorbic acid are recommended to avoid toxicity.[305]

Intravenous Nutrition Limited to Hemodialysis

For AKI patients with marginally adequate intakes, supplemental amino acids, glucose, or lipids may be infused during the hemodialysis treatment (i.e., intradialytic parenteral nutrition [IDPN]).[306] This avoids the need to catheterize a central or peripheral vein and reduces the problems of excessive fluid administration. Evidence does not demonstrate a clear benefit of IDPN.[306] IDPN reportedly improves protein synthesis and energy balance during hemodialysis, leading to an increase in serum albumin and BWef, but the studies were not well controlled.[306] Stationary bicycle exercise during hemodialysis in patients receiving IDPN reportedly improves protein balance, but it is not clear if mortality is improved with IDPN.[307,308] Based on these reports, we conclude that IDPN is indicated only for malnourished MHD patients who are unable to eat or tolerate tube feeding. Because most patients requiring IDPN have decreased intakes of energy and nitrogen, we give 40 to 42 g of EAAs and NEAAs and about 200 g of D-glucose (about 150 g of D-glucose if the dialysate contains glucose) and usually 250 mL of a 10% or 20% lipid solution (i.e., 25 to 50 g of fat) throughout the dialysis procedure. The nutrients may be used more efficiently if given continuously rather than as a bolus. Only small amounts of amino acids are lost into hemodialysate during IDPN.[313] Patients with low serum phosphorus levels may need supplements during the IDPN. If the dialysate does not contain glucose, the infusion should be maintained for 20 to 30 minutes after the dialysis to prevent hypoglycemia.

Nutritional Hemodialysis and Nutritional Peritoneal Dialysis

Amino acids and glucose may be added to the dialysate in order to increase their uptake. Lowering the dialysate flow rate may increase the uptake of amino acids and glucose when the nutrients are added to the hemodialysate. Thus, some investigators have reduced the dialysate flow rate to increase the fractional extraction of amino acids and glucose.[310] This reduces the costs of the nutrients but also decreases the efficiency of dialysis. When 46 g of a mixture of 20 amino acids are added to the hemodialysate, the amino acid concentrations are similar to those in the plasma of fasting patients and amino acid losses are reduced.[233] When 139 g of the same amino acid mixture is present, there is a net transfer of about 39 g of amino acids from the dialysate into the patient.

Adding amino acids to the peritoneal dialysate appears to increase Bn, protein synthesis, and the concentrations of several serum proteins.[311] It also allows a reduction in the dialysate glucose concentration. Generally, a mixture of both EAAs and NEAAs are added to a 1.1% dialysate solution. This amount is used for one to two peritoneal dialysate exchanges, and dwell times of 4 to 6 hours are used to ensure an uptake of about 80% of the amino acid content. The calorie load from these solutions is small and it is suggested that the dialysis be undertaken during major meals in order to provide calories and other nutrients with the amino acid load from the dialysate. Still, the patient should be counseled to eat regular food or undertake tube feeding before turning to these more expensive and incomplete nutritional supplements.

DIETARY THERAPY FOR RENAL TRANSPLANTATION

Following a successful kidney transplantation, patients often have an improvement in their appetite, in part due to glucocorticoid therapy. Generally, there is a gain in body weight and fat.[312,313] Other nutritional problems include the development of obesity, insulin resistance and diabetes mellitus,[313] impaired growth in children, protein wasting,[314] altered serum lipid and homocysteine concentrations,[315] and abnormalities in bone, mineral, and vitamin metabolism.[316] These complications are concerning because these patients are at risk for cardiovascular disease. An important cause of these disorders is prednisone because glucocorticoids cause metabolic changes, including enhanced gluconeogenesis, protein degradation, lipolysis, reduced protein synthesis, and increased glucose uptake. They also can increase serum cholesterol, inhibit intestinal calcium absorption, and reduce serum levels of 25-hydroxycholecalciferol and 1,25-dihydroxycholecalciferol.[317] The latter changes participate in negative calcium balance and osteoporosis. In addition, cyclosporine or tacrolimus can cause glucose intolerance. Kidney transplant patients treated with high doses of prednisone have sustained negative Bn[314,318] and this can be aggravated further by proteinuria. A report from a nonrandom-

ized study of kidney transplant patients receiving prednisone at 120 mg per day with tapering to 70 to 90 mg per day over approximately 10 to 14 days had intakes of protein and energy of 1.30 ± 0.06 (SEM) g/kg/day and 33 ± 3 kcal/kg/day.[314] However, their estimated Bn was still negative. This study points out the problems with using glucocorticoids. In another study[318] of 12 nondiabetic kidney transplant recipients with diets of 2 ± 0.03(SD) g protein/kg/day and only 28 ± 2 kcal/kg/day, Bn was more positive and potassium was lower with a more positive sodium balance. Lower doses of prednisone (i.e., 10 mg per day) do not appear to impair body composition or resting energy expenditure.

