SEMINARS IN
NEPHROLOGY

Nutrition and Metabolism in Kidney Disease

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Nutritional and metabolic derangements are highly prevalent in patients with chronic kidney disease (CKD) and patients on renal replacement therapy. These derangements, which can be termed *uremic malnutrition*, significantly affect the high morbidity and mortality rates observed in this patient population. Uremic malnutrition clearly is related to multiple factors encountered during the predialysis stage and during chronic dialysis therapy. Several preliminary studies suggested that interventions to improve the nutritional status and metabolic status of uremic patients actually may improve the expected outcome in these patients, although their long-term efficacy is not well established. It therefore is important to emphasize that uremic malnutrition is a major comorbid condition in CKD and renal replacement therapy patients, and that all efforts should be made to try to understand better and treat these conditions effectively to improve not only mortality but also the quality of life of chronically uremic patients. In this article we review the current state of knowledge in the field of nutrition and metabolism in all stages of CKD and renal replacement therapy, including kidney transplant. We also address questions that face investigators in this field and suggest where future research might be headed.
Semin Nephrol 26:134-157

KEYWORDS nutrition, metabolism, dialysis, kidney disease, kidney transplant

Despite substantial improvements in the science and technology in nephrology over the past decades, morbidity and mortality of patients with chronic kidney disease (CKD) remain high.[1] Among the many factors that affect outcome in this patient population, a state of metabolic and nutritional derangements seem to play a major role.[2,3] Multiple studies now indicate that these derangements are associated closely with important clinical outcomes such as hospitalization and death rates in CKD patients. It therefore is important to understand the mechanisms that cause or promote poor nutritional status in these patients. This article reviews the current state of knowledge in the field of nutrition and metabolism in all stages of CKD. Because the prevalence and mechanisms of nutritional and metabolic derangements are different for each stage of CKD, we separately discuss each stage of CKD and renal replacement therapy options, including kidney transplant. Finally, within each section of this review we address questions that face investigators in this field and suggest where future research might be headed. The article is divided into 5 sections: (1) definition and diagnosis of uremic malnutrition, (2) prevalence of uremic malnutrition, (3) the impact of uremic malnutrition on morbidity and mortality, (4) factors affecting the nutritional status in CKD, and (5) prevention and treatment strategies.

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Supported in part by National Institutes of Health grants R01 45,604 and 1K24 DK62849, Food and Drug Administration grant 000943, Norman S. Coplon Extramural Award from Satellite Health (L.B.P. and T.A.I.), Clinical Nutrition Research Unit grant DK-26,657, and General Clinical Research Center grant RR 00,095. Supported in part by the Vanderbilt Physician-Scientist Development Program, and the Marilyn Simpson Charitable Trust Young Investigator grant of the National Kidney Foundation (L.B.P.), and by the Oswaldo Ramos Foundation (L.C.).
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Definition and Diagnosis of Uremic Malnutrition

For decades, the state of nutritional and metabolic derangements observed in patients with CKD has been identified as a state of protein-energy malnutrition. Although it is not the aim of this article to discuss the nomenclature, it is important to mention that the inappropriateness of the term *malnutrition* has been discussed recently.[4,5] Malnutrition is defined as poor nutritional status as a result of poor nutrient intake.[6] Nonetheless, available data indicate factors other than insuf-

 0270-9295/06/$-see front matter
doi:10.1016/j.semnephrol.2005.09.010

Table 1 Most Commonly Used Nutritional Markers in Uremic Patients

Biochemical
Serum albumin <4.0 g/dL
Serum transferrin <200 mg/dL
Serum IGF-1 <200 ng/mL
Serum prealbumin <30 mg/dL or an apparent decreasing trend
Altered profile or abnormally low plasma and muscle amino acid concentrations
Relatively low serum creatinine level with other signs of uremia or low creatinine kinetics
Anthropometrics
Body weight: continuous decrease or low % of ideal body weight (<85%)
Abnormal skinfold thickness, midarm muscle circumference, and/or muscle strength
Body composition
Abnormally low lean body mass by BIA and/or DEXA
Low total body nitrogen and/or nitrogen index (observed nitrogen/predicted nitrogen)
Dietary assessment
DPI <0.7 g/kg/d in CKD patients (by 24-h urea nitrogen excretion)
DPI <1.0 g/kg/d in CDT patients (by protein catabolic rate)

ficient intake as the leading cause of nutritional and metabolic disturbances in uremic patients. In these patients, low concentrations of serum and somatic proteins may occur despite dietary protein and energy intake that is based on standard nutrition guidelines for this population. In fact, some uremic patients are identified as malnourished by means of low levels of protein stores regardless of their weight, with some actually being overweight. This corroborates the suggestion that malnutrition is not an appropriate nomenclature when used to define the metabolic abnormalities that ultimately lead to a state of protein catabolism and loss of lean body mass in CKD patients. Although there is no specific definition for such derangements, we refer to it as a state of *uremic malnutrition* in this article.

Multiple epidemiologic studies have confirmed the close association between commonly available nutritional markers and clinical outcomes in CKD patients, especially stages 4 and 5 CKD patients. An important caveat that needs to be considered is that most readily available nutritional biomarkers may reflect a general health status rather than exclusively reflecting the nutritional status of CKD patients of all stages, as is believed to be the case with serum albumin levels.[7-9] Similar arguments can be applied to other nutritional markers. An ideal nutritional marker not only should predict hospitalization and death but also identify patients who should receive nutritional intervention. Therefore, the validity and the applicability of these measures to reflect nutritional status are extremely important.

A detailed description of the multitude of available tools to diagnose and monitor nutritional status is out of the scope of this review and can be found elsewhere.[10] Nonetheless, in this article we provide an overview of the measures that are relevant to both clinical and research settings. Among these, there are relatively simple biochemical measures reflecting the protein stores, such as serum albumin, cholesterol, and creatinine levels,[11,12] and more complex and not readily available parameters such as plasma and muscle amino acid profiles,[13] prealbumin levels,[14] and insulin-like growth factor-1 (IGF-1) levels.[15] In addition, analysis of body composition with different techniques such as anthropometric,[16] bioelectrical impedance analysis (BIA),[17-20] dual-energy radiograph absorptiometry (DXA),[21-23] and total body nitrogen[24,25] are markers of somatic protein stores. Composite assessments include subjective global assessment (SGA) and composite nutritional index (CNI). More sophisticated methodologies include indirect calorimetry for energy balance assessment, and protein kinetics for protein turnover assessment. Table 1 shows a list of these tools with their most common use in diagnosing and monitoring uremic malnutrition.

Serum Markers

Serum albumin level is the most extensively examined nutritional marker in almost all patient populations, probably because of its easy availability and strong association with hospitalization and death risk.[26,27] In fact, low serum albumin concentrations usually are accompanied by other markers of nutritional state in multiple studies with different patient populations, including CKD patients.[16,28-30] These observations led to the misconception that an abnormal serum albumin concentration by itself usually is sufficient to diagnose uremic malnutrition. Although rapid (short-term) decreases in the rate of albumin synthesis occur as a result of insufficient energy and protein intake,[31] the impact of altered dietary intake on albumin level in the long term is subtle. This is because decreases in albumin breakdown are compensated by shifts from the extravascular to the intravascular space in attempts to maintain adequate serum albumin concentrations. Therefore, because serum albumin has a relatively long half-life (≈20 d) and a large pool size,[32] the impact of altered dietary intake may be subtle on serum concentrations. In addition, there are nonnutritional causes of hypoalbuminemia such as decreased synthesis as a result of hepatic disease, increased transcapillary loss, increased loss through the gastrointestinal tract and kidneys, and from tissue injuries such as wounds, burns, and peritonitis.[33] Furthermore, serum albumin levels have been shown to decrease in situations of volume overload, which is highly prevalent in CKD patients.[34] Serum albumin, as a negative acute-phase reactant,

also is affected by conditions with acute-phase response, such as inflammation, infection, and trauma, that lead to prompt and usually substantial decreases in serum concentrations.[35] In this context, the decrease in serum albumin concentrations more closely may reflect the degree of illness and inflammation, rather than the overall nutritional status.[36,37] A study by Kaysen et al[34] reported that hypoalbuminemia in advanced CKD patients may reflect nonnutritional factors, such as external losses and decreased synthesis. Taking all these limitations into account, concerns have been raised regarding the appropriateness of serum albumin concentration to assess nutritional status in CKD patients, especially if confounding factors such as inflammation are not taken into account. Nonetheless, low levels of serum albumin are highly predictive of poor clinical outcomes in all stages of CKD and, therefore, serum albumin still is considered a reliable marker of general clinical status.[38,39] The National Kidney Foundation—Kidney Disease Outcomes and Quality Initiative (NKF-K/DOQI) nutrition guidelines recommend a value of 4.0 g/dL or greater for serum albumin in stage 5 CKD patients.[40] Further research still is needed to understand better the use of serum albumin as a nutritional marker for CKD patients.

In addition to serum albumin, several other serum proteins have been identified as diagnostic tools to assess protein and energy stores, including serum transferrin and serum prealbumin. With a half-life of only about 8 to 10 days and its small body pool, serum transferrin responds more rapidly to short-term changes in protein status compared with serum albumin.[41,42] However, serum transferrin concentrations are affected by iron metabolism, which frequently is altered in CKD patients, making its use as a marker of protein stores somewhat problematic.[12] Therefore, serum transferrin is not a recommended nutritional marker in CKD patients, especially in stages 4 and 5.

The serum prealbumin level is more sensitive than the serum albumin level in detecting subtle changes in visceral protein stores because of its lower body pool and shorter half-life (2-3 d).[41,43] Reduced protein and energy intake decrease serum prealbumin concentrations, which can be restored by refeeding,[44,45] making it a useful tool to monitor nutritional support.[46] In addition, serum prealbumin level has been reported to be a significant predictor of death rate in dialysis patients.[47] However, similar to serum albumin, serum prealbumin levels decrease in response to inflammatory stimuli.[48] In patients with progressive CKD, serum prealbumin concentration tends to increase as a result of reduced renal catabolism, which makes its use as a nutritional marker to some extent complicated. However, in stage 5 CKD patients on dialysis in whom kidney function is relatively stable, serum prealbumin level may be a useful tool and a level less than 30 mg/dL has been recommended to identify protein depletion even though this is a normal range value for individuals with normal kidney function.[14,49]

Other serum markers can be useful in the evaluation of poor nutritional status in CKD patients. Serum concentration of C-reactive protein (CRP) is correlated strongly and negatively with concentrations of serum albumin,[43,50] and chronic dialysis patients with hypoalbuminemia tend to have higher values of CRP compared with patients with normal serum albumin levels.[28,51] In practical terms, it is important to keep in mind that very low levels of most visceral proteins may be caused by nonnutritional sources of protein depletion, especially a negative acute phase response to inflammatory stimuli, which may warrant clinical investigation and proper treatment.

Low predialysis serum concentrations of creatinine also are associated with poor clinical outcome in maintenance dialysis patients.[50] Therefore, the NKF-K/DOQI nutrition guidelines recommend that patients with predialysis serum creatinine concentrations of less than approximately 10 mg/dL should be evaluated for muscle wasting.[40]

Serum cholesterol concentration is an independent predictor of mortality in chronic dialysis patients, and very low serum cholesterol concentrations can be indicative of chronically low dietary intake, especially energy intake.[50] Therefore, for stages 4 and 5 CKD patients with serum cholesterol concentrations less than 150 mg/dL, or for those with gradual and persistent serum cholesterol reduction, a careful evaluation of nutritional status and of other comorbidities is recommended.[40]

Serial measurements of blood urea nitrogen (BUN) can be useful to monitor protein intake in chronic hemodialysis (CHD) patients with little or no residual renal function. Not only are low BUN concentrations associated with higher mortality in dialysis patients, but its concentrations decrease gradually (from a predefined baseline value) in CKD patients with established uremic malnutrition or increased risk for poor nutritional status.[3] However, BUN levels can be increased in protein catabolic conditions, even with reduced protein intake. Thus, it is important to evaluate BUN concentrations along with other tools of protein intake.

Body Composition

In addition to serum protein concentrations, analysis of body composition is another important tool for the assessment of nutritional status in uremic patients. The most simple but unfortunately the least reliable technique for patients with kidney failure is anthropometry. This relatively easy but largely subjected to intraobserver and interobserver variability methodology is available readily and may be used as a confirmatory tool when uremic malnutrition is suspected, or to detect long-term changes in the nutritional status.[52,53] There are more reliable and accurate, although less available, methods of body composition analysis, such as prompt neutron activation analysis, which measures total body nitrogen content, and DXA, which also is reported to be reliable in patients with kidney failure.[25,54,55] Nonetheless, these measurements require costly equipment and trained personnel that only are available in few centers. A promising and more available method for body composition assessment is BIA, which has been proposed as an accurate and reproducible measure of body composition in many different patient populations, including CKD patients.[17,56] Because BIA does not detect acute changes in body water and does not take into

account the presence of peritoneal dialysis fluid, its use in uremic patients needs consistency for accurate measurements. It is suggested that the measurements be performed before dialysis or 30 minutes after dialysis in hemodialysis patients and without the dialysate in peritoneal dialysis patients.[56] Body composition also can be estimated by creatinine kinetics, which correlates well with other lean body mass measurements.[57]

Composite Assessment

Composite assessments include SGA but also the CNI and the malnutrition-inflammation score (MIS). They are clinically useful tools for evaluating nutritional status at a broader perspective, including medical history, symptoms, and physical parameters. SGA was used originally to predict outcomes in surgical patients and has been validated as a screening tool for this population.[58] The use of SGA as a nutritional assessment tool for CKD patients of different stages is growing in both clinical and research settings.[59] Despite using a great variety of modified score systems, studies in hemodialysis and peritoneal dialysis patients have shown that SGA reasonably may detect both the presence of uremic malnutrition and increases in mortality risk.[8,60-62] However, some reports have shown significant differences between SGA scores and some traditional nutritional markers including serum albumin level, serum prealbumin level, body mass index (BMI), midarm muscle circumference, and fat and lean body mass.[63,64] In addition, concerns have been raised regarding the poor sensibility of SGA in detecting the degree of uremic malnutrition and small changes in nutritional status.[65] The CNI takes into account SGA, anthropometric indices, and serum albumin level to draw nutritional scores; a score of zero indicates normal nutrition and increasing scores indicate worsening nutritional status.[66] Jones et al[65] compared SGA and CNI scores in 72 chronic hemodialysis patients and found that SGA scores discriminated between the best-nourished versus the worst-nourished patients as judged by the composite score. However, a number of patients with evidence of significant malnutrition on the CNI presented with normal SGA scores. Finally, the MIS system uses a revised form of the SGA scoring system and adds BMI, serum albumin level, and total iron-binding capacity to create a more quantitative score.[67] The MIS has been identified as a strong outcome predictor in hemodialysis patients.[61] Its exclusive feature as compared with other indices is the inclusion of inflammation, which relies on measures of total iron-binding capacity, normally affected by iron metabolism, which is altered in CKD.[12] Therefore, as with any method for nutritional status assessment, SGA, CNI, and MIS should be used in conjunction with other methods, and prospective controlled studies including a large and representative sample of CKD patients of all stages are needed to establish these tools for clinical and research applicability.

Dietary Intake

Estimation of energy and protein intake by different methods also can be used as a marker of overall nutritional status in CKD patients. Although dietary diaries and history are direct and simple measures of dietary intake, several studies have shown that these methods lack accuracy in estimating the actual intake of patients, even in experimental settings.[68-70] Differently from energy intake, which can be estimated only by using less accurate methods, dietary protein intake (DPI) can be measured by other more reliable means, such as 24-hour urine urea nitrogen excretion in CKD patients not yet on dialysis[71] or protein equivalent of total nitrogen appearance (PNA) in dialysis patients. However, it should be noted that these indirect estimations of DPI are valid only in clinically stable patients, and easily may overestimate the actual intake in catabolic patients, in whom endogenous protein breakdown may lead to a high urea nitrogen appearance.[72] Concerns also have been raised regarding whether PNA is linked mathematically to Kt/V rather than an independent nutritional parameter.[66,73] Although this question has not yet been elucidated, a recent study including adequately dialyzed hemodialysis patients (Kt/V $>$ 1.20) showed that PNA correlates with hospitalization and mortality but not with Kt/V.[74] However, considering that there still are uncertainties regarding the relationship between PNA and nutritional status, PNA results should be analyzed with caution and in conjunction with other more reliable markers of malnutrition.

Energy Expenditure

Resting energy expenditure (REE) comprises about 60% to 75% of total energy expenditure[75] and refers to the energy expended for maintenance of normal body functions and homeostasis. Lean body mass is the primary determinant of energy expenditure and generally explains about 70% to 80% of the variance in REE.[76,77] Other factors influencing REE include nutritional status, endocrine status, inherited variations, and acute and chronic diseases.[76,77] Many methods of measuring REE have become available over the years but the most widely used is indirect calorimetry, which can be measured mainly by 2 methods: the metabolic cart and the metabolic chamber. Indirect calorimetry measures REE based on oxygen consumption (V_{O_2}) and carbon dioxide production (V_{CO_2}). More recently, a hand-held indirect calorimeter monitor was developed, which is similar to the metabolic cart and chamber methods except it does not measure V_{CO_2} but assumes a constant respiratory quotient of 0.85. Although not yet validated formally, a recent study by St-Onge et al[78] found no differences in REE between the hand-held calorimeter and a metabolic cart. Finally, when there is limited access to equipment to measure REE, less reliable but readily available predictive equations can be used such as the Harris Benedict equation.[79] Measurement of REE alone is not sufficient to diagnose poor nutritional status because of the high interindividual variability in REE caused by metabolic status and/or comorbid conditions. Nonetheless, it can be useful when interpreted in conjunction with dietary energy intake (ie, energy balance = energy intake - energy expenditure), mainly to tailor nutritional support, both in the clinical and in the research setting.