Kidney transplant patients often have increased serum triglycerides, VLDL triglycerides, and LDL, and total LDL cholesterol concentrations. HDL cholesterol is often low with an increased LDL/HDL cholesterol ratio.[319] Serum triglyceride levels are correlated with the prednisone dose plus obesity and the stage of CKD. These changes are relevant because there is a correlation between increased serum lipids and the risk of cardiovascular disease, graft failure, and fatality in kidney transplant recipients.[320] In most but not all studies, dietary counseling can reduce the energy intake, weight gain, and levels of serum total cholesterol, LDL cholesterol, and triglycerides, without changing the serum HDL cholesterol.[321] A low cholesterol, high fiber diet with a polyunsaturated saturated fatty acid ratio >1.0 was found to lower serum total cholesterol and LDL cholesterol after kidney transplantation.[321] A combination of a similar diet plus regular exercise can improve the plasma lipid pattern.[322] With 3 g per day of omega-3 fatty acids (as in fish oil), given over 3 months, serum triglycerides and VLDL cholesterol were decreased without a change in serum total cholesterol or LDL cholesterol. The effects of diet on the improvement in the serum lipid pattern tend to be modest and we recommend combining dietary therapy with statins as the more effective strategy for reducing serum total and LDL cholesterol.[323]

High plasma homocysteine concentrations could be a risk factor for cardiovascular complications and mortality in kidney transplant patients.[324] The causes of hyperhomocysteinemia include reduced kidney function and, less importantly, a low serum folate level and, possibly, cyclosporine A. There are conflicting reports about cyclosporine A versus tacrolimus and hyperhomocysteinemia.[326] Supplements of folic acid can decrease homocysteine, and it has been suggested that this benefit can be augmented by adding pyridoxine HCl (50 mg per day) and vitamin B12 (0.4 mg per day).[327]

Serum folate levels can be low for prolonged periods after kidney transplantation.[315] This could be linked to the finding that 52% of the patients develop macrocytosis, but even in this case, the patients were treated with azathioprine, which could have increased folate use. After a successful kidney transplant, serum vitamin A may not fall to normal for years.[328] Low plasma and hair zinc and urinary zinc losses have been observed after 1 year in kidney transplant patients.[329] This may be a reflection of more advanced kidney failure. Immunosuppressive medicines may affect the nutritional status of kidney transplant patients because cyclosporine A may increase serum LDL cholesterol and triglycerides, promote potassium retention with hyperkalemia,[320] cause urinary magnesium wasting with hypomagnesemia,[330] and promote early satiety during eating. Tacrolimus and sirolimus also increase serum LDL cholesterol levels.

Recommended Nutrient Intake for Renal Transplant Recipients

The nutritional requirements for kidney transplant patients are not established and our recommendations should be considered tentative. Immediately after kidney transplant surgery, especially if there is catabolism and/or prednisone at ≥30 mg per day, we recommend a diet of 1.3 to 1.5 g of protein per kilogram per day. If treatment with CVVH/CVVHD/CVVHDF or SLED is required, protein intake may be increased to 2.0 g/kg/day. If the daily prednisone dose is <30 mg per day, protein intake should be decreased. Although some reports suggest that low protein diets can retard the progression of kidney failure, it was not determined if the kidney transplant recipients who are receiving angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) had an additional benefit from low protein diets. In general, dietary protein is not restricted when the eGFR is >60 mL per minute unless there is a progressive loss of eGFR. If the patient is receiving >15 mg of prednisone per day, a protein intake of 0.60 to 0.80 g/kg/day is prescribed, but with higher doses of prednisone, the protein intake should be raised to 0.80 to 1.2 g/kg/day. If, however, the patient has an eGFR of 20 to 25 mL per minute or lower progressive less of GFR, then the patient is prescribed 0.6 g of protein per kilogram per day with at least 0.35 g of high biologic protein per kilogram per day. With a GFR of 20 to 25 mL/min or lower, some authorities would prescribe a very low-protein diet supplemented with a ketoacid plus essential amino acid mixture (see previous). Protein intake may be adjusted upward for acute increases in prednisone dosage or for large urinary protein losses as with nephrotic patients.[331]

A diet low in carbohydrates and modestly restricted in calories may reduce glucocorticoid toxicity.[318] However, diets that are moderately restricted in energy intake should be limited to short periods when the prednisone dosage is >40 mg per day in order to minimize the development of protein catabolism. Although a higher protein intake accompanying such diets (e.g., 2 g of protein per kilogram per day) may reduce protein malnutrition, there is the complicated problem of lipid abnormalities developing if lipids are substituted for carbohydrates in an attempt to avoid the Cushingoid complications (glucocorticoid toxicity). Kidney transplant patients should be encouraged to ingest a National Cholesterol Education Program Therapeutic Lifestyle Changes (TLC) diet as described earlier for CKD and MHD patients.[258] Patients also should be encouraged to exercise regularly and to maintain a normal body weight.[278,279] When superimposed

catabolic illnesses are present, 30 to 40 kcal per kilogram per day can be prescribed. If dietary therapy does not reduce serum LDL cholesterol to 70 mg per deciliter, statins should be used for patients with cardiovascular disease risk factors.[323]

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