Protein Homeostasis

There are 2 major methodologies that accurately measure protein homeostasis in human beings: nitrogen balance and stable isotope infusion techniques. Classic nitrogen balance techniques constitute a sensitive and accurate tool for assessing the nutritional and metabolic response to changes in nutritional status,[80] although it is not a tool that can be used in routine clinical practice. It requires a well-trained team and a period of equilibration of 10 to 14 days, after which nitrogen balance can be measured over a period of 5 to 10 days.[81-83] Therefore, the technique can be cumbersome when trying to assess, for example, the effects of a nutritional intervention. The use of PNA could be an alternative approach for interpreting nitrogen balance in end-stage renal disease (ESRD) patients with edema-free and metabolic steady-state conditions.[80] Stable isotope infusion techniques constitute a more precise protein homeostasis methodology because it quantifies the protein turnover in the body, an event much more variable than DPI in very short periods of time.[84] An effective method for assessing protein balance (protein synthesis minus protein breakdown) is the use of isotopically labeled amino acids (tracers) such as leucine, valine, and lysine for the whole-body component, and phenylalanine for the skeletal muscle component. In brief, the rate of appearance of endogenous leucine in the plasma is an estimate of whole-body protein breakdown and the nonoxidative leucine disappearance rate from the plasma is an estimate of whole-body protein synthesis.[85] Similar calculations are used to assess protein turnover in skeletal muscle, but with the use of isotopically labeled phenylalanine because phenylalanine is neither synthesized de novo nor metabolized by skeletal muscle. Therefore, the rate of appearance of unlabeled phenylalanine reflects muscle protein breakdown and the rate of disappearance of labeled phenylalanine estimates muscle protein synthesis.[86] The detailed techniques are beyond the scope of this review and can be found elsewhere.[87,88] Studies in ESRD patients have shown the use and validity of stable isotope techniques as precise tools for evaluating metabolic responses to nutritional interventions, and the metabolic responses to the hemodialysis procedure.[89-92] The use of this methodology, even for research purposes, is limited because of its high cost and the requirement of a very specialized team. Nevertheless, it provides the most precise estimate of protein and energy homeostasis.

Prevalence of Uremic Malnutrition

Virtually every study evaluating the nutritional status of CKD patients reports some degree of inadequate nutritional status in this population, particularly regarding protein and energy depletion. Because of the many different diagnostic tools used in separate studies, the prevalence of uremic malnutrition varies widely among different reports, ranging from 20% to 50% at different stages of CKD.[63,93,94] In this section we provide a summary of the available literature on the prevalence of uremic malnutrition in CKD, dialysis (hemodialysis and peritoneal dialysis), and kidney transplant patients.

CKD Patients

Data regarding the prevalence of inadequate nutritional status in CKD patients are limited when compared with that of patients commencing or already on chronic dialysis therapy. Although there is some evidence showing a worsening in the nutritional parameters with the progression of CKD,[95,96] uremic malnutrition seems to be more evident in stage 5 CKD, especially in patients not previously submitted to dietary counseling.[97] In fact, the prevalence of uremic malnutrition assessed by SGA was found to be about 40% in patients with a glomerular filtration rate (GFR) off less than 15 mL/min.[63,98] Despite a progressive decrease in DPI as kidney function deteriorates,[99] a number of studies indicate that CKD patients who are prescribed low or even very low protein diets are able to maintain adequate nutritional status as CKD advances, provided that they are monitored carefully with regard to dietary intake and clinical conditions.[100-103] In the 2-year follow-up analysis of the Modification of Diet in Renal Disease (MDRD) study a significant increase in serum albumin level and only subtle reductions in anthropometric parameters were observed in a group of carefully monitored patients prescribed a low-protein diet. There were only 2 withdrawals from the MDRD study because of deterioration of nutritional status.[103]

In addition to uremic malnutrition, another nutritional abnormality that deserves mention in CKD patients is the relatively high prevalence of overweight and obesity, documented by increased body fat and BMI, that has been reported in this population.[96,103,104] This issue calls for further attention when the strong inverse association between higher BMI and death rate in stage 5 CKD is considered. This finding is different than what is observed in the general population and the exact mechanism underlying the pathophysiologic link remains to be elucidated. It is possible that the excess of body fat is a consequence of or associated with depletion of protein stores, but these possible relationships remain to be investigated. Studies using accurate and sensitive methods to evaluate body composition compartments and how they relate to one another are needed to better characterize the nutritional status of patients at different stages of CKD and the impact of fat tissue stores on metabolism.

Dialysis-Dependent Patients

CHD patients

Once CKD patients are initiated on hemodialysis, the extent of uremic malnutrition becomes more evident. Although there is evidence of improvement in nutritional parameters within 3 to 6 months after initiation of hemodialysis,[105,106] uremic malnutrition still is present in up to 40% or more of the CHD population.[93] A great variety of nutritional parameters have been used in the many studies designed to detect uremic malnutrition in hemodialysis patients. Serum albumin level has been by far the most widely used marker, and many epidemiologic reports on nutrition in hemodialysis pa-

tients have been based mainly on serum albumin concentrations. In earlier studies, albumin concentrations have been found to be less than 3.7 g/dL in 25% of the 12,000 CHD patients studied.[7] In the baseline phase of the Hemodialysis study (HEMO), 29% of the patients had albumin levels less than 3.5 g/dL.[107] More recently, SGA has become a commonly used marker for nutritional status in stage 5 CKD patients, along with serum albumin level. Results from the Dialysis Outcomes and Practice Patterns Study showed a prevalence of 15.4% and 6.5% for moderately and severely malnourished CHD patients, respectively, as diagnosed by SGA.[108] Several smaller studies have shown evidence for uremic malnutrition in CHD patients, ranging from 45% to 60%, using either a single tool or a combined diagnostic assessment of uremic malnutrition.[13,15,109,110] Therefore, despite the great variability in the prevalence rates of uremic malnutrition in CHD among studies, it is evident that nutrition abnormalities exist in a substantial number of CHD patients.

Peritoneal dialysis patients

The prevalence of uremic malnutrition in peritoneal dialysis (PD) patients is relatively similar to that of patients on CHD. Although one study reported a higher prevalence of uremic malnutrition in continuous ambulatory PD (CAPD) patients compared with CHD patients,[111] others did not confirm such differences.[112,113] Young et al[114] studied 224 CAPD patients in 6 centers in Europe and North America and reported mild to moderate malnutrition in 32.6% of patients, whereas 8% of the patients were severely malnourished, as judged by SGA. In a multicenter study in Japan, Kumano and Kawaguchi[115] found 26.2% and 3% of CAPD patients with moderate and severe uremic malnutrition, respectively. By using a composite nutritional index, Harty at al[66] found a prevalence of 17% of severe uremic malnutrition in 157 CAPD patients. More recently, the European Automated Peritoneal Dialysis study found an even higher prevalence of poor nutritional state, reaching an alarming rate of 53%, among 177 anuric patients on automated PD.[116] Evidence of inadequate nutritional status also has been reported in several studies using either anthropometric, biochemical, or body composition parameters.[117,118] Accumulation of body fat mass has been reported during the first year of PD,[117,119] although there also is evidence that in the long term, PD patients lose lean body mass.[120-123]

Transplant patients

The information on the nutritional state of transplant patients is limited. Because weight gain during the posttransplant period is common, more attention has been paid to obesity rather than malnutrition in transplanted patients.[124] Nonetheless, as with dialysis, there also is evidence of protein-store depletion in kidney transplant patients. A report from Djukanovic et al[125] showed that 15% of their 452 kidney transplant patients had a BMI of less than 21 kg/m2, which the investigators attributed to malnutrition. A study by Williams et al[126] reported significantly lower whole-body contents of nitrogen, serum potassium, and serum calcium in kidney transplant patients, especially during the first year posttransplant. Verran et al[127] found a slightly decreased body protein content in 5 transplanted patients as compared with the predicted values for healthy subjects, and Miller et al[128] showed that 42% of diabetic and 29% of nondiabetic kidney transplant patients had midarm muscle circumference less than the 5th percentile at 22.6 ± 23.8 months after transplantation, despite improvements in several indices of nutrition after transplantation. A study by Qureshi et al[129] suggested that there is depletion of protein stores at the cellular level after 45 days of transplantation, which normalize in the long term. Finally, a study by El Haggan et al[130] showed significant decreases in serum albumin, serum transferrin, and retinol binding protein levels in 44 patients during the first year posttransplant. Two more recent studies reported maintenance of lean body mass, examined by DXA, in early kidney transplant patients.[130,131] Heaf et al[132] recently compared the lean body mass of 115 transplanted patients (6.6 ± 5.9 years after transplantation) with healthy individuals, evaluated by DXA, and found it to be 4% to 5% lower than in healthy subjects. Nevertheless, the actual prevalence and incidence of poor nutritional state, especially as it relates to episodes of graft failure, remain to be examined, and studies in this patient population should be encouraged.

The Impact of Uremic Malnutrition on Morbidity and Mortality

A number of studies have documented a close relationship between measures of uremic malnutrition and increased hospitalization and death rates, especially in stage 5 CKD patients on chronic dialysis.[2,3] The association of poor nutrition and outcome also has been observed in patient populations other than CKD, particularly in acutely ill and elderly patients.[29,36] It is interesting to note that malnutrition rarely is documented as a cause of death. Nevertheless, there is a body of evidence to suggest that the nutritional status of CKD patients plays a major role in the outcome of these patients. In fact, the first apparent indication of suboptimal nutrition and related poor outcome in dialysis patients came from the analysis of the National Cooperative Dialysis Study results. In this well-known comprehensive study of 262 CHD patients, the patient group with the lowest PNA, which presumably reflects DPI in stable CHD patients, had the highest treatment failure and drop-out rate.[133] In addition, this group of patients had the highest death rate after the termination of the study. This observation was confirmed later by some[74,134] but not by other investigators.[62,135] Possibly the close relationship between PNA and Kt/V and between Kt/V and outcomes could have led to the contrasting results in different studies.

The most studied nutritionally related parameter in predicting outcomes in the dialysis population is serum albumin level and one of the most comprehensive studies on this issue was reported by Lowrie and Lew.[7] In their analysis of more than 12,000 CHD patients, they identified serum albumin concentration as the most powerful indicator of death rate. The risk for death in patients with a serum albumin concen-

tration of less than 2.5 g/dL was close to 20-fold compared with patients with a serum albumin level of 4.0 to 4.5 g/dL, which is considered to be the reference range. However, as stated previously, such a low level of serum albumin hardly ever results from pure protein-energy malnutrition, suggesting that the observed increased risk for death most likely is caused by a combination of multiple nutritional and metabolic derangements. Nevertheless, when compared with this reference range, even serum albumin values of 3.5 to 4.0 g/dL resulted in a 2-fold increase in the relative risk for death, which could be a reflection of a state of nutritional deficiency. Considering the close relationship among inflammation, malnutrition, and hypoalbuminemia, it is difficult to separate their associated effects in predicting clinical outcomes. This issue has been analyzed recently in a study performed at our laboratory, in which 194 CHD patients were followed-up over a 57-month period and markers of uremic malnutrition, including serum albumin level, were found to be significant predictors of all-cause mortality even after adjustment for the serum CRP level, a putative marker for inflammatory state.[9]

Similar observations were made in PD patients. For example, serum albumin concentrations ranging from 3.0 to 3.5 g/dL have been associated with an increased risk for mortality in CAPD patients.[136,137] Avram et al[138] also reported the independent association of serum albumin level with increased risk for death in the patients who were followed-up for up to 7 years. In a large prospective cohort of 680 CAPD patients from Canada and the United States a strong inverse association between serum albumin concentration and either length of hospitalization or mortality was shown.[8] Importantly, the relative risk for death for patients with low serum albumin level was the same for CHD and PD patients, suggesting that peritoneal losses of albumin do not mitigate against serum albumin as a prognostic factor of the patients' death risk.

In addition to serum albumin level, low levels of other biochemical nutrition markers, namely serum creatinine, serum BUN, serum cholesterol, serum transferrin, serum prealbumin, serum IGF-1, total lymphocyte counts, and plasma amino acid profiles, also are associated with increased risk for death in the dialysis population.[7,29,139,140] However, most of these studies were performed in small study populations and their validity as outcome predictors remains to be determined.

With regard to anthropometric parameters, the relationship between low values and increased mortality, especially with body weight and BMI, is not as clear-cut as with serum proteins. The relationship between overweight and mortality in CHD patients, for example, has been a subject of debate over the past few years. A BMI of less than 24.4 kg/m^2 has been shown to increase mortality significantly during a 5-year observation in more than 3,000 CHD patients.[141] In the Dialysis Outcomes and Practice Patterns study, a BMI of less than 21.1 kg/m^2 was associated with a mortality risk 60% higher than that of patients with a BMI of more than 28.1 kg/m^2. More importantly, the mortality risk significantly increased among patients with a decrease in BMI greater than 3.5% in 6 months.[62] Kopple et al[142] studied a sample of nearly 13,000 patients undergoing CHD and showed an independent and inverse relationship between weight-for-height and mortality rates in patients with weight-for-height less than the 50th percentile. Contrarily, Fleischmann et al[143] reported an inverse relationship between BMI and death, that is, that "higher than normal" BMI was associated with a reduced risk for death. However, in an elegant accompanying editorial, Hakim and Lowrie[144] questioned the definition of "normal weight" and proposed some potential confounding factors for such a paradoxic association. Importantly, most of these studies evaluated a single measure of body weight rather than serial measurements over time. There seems to be, however, a reduction in body weight in most patients with advanced CKD,[142] or an inverse relationship between BMI and duration of dialysis,[143] all suggesting a variation in body weight in the long term. Therefore, changes in body weight and how these changes may affect outcome in stages 4 to 5 CKD patients need to be studied further.

There are a limited number of studies evaluating the impact of body compartment size and ratios on clinical outcomes. By using DXA, Kato et al[145] reported that a reduced limb/trunk lean mass in men and a lower percentage of fat trunk mass in women were significant determinants of 5-year mortality in CHD patients. In incident CAPD patients, lean body mass estimated by creatinine kinetics seems to be an independent predictor of death.[146] Parameters derived by BIA (ie, phase angle and reactance) also have been associated with clinical outcomes.[147,148]

With regard to SGA, an increasing number of prospective studies recently have shown an association between SGA scores with clinical outcomes both in CHD and PD patients in past years, regardless of the version of SGA used.[8,62,67,149]

To the best of our knowledge, the association between uremic malnutrition and outcomes in the earlier stages of CKD (stages 1-3) has not been investigated. Nevertheless, there is good evidence to suggest that the predialysis nutritional status of CKD affects their outcome after the initiation of chronic dialysis therapy.[150] Specifically, patients who initiate chronic dialysis with evidence of uremic malnutrition have the highest risk for death during the course of dialysis therapy.[105,138,151]

Very limited information is available with regard to the association between nutritional status and morbidity and mortality in kidney transplant patients. As stated previously, transplant patients appear to have decreases in serum albumin concentrations and lean body mass, especially during the early phases of transplantation. However, there are no published studies, at least to our knowledge, that evaluated the predictive power of poor nutritional status on either allograft or patient outcome. Of note, the higher BMI, which seems to be protective in patients on dialysis, is associated directly with worse hospitalization and death rates in transplant patients. This observation suggests that the replacement of kidney function (or the loss of it) has a distinct influence on how the fat stores exert their metabolic effects. This interesting yet not elucidated relationship needs to be explored in large long-term studies comparing dialysis and transplant patients.

Factors Affecting the Nutritional Status in Uremia

Multiple factors play important roles in the development of uremic malnutrition, many of which act concurrently. In this article we provide a review of studies on these factors as they pertain to CKD and renal replacement therapy, including kidney transplant, as applicable. Nonetheless, most of these factors may overlap between the various stages and therapies of CKD whereas others may persist through all stages of CKD.

Poor Dietary Nutrient Intake

Anorexia, as evidenced by decreased dietary protein and energy intake, is a hallmark of advanced CKD.[152] Studies have shown that dietary nutrient intake decreases as a result of worsening kidney function, and emphasizes the adverse effects of decreased food intake on nutritional status.[95,103,153] An early cross-sectional study of 900 CKD patients reported spontaneous decreases in food intake, specifically of high-protein products, with decreasing kidney function.[154] Likewise, the MDRD study suggested a positive correlation between the GFR and the actual and reported protein and energy intake, that is, the lower the GFR, the lower the protein and energy intake.[155,156] The investigators suggested that the signs of protein and energy depletion become more evident when the GFR is less than 10 mL/min. Similarly, in a prospective analysis of protein intake by patients with progressive CKD but with minimal dietary interventions, many patients spontaneously restrict their protein intake with progression of kidney disease, with DPI less than 0.6 g/kg/d when creatinine clearance was less than 10 mL/min.[99] In this study, it was reported that other markers of nutrition such as weight and IGF-1 concentrations correlated with kidney function and protein intake. More recently, Duenhas et al[96] examined spontaneous food intake and nutritional parameters in 487 patients with different degrees of CKD without dietary interventions. They found that both energy and protein intakes were significantly lower in patients in the lower quartile of creatinine clearance (<19.9 mL/min/1.73 m^2) compared with the highest quartile (>43 mL/min/1.73 m^2). In this study, other nutritional parameters such as BMI, percent of ideal body weight, percent of midarm muscle circumference, and percent of triceps skin-fold thickness also were significantly lower in the lowest quartile when compared with the highest quartile of creatinine clearance.

Although the exact mechanism by which uremia leads to anorexia has not been elucidated, a landmark study by Bergstrom et al showed that accumulation of a low molecular weight substance (<5 kd), isolated from uremic plasma ultrafiltrate and normal urine, and injected into otherwise healthy rats, induced a dose-dependent suppression of appetite.[157] Although a cause and effect relationship cannot be extrapolated readily to human beings, these findings suggest that a relationship exists between the extent of kidney disease, as assessed by uremic toxin accumulation, and spontaneous dietary protein and energy intake and nutritional status.

Evidently these observations do not apply to patients who may be prescribed protein-restricted diets, supplemented or not with essential amino acids and/or their ketoanalogs. Several studies, including the MDRD study, have shown that with close supervision and a heavy emphasis on energy intake, patients may have protein-restricted diets without the development of overt malnutrition.[101,158,159] This was recently confirmed by Feiten et al,[102] who evaluated the effects of a very low protein diet supplemented with ketoacids in comparison with a conventional low-protein diet on nutritional and metabolic parameters in 24 CKD patients with advanced CKD. The investigators showed that after 4 months of follow-up evaluation, nutritional status was maintained adequately with both diet regimens. Although the clinical efficacy and cost of such interventions have been questioned,[151,160] such interventions could not be applied easily to the majority of patients with CKD; thus, in the majority of patients who are not on a closely supervised diet, the development of progressive CKD is followed by a worsening in anorexia, decreased food intake, and, possibly, the development of uremic malnutrition.

Metabolic and Hormonal Derangements

Metabolic acidosis, which commonly accompanies progressive CKD, also promotes uremic malnutrition, by increasing protein catabolism.[161,162] Landmark studies by Mitch et al[163-167] showed that muscle proteolysis is stimulated by an adenosine triphosphate–dependent pathway involving ubiquitin and proteasomes during metabolic acidosis. Ballmer et al[168] reported that a state of metabolic acidosis induced by high doses of ammonium chloride (NH_4Cl) (4.2 mmol/kg), lasting for 7 days, significantly reduces albumin synthesis and induces negative nitrogen balance in otherwise healthy subjects. Studies by Mochizuki[169] showed that acidosis increases the degradation of branched-chain amino acids and branched-chain ketoacids in CKD patients. Reaich et al[170] studied leucine kinetics and showed that the high rate of leucine oxidation in acidotic CKD patients, a potential catabolic factor, could be corrected after a 4-week treatment period with sodium bicarbonate and sodium chloride. A relevant issue that needs mentioning is that in CKD patients total bicarbonate concentrations generally decrease as kidney function worsens.[171] Because nPNA is estimated by measuring urinary urea nitrogen excretion in stable patients, considering the catabolic effects of metabolic acidosis,[71] the spontaneous DPI may be overestimated in patients with advanced CKD, when metabolic acidosis is most apparent. Once chronic dialysis is initiated, one would expect that the partial correction of serum bicarbonate concentrations caused by dialysis would overcome, at least in part, the catabolic consequences of metabolic acidosis. Surprisingly, there is evidence that the catabolic effects associated with metabolic acidosis are not totally negligible even after dialysis is initiated.

Lofberg et al[172] measured the concentrations of branched-chain amino acids in the intracellular fluid of muscle biopsy specimens obtained from CHD patients. They found that the

intracellular valine concentration was correlated negatively with the level of plasma bicarbonate concentrations. Further, in this study higher muscle intracellular concentrations of valine, leucine, and isoleucine were observed after providing dialysis patients with supplemental sodium bicarbonate for a period of 6 months. Similarly, Pickering et al[173] examined muscle tissue and evaluated whether increasing the serum bicarbonate concentration would improve events related to muscle catabolism in CAPD patients. Their results showed that 4 weeks of increased bicarbonate in the dialysate (from 35 mmol/L to a 40 mmol/L lactate dialysate) resulted in significant increases in weight, BMI, and plasma branched-chain amino acid concentrations, whereas muscle levels of ubiquitin messenger RNA (mRNA) decreased significantly. These data suggest that even a small correction of serum bicarbonate concentrations improves nutritional status and downregulates muscle proteolysis via the ubiquitin-proteasome system. Nonetheless, despite these strong experimental data, the long-term clinical relevance of correcting metabolic acidosis in dialysis patients has yet to be defined by prospective longer-term studies.

Several hormonal derangements including insulin resistance, increased glucagon concentrations, and secondary hyperparathyroidism also are implicated as factors in the development of uremic malnutrition in CKD patients.[162] A postreceptor defect in insulin responsiveness of tissues, mostly involving phosphatidylinositol-3 kinase, is the most likely cause of insulin resistance and associated glucose intolerance in uremia.[174-176] Because the anabolic effects of insulin are thought to be mediated by activation of phosphatidylinositol-3 kinase, suppressed phosphatidylinositol-3 kinase activity may lead to activation of the ubiquitin-proteasome pathway and muscle protein degradation.[175,177] It also has been suggested that hyperparathyroidism usually seen in CKD is, at least in part, responsible for this decreased tissue responsiveness to insulin via inhibition of insulin secretion by pancreatic β cells.[178,179] Increased concentrations of parathyroid hormone have been implicated as a protein catabolic factor in uremia by enhancing amino acid release from muscle tissue.[180] Finally, there are several abnormalities in the thyroid-hormone profile of uremic patients, characterized by low thyroxine and tri-iodothyronine concentrations.[181] These changes resemble the changes seen in prolonged malnutrition in other patient populations[182] and it has been suggested that the thyroid-hormone profile of malnutrition,[183] and possibly of kidney failure, is a maladaptive response to decreased energy intake in an effort to preserve overall energy balance.

Abnormalities in the growth hormone and IGF-1 axis also have been suggested as important factors in the development of uremic malnutrition in CKD patients.[184] Growth hormone is the major promoter of growth in children and exerts several anabolic actions in adults such as enhancement of protein synthesis, increased fat mobilization, and increased gluconeogenesis, with IGF-1 as the major mediator of these actions.[185-187] Although several studies have shown that plasma concentrations of growth hormone actually increase during the progression of CKD, probably because of its reduced clearance, recent evidence suggests that uremia per se is associated with the development of resistance to growth hormone actions at cellular levels.[188] This subject is reviewed in detail in an editorial by Krieg et al.[184] In this context, studies by Chan et al[189] and Tonshoff et al[190] have shown elegantly that in experimental settings, uremia is characterized by reduced hepatic growth hormone receptor mRNA and hepatic IGF-1 mRNA expression. This blunted response would be expected to attenuate the anabolic actions of these hormones. Interestingly, these abnormalities also can be observed with decreased food intake and in experimental metabolic acidosis.[191] Metabolic acidosis and decreased dietary protein and energy intake also are associated with decreased IGF-1,[168,192] although it is not clear which is the primary response and which is the secondary effect.[193] Thus, the current evidence suggests an interesting and as yet not well defined interrelationship between these hormonal, metabolic, and nutritional factors that are involved in the evolution of uremic malnutrition.

Comorbid Conditions

Specific comorbid conditions also can facilitate the development of uremic malnutrition in CKD patients. Patients with CKD secondary to diabetes mellitus (DM), which is the leading cause of ESRD in the United States, have a higher incidence of uremic malnutrition as compared with patients who are not diabetic. The etiology of this observation is multifactorial. In addition to the protein catabolic effects of insulin resistance,[176,194,195] diabetic CKD patients are likely to be more prone to protein depletion because of associated gastrointestinal symptoms such as gastroparesis, nausea and vomiting, bacterial overgrowth in the gut, pancreatic insufficiency, and high occurrence of nephrotic syndrome and related complications.[3,196] Once diabetic patients initiate chronic dialysis, some of these symptoms can be attenuated and the catabolic effects of insulin resistance or the increased muscle protein breakdown caused by hypoinsulinemia still persist. Studies by Mitch et al[164,197] have shown elegantly that in insulin-deprived animals, muscle protein breakdown is increased significantly and that this process is mediated by the proteasome-ubiquitin pathway. Insulin deprivation increases protein breakdown, whereas insulin increase blunts protein breakdown, and insulin interacts with amino acid availability to regulate protein synthesis.[198] Biolo et al[199] examined protein metabolism in insulin-dependent DM patients and healthy subjects and found no differences in protein turnover in the fasting or fed state between the 2 groups. Luzi et al[200] found no difference in protein turnover changes in response to euglycemic insulin clamp, with and without hyperaminoacidemia, in non–insulin-dependent diabetic patients and healthy subjects. We recently showed a significantly more negative net protein balance in the muscle compartment in CHD patients with DM compared with matched CHD patients without DM (-59 $\pm$ 4 versus -9 $\pm$ 6 μg/100 mL/min, $P < .05$). Of note, the diabetic population we studied was under suboptimal glycemic/insulinemic control, as determined by plasma glucose concentrations of 113 $\pm$ 16

and plasma insulin concentrations of 25.3 ± 9.6 μU/mL.[201] Further studies with tightly controlled insulin and glucose concentrations are warranted to define further the mechanisms of impaired protein metabolism in CKD patients with type 2 DM.

With regard to chronic inflammation, recent studies from our laboratory and others have shown that chronic inflammation is highly prevalent in CHD patients.[9,202] Chronic inflammation and uremic malnutrition tend to coexist in CHD patients, and increased concentrations of serum CRP and proinflammatory cytokines are strong predictors of uremic malnutrition and mortality in advanced CKD,[203-205] suggesting that chronic inflammation may be a causative factor for increased muscle protein catabolism, leading to uremic malnutrition. Based on these findings, Stenvinkel et al[206] suggested that there may be 2 types (at least) of malnutrition in ESRD: true protein-energy malnutrition and wasting syndrome. In the first type, it is proposed that the most prominent feature is indeed inadequate nutritional intake (leading to decreased anabolism) whereas the second type is characterized by a protein catabolic state leading to muscle protein breakdown. Importantly, certain metabolic derangements and comorbid conditions such as inflammation and DM, which are known to mediate this process, are also highly prevalent in CKD patients. Although such classification has not been confirmed yet by mechanistic studies, such a subdivision of the uremic malnutrition syndrome may be important and useful in defining therapies because the first may be more amendable to provision of nutritional supplements whereas the latter would require more specific anticatabolic interventions.

Interestingly, CKD patients with uremic malnutrition tend to have not only signs of chronic inflammation but also a higher incidence/prevalence of cardiovascular disease,[63,207] the ultimate leading cause of death in ESRD patients.[208] Therefore, it has been suggested that malnutrition is in part a consequence of chronic heart failure and/or infection and inflammation, which not only worsens the nutritional status but also triggers the development of atherosclerotic disease, resulting in increased mortality in patients with advanced CKD.[208] Clearly, further mechanistic prospective studies are needed to identify the cause and effect relationship between uremic malnutrition, inflammation, and cardiovascular disease.

Depression, which is seen commonly in CKD patients of all stages, also is associated with anorexia. In addition, CKD patients usually are prescribed a large number of medications, particularly sedatives, phosphate binders, and iron supplements, which also are associated with gastrointestinal complications.

Increased protein and energy requirements

In general, the minimal daily protein requirement is one that maintains a neutral nitrogen balance and prevents malnutrition; this has been estimated to be a DPI of approximately 0.6 g/kg in healthy individuals, with a safe level of protein intake equivalent to the minimal requirement plus 2 SDs, or approximately 0.75 g/kg/d.[209,210] This suggested intake of protein for normal individuals does not necessarily apply to dialysis-dependent patients, who may require higher levels because of concurrent abnormalities. Indeed, Borah et al[211] showed that for CHD patients a DPI of 1.4 g/kg/d is needed to maintain a positive or neutral nitrogen balance during nondialysis days and even this high protein intake may not be adequate for dialysis days. Other studies evaluating the actual protein requirements of dialysis patients suggested a minimum of 1.2 g/kg/d as a safe level of DPI for CHD and PD patients, based on several metabolic balance studies.[212] The NKF-DOQI nutritional guidelines recommend a minimum DPI of at least 1.2 g/kg/d for stable CHD patients.[40] Of note, these recommended protein intake levels were derived mainly from short-term nitrogen balance studies in a small number of patients, which were performed at a time when dialysis techniques were not optimal.[211,213] Protein requirements in adequately dialyzed CHD patients with biocompatible membranes presently are not well-established. The suggested levels of protein intake clearly are much higher (almost 2-fold) than what is required for the normal population and CKD patients. Obviously, despite the dialysis technology in use, there are a number of identified factors derived from more recent studies that may justify the recommendations for increased requirement of protein intake in dialysis patients.

Catabolic effects of the hemodialysis procedure

Earlier nitrogen balance studies by Borah et al[211] and Lim and Flanigan[214] suggested that the nitrogen appearance was higher on dialysis days even at high protein intake levels. Gutierrez et al,[215] using sham dialysis in healthy subjects, found increased amino acid release from the leg with bioincompatible hemodialysis membranes, but not with a biocompatible membrane. A subsequent study also with bioincompatible membranes using stable isotopes infusion techniques found significantly more negative net whole-body protein balance during dialysis compared with predialysis, mainly owing to decreased protein synthesis during dialysis, which the investigators attributed to the leucine loss into the dialysate.[89] A recent study by Veeneman et al,[216] however, did not confirm these findings. They studied whole-body protein metabolism during hemodialysis by using Cuprophane membranes on one occasion and polysulfone/cellulose triacetate on another occasion for the same patients. They found that although Cuprophane membranes were more powerful activators of the complement system compared with the other membranes, protein metabolism parameters were not different and resulted in the same negative protein balance during polysulfone/cellulose triacetate and cuprophane dialysis. By using biocompatible membranes, we further explored this issue by studying not only whole-body but also skeletal muscle protein metabolism by using stable isotope infusion techniques. We also corrected leucine flux for leucine loss into the dialysate and followed-up the patients for 2 hours after the hemodialysis procedure was completed.

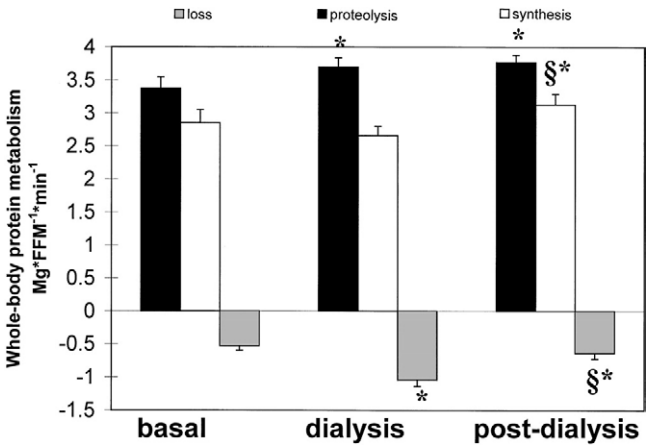

Figure 1 Whole-body protein metabolism. Values reported are means ± SEM for each period. FFM, fat-free mass. *Significant difference from the basal period ($P < .05$). §Significant difference between the dialysis and postdialysis periods ($P < 0.05$). Reprinted with permission from the American Physiological Society.[90]

Our results showed significantly more negative whole-body and skeletal muscle protein balance during hemodialysis, which remained significantly more negative than baseline even after the procedure was completed. The marked catabolism observed in our studies mainly was caused by increased protein breakdown, not accompanied by sufficient increases in protein synthesis, both in whole-body and skeletal muscle compartments (Fig 1 shows whole-body data).[90]

Two subsequent studies corroborated these findings. Veeneman et al[217] reported similar findings by measuring whole-body protein metabolism in CHD patients using L-(1-^{13}C) valine rather than leucine as the stable isotope. They confirmed the previous finding that hemodialysis significantly deepens the negative whole-body protein balance during fasting when compared with predialysis and a nondialysis day. Similarly, Raj et al[218] observed a net increase in protein catabolism caused by hemodialysis, although in this study synthesis also was increased at a lesser extent. Overall, these studies confirmed that hemodialysis leads to a net protein catabolic state by promoting imbalances between protein synthesis and protein breakdown.

Dialysis dose

An important and readily treatable cause of uremic malnutrition in CHD patients is underdialysis, which can lead to anorexia and decreased taste acuity. The results of the National Cooperative Dialysis Study showed an association between lower dietary protein intake and higher time-averaged urea concentrations, suggesting a relationship between underdialysis and anorexia.[70] Similarly, Lindsay et al[219] suggested that PNA (polymerase chain reaction) is dependent on the type and the dose of dialysis. Bergstrom and Lindholm[220] also have reported a significant linear relationship between Kt/V and PNA, all suggesting that anorexia is related to underdialysis. However, these retrospective and/or cross-sectional studies did not definitively show a cause and effect relationship between dose of dialysis and nutritional status. Furthermore, both Kt/V and PNA are calculated from similar measures and therefore whether there is a mathematic link between the 2, and whether decreased PNA really would reflect the nutritional status of these patients, still is a subject of debate. In this respect, in a large cross-sectional study by Owen et al,[38] no statistically significant relationship between serum albumin and dose of dialysis was seen. Nevertheless, it is quite clear that decreasing clearance of uremic substances is associated with progressive anorexia at all stages of kidney failure.

Factors more exclusively related to PD

Observations similar to the ones described earlier for hemodialysis have been made for PD patients. However, PD patients require a lower dialysis dose as compared with CHD patients to achieve a given DPI.[220,221] It has been suggested that this might be owing to a better removal of middle molecules by the peritoneal membrane compared with the hemodialysis membrane because these molecules are thought to be anorexic. A higher incidence of malnutrition has been reported in patients who are treated with CAPD for longer than 3 months compared with patients who were treated for less than 3 months, suggesting that as residual kidney function decreases (a major contributor to total clearance in PD patients), indices of malnutrition become more evident.[222] Keshaviah and Nolph[223] also have suggested that as residual kidney function decreases in CAPD patients, PNA also decreases. Teehan et al[224] and Lameire et al[225] reported higher survival rates and better nutritional markers with higher Kt/V. Losses of proteins and amino acids into the dialysate fluid have long been identified as catabolic factors in PD patients. Several studies have reported a loss of 5.5 to 11.8 g of proteins into the dialysate daily.[226] A large amount of these losses consist of albumin along with immunoglobulins and amino acids. Free amino acid losses have been estimated to be in the range of 1.7 to 3.4 g/d according to different studies.[227] Most importantly, during episodes of peritonitis, these losses of proteins and amino acids increase substantially.[226] The generally lower serum albumin concentrations and several abnormalities in plasma amino acid profiles seen in PD patients are presumed to be a result of these inevitable losses. Conversely, the amount of energy intake, at least indirectly, is relatively higher in PD patients because of the absorption of glucose from the dialysate fluid. This absorption usually provides energy in the range of 5 to 20 kcal/kg/d in many patients and it is a possible explanation for the relatively lower REE levels observed in this patient population.[228] Unfortunately, this absorption of glucose also may predispose these patients to further anorexia as a result of its satiety effect, in addition to the feeling of fullness related to the fluid in the peritoneal cavity. The extensive presence of protein depletion in these patients, despite this increased energy consumption, is probably related to their inadequate intake of dietary protein because protein intake affects nitrogen balance more profoundly than the overall energy intake.[229]

With regard to bioincompatibility, there are important differences comparing CHD and PD patients. In PD, biocom-

patibility refers to the ability of a solution to allow adequate long-term dialysis without a clinically significant undesirable host response, systemically and locally (intraperitoneal). PD bioincompatibility is caused by continuous exposure to solutions with high concentrations of glucose, glucose degradation products, lactate, low pH level, and high osmolality, all of which may change the structure and function of the peritoneal membrane in the long term. The use of a high concentration of bicarbonate as the solution buffer instead of lactate, or a physiologic concentration of bicarbonate together with a markedly reduced concentration of lactate, provides a means to deliver glucose-based solutions at a physiologic pH.[230,231] Such solutions have a composition that is closer to that of the interstitial fluid, and therefore may be more biocompatible with respect to peritoneal cells, while at the same time providing equivalent or better correction of acidosis. Furthermore, the dual-chambered bag used to deliver these solutions has been designed to minimize the formation of glucose degradation products during heat sterilization. One compartment contains electrolytes at a high pH level, whereas the other contains a high concentration of glucose at a low pH level. Although these new PD solutions have not been associated with better nutritional outcomes, studies have suggested potential favorable effects on nutritionally related conditions, such as metabolic acidosis.[232-234]

Medical problems inherent to maintenance dialysis

In addition to the earlier-mentioned factors, placement of permanent or temporary vascular accesses in CHD patients and the use of the peritoneal cavity in PD patients induce additional medical problems and hospitalizations because of infections and/or access revisions. Increased frequency of hospitalizations may affect the nutritional status of dialysis patients adversely.[235] The actual daily protein intake of CHD patients admitted to a regular ward is at very low levels (0.55 $\pm$ 0.33 g/kg/d) and simultaneous calculations of PNA by urea kinetics shows a negative nitrogen balance in 80% of hospitalized patients.[72] Along with decreased PNA, serum albumin concentrations also decrease significantly with hospitalizations. Therefore, frequent hospital admissions also may be an insidious and important cause of poor nutrition in chronic dialysis patients.

Factors related to kidney transplantation

Although kidney transplantation probably offers the best nutritional rehabilitation for CKD patients at present, it still is associated with some degree of nutritional derangements, despite substantial reversal of the uremic state. The causes are multifactorial but can be divided into early and late phases. During the initial 6 weeks after the surgery, there is an increased nutritional requirement caused by the surgical metabolic stress itself and by the high doses of immunosuppressive medications, especially corticosteroids. Acute rejection and infection also may occur in the early phase and contribute to nutritional deficit. It is well known that corticosteroids are associated with increased hepatic gluconeogenesis, associated with increased protein catabolism and decreasing visceral protein concentrations.[236-239] Studies by Miller et al[128] and Horber et al[238] have identified corticosteroid-associated abnormalities in anthropometrics, and abnormalities in skeletal muscle ultrastructure in kidney transplant patients. Hoy et al[240] also reported that increases in corticosteroid dosage further increases PNA. The late phase (after 6 weeks) still is marked by the deleterious effects of corticosteroid use, despite their adjusted doses. The nutritional problems commonly encountered during this phase are protein hypercatabolism, obesity, insulin resistance, and dyslipidemia. Studies have shown weight gain in a large number of transplant patients, mainly caused by increased body fat,[241] which can be explained partially by the chronic use of immunosuppressive agents. Nonetheless, serum albumin concentrations still may be low after 1 year of kidney transplant, accompanied by increased concentrations of plasma and muscle amino acids.[129] A study by El Haggan et al[130] showed significant decreases in serum albumin, serum transferrin, and retinol binding protein levels in 44 patients during the first year posttransplant.

Another issue related to kidney transplant patients is the use of low-protein diets to alter the course of rejection. Although several uncontrolled and short-term studies suggested some preliminary immunologic benefit on rejection, in a relatively well-designed study significant decreases in the levels of almost all serum proteins, including serum total protein, albumin, prealbumin, and transferrin, were observed with a diet consisting of 0.5 g/kg/d (low-protein) in kidney transplant patients with chronic rejection, although no significant changes occurred in GFR.[242,243] More recently, Bernardi et al[244] showed that a moderate protein intake of 0.8 g/kg/d along with sodium restriction, in attempts to avoid kidney hyperfiltration, stabilized long-term kidney function and maintained adequate nutritional status. The results of another small-scale study actually suggested beneficial effects of a high-protein diet with regard to side effects of corticosteroids.[245] Whether other factors, such as frequency of acute rejections, number of infectious complications, presence of chronic rejection, and other immunosuppressive agents play any role on the overall nutritional picture of the transplant patient remains to be determined.

Prevention and Treatment of Uremic Malnutrition

Given the significance of the problem and the complexity of the pathophysiologic basis of uremic malnutrition, it is evident that the prevention and treatment options of uremic malnutrition are both critical and complex. To date, there is not a single treatment approach that will alleviate the multiple adverse consequences of uremic malnutrition. In the subsequent section, we provide an overview of established prevention and treatment options for uremic malnutrition (general aspects) and specific therapeutic options for each group of patients (CKD, PD, CHD, and transplant), in addition to an overview of certain promising novel strategies.

Table 2 Therapeutic Options for Uremic Malnutrition

CKD patients
Optimal dietary protein and energy intake
Optimal timing for initiation of dialysis, before onset of indices of malnutrition
CDT patients
Appropriate amount of dietary protein intake (>1.2 g/kg/d) along with nutritional counseling to encourage increased energy intake
Optimal dose of dialysis (Kt/V >1.4 or URR >65%)
Use of biocompatible dialysis membranes
Enteral or intradialytic parenteral nutritional supplements (hemodialysis) and AAD (PD) if oral intake is not sufficient
Growth factors (experimental):
rhGH
Recombinant human IGF-1
Appetite stimulants (experimental)
Anti-inflammatory interventions (experimental)
Transplant patients
Appropriate amount of dietary protein intake
Avoidance of excessive use of immunosuppressive agents
Early re-initiation of dialytic therapy with proper steroid tapering in patients with chronic rejection

General Aspects

Because of the number of factors affecting nutritional status in patients with CKD or ESRD, treatment should involve a comprehensive combination of maneuvers to diminish protein and energy depletion, in addition to therapies that will avoid further losses. Unfortunately, for some of the therapies currently in use, there are only empiric data showing clear benefits, if not data showing lack of benefits, although some are derived from secondary outcomes as part of large clinical trials. These include provision of adequate dialysis, treatment of metabolic acidosis, adjustments of dietary requirement and intake, prophylaxis and treatment of infections, and even factors that are not linked obviously to nutrition but affect the CKD or the ESRD patient in a way that may affect nutrition further such as fluid overload. In general, increased dialysis dose always is recommended in patients with anorexia and insufficient dietary intake, unless there is no reason to believe the patient is underdialyzed and other factors for anorexia and low intakes have been identified. With regard to metabolic acidosis, even slight degrees should be corrected by oral supplementation with sodium bicarbonate or by altering dialysate buffer concentration. Exercise performance is another evolving therapeutic option that should be encouraged. Comorbid conditions such as DM and cardiovascular disease should be treated actively, and infectious diseases should be avoided and treated promptly. Likewise, signs of chronic inflammation should be elucidated and all attempts should be made to eliminate the cause of the inflammatory response.

Chronic Kidney Disease Patients

A list of measures to prevent and/or to treat malnutrition at different stages of renal failure is presented in Table 2. The earlier-mentioned hormonal and metabolic derangements, such as insulin resistance and amino acid abnormalities, currently are not treatable in patients with progressive CKD. However, other factors that affect the nutritional status of CKD patients adversely, such as the extent of anorexia, may be altered. In light of the evidence suggesting that decreasing spontaneous dietary protein and energy intake is a prominent feature of decreasing kidney function and correlates with worsening in nutritional markers, it is obvious that any dietary intervention designed to limit dietary intake during the predialysis stage must be undertaken cautiously. Patients on restricted diets should be followed-up very closely for signs and symptoms of malnutrition and necessary adjustments must be made if malnutrition is suspected. In particular, patients on dietary protein restriction should have provision for adequate energy intake.

For the majority of patients who are not on a closely monitored dietary protein restriction, evident signs of poor nutrition, such as spontaneous DPI less than 0.75 g/kg/d, energy intake less than 20 kcal/kg/d, serum albumin concentration of less than 4.0 g/dL, apparent decrements in other nutritional indices, such as transferrin, prealbumin, IGF-1, and lean body mass, may warrant initiation of hemodialysis or be an indication for kidney transplant.[151] Of note, patients initiating hemodialysis often already show signs of uremic malnutrition.[105,106] Several studies have suggested better outcomes with early initiation of hemodialysis. Specifically, the length of hospital stay, the mortality within the first 90 days after initiation of dialysis, and the long-term mortality rate all were better in patients who were initiated on dialysis early in their course of kidney failure compared with patients who were referred to dialysis rather late.[151,246] It is possible that early initiation of dialysis prevents the development of malnutrition and its related complications and improves long-term outcome. These comments should not be taken to imply that a high protein intake should be encouraged in patients with CKD; rather, we suggest that in cases in which there is low protein and energy intake in patients on spontaneous (unrestricted) diets, a DPI of less than 0.75 g/kg/d is an early warning sign for the development of uremic malnutrition.

Table 3 Suggested Guide for Monitoring Nutritional Status and Guiding Therapy

Simple (monthly) assessment	Findings	Possible Interventions
BW	Continuous decrease or <85% IBW	Suspect uremic malnutrition and perform more detailed nutritional assessment
Serum albumin	<4.0 g/dL	
Serum creatinine	Relatively low predialysis values	No intervention needed at this point
Detailed assessment		Simple
Serum prealbumin	<30 mg/dL, and/or	Dietary counseling: DPI ≥ 1.2 g/kg/d, energy intake 30-35 kcal/d
Serum transferrin	<200 mg/dL, and/or	CHD and PD
IGF-I	<200 ng/mL, and/or	Increase dialysis dose to Kt/V>1.4 Use biocompatible membranes
LBM and/or fat mass	Unexpected decrease	Uppeer gastrointestinal motility enhancer
SGA	Worsening	CKD
		Consider timely initiation of CDT
Repeat detailed assessment (2-3 months from previous)		**Moderate to complex**
Serum prealbumin	<30 mg/dL, and/or	Nutritional supplements
Serum transferrin	<200 mg/dL, and/or	Oral, enteric tube feeding, IDPN (requires Medicare approval)
IGF-I	<200 ng/mL, and/or	Anabolic factors (experimental)
Serum creatinine	Relatively low predialysis values, and/or	rhGH, rhIGF-I
LBM and/or fat mass	Unexpected decrease	Appetite stimulants (experimental)
CRP	>10 mg/L	Anti-inflammatory (experimental)

Abbreviations: BW, body weight; IBW, ideal body weight; LBM, lean body mass.

Chronic Dialysis Patients

Table 3 shows an algorithm of assessment of the nutritional status and dietary interventions in CKD and chronic dialysis patients. These interventions are discussed in detail later.

Dose of dialysis

In general, based on the previously mentioned studies, it seems clear that an adequate dose of dialysis is required to prevent the development of uremic malnutrition. Studies by Lindsay et al[247] showed that PNA increased significantly in patients whose Kt/V values were increased, compared with no change in PNA in patients whose Kt/V values remained the same. Similarly, Acchiardo et al[248] and Burrowes et al[249] observed significant increases in serum albumin concentrations in CHD patients after increasing the dialysis dose to adequate levels. Hakim et al,[73] in a 4-year prospective cohort, observed a decrease in mortality rates from 22.8% to 9.1% when dialysis dose was increased intentionally to 1.33 (measured by delivered Kt/V) in 130 CHD patients. With regard to the adequacy of CAPD, similar conclusions can be derived from several retrospective studies that showed significant correlations between dialysis dose and nutritional parameters.[250] A large-scale multicenter prospective study suggested a positive relationship between adequacy of dialysis and nutritional status in CAPD patients.[251,252] Therefore, there is evidence that an increased dose of dialysis is beneficial or that we at least should attempt to maintain an adequate dose of dialysis, as recommended by the K/DOQI guidelines (minimum spKt/V of 1.2 or urea reduction rate (URR) of 65%), to avoid uremic malnutrition. However, we must comment on the surprising results from the HEMO study and from the Adequacy of PD in Mexico (ADEMEX) study, which does not necessarily encourage an increased dose of dialysis for better outcomes. Specifically, results from the HEMO study showed no difference in outcomes, including a decrease in serum albumin level, when comparing high hemodialysis dose (achieved spKt/V of 1.71 ± 0.11) versus low hemodialysis dose (achieved spKt/V of 1.32 ± 0.09).[253] Among many methodologic points that have been discussed, it is noteworthy that both high and low HEMO study groups received, on average, a spKt/V greater than the NKF-K/DOQI recommendations, which might have contributed to the lack of differences reported. Although no definitive conclusion has been achieved as to whether increasing the dose of dialysis to greater than NKF-K/DOQI guidelines will ameliorate outcomes, including nutritional status, we believe that these results give us no reason to aim for a dialysis dose lower than the NKF-K/DOQI recommended spKt/V of 1.2 or greater (URR, ≥65%).[254]

The ADEMEX trial was also a randomized trial that tested the hypothesis that a peritoneal Kt/V of 1.7 would give equivalent mortality outcomes to a peritoneal Kt/V of 2.1.[255] The NKF-K/DOQI guidelines recommend a Kt/V (kidney plus peritoneal) of 2.0 for all CAPD patients. The results from the ADEMEX study showed that Kt/V values greater than 1.7 provided no survival advantage and no difference in the changes in serum albumin, serum prealbumin, and serum transferrin levels, although they observed higher serum albumin concentrations in the high-dose group, which was attributable to the slightly higher baseline value for this group. Similar to the HEMO study, ADEMEX had some method-

ologic limitations, including the mix of incident and prevalent patients. Therefore, caution should be taken in presuming that all PD patients can be prescribed safely a peritoneal Kt/V of 1.7.[256] In summary, all the available evidence in chronic dialysis patients therefore confirms the close positive association between dialysis dose and nutrition despite the controversies that emerged with the findings of the HEMO and ADEMEX studies. It is noteworthy that nutritional variables were secondary outcomes in both the HEMO and ADEMEX studies. It also is important to note that the specific level of the optimal dose of dialysis, after which no further improvement in nutritional status is observed, has not been established yet. Therefore, although further investigations elucidate these controversies, these findings should be rather reassuring to the nephrology community in that NKF-K/DOQI targets might be sufficient, as recently highlighted by Prichard[256] and Schulman,[256,257] at least for mortality outcome

Dialysis membrane

The use of bioincompatible membranes has become very sporadic in many countries over the past decade. Nonetheless, because these membranes are still in use in some centers, we must comment on their catabolic and anorectic effects.[247,258] In a study comparing nutritional outcomes in patients dialyzed with biocompatible versus bioincompatible membranes, Parker et al[259] showed that the biocompatible group significantly increased dry body weight, whereas no change in weight was observed in the bioincompatible group. In addition, the biocompatible group had an earlier and more marked increase in serum albumin concentrations and consistently higher IGF-1 values.[259] Consistently, reports from the US Renal Data System have suggested that the use of bioincompatible membranes are associated with increased risk for death in comparison with biocompatible membranes.[260] Whether altered nutritional status plays a role in this process is not clear. With all that said, it seems as though the nephrology community has decided to abolish the use of bioincompatible membranes, whatever the primary motivation is. Therefore, this issue soon will be of historical significance.

Treatment of the protein catabolic effects of the hemodialysis procedure

Provision of nutrients during the hemodialysis procedure (ie, intradialytic parenteral nutrition [IDPN] or intradialytic oral nutrition) has been shown to be a safe and convenient approach to overcome the catabolic effects of hemodialysis.[261] Although there is some evidence for nutritional improvements with the use of IDPN, others studies showed no benefit. This could be in part because many studies focusing on IDPN involved a small number of patients for a limited period of time, and the results have not been consistent.[262-267] The reason for the small magnitude in most studies is likely to be the cost and regulatory concerns[268] and because of the fact that most studies on the nutritional effects of IDPN were based on estimates of the body pool of protein stores (mainly biochemical markers of nutritional status) rather than measures of protein metabolism. As a result, there is substantial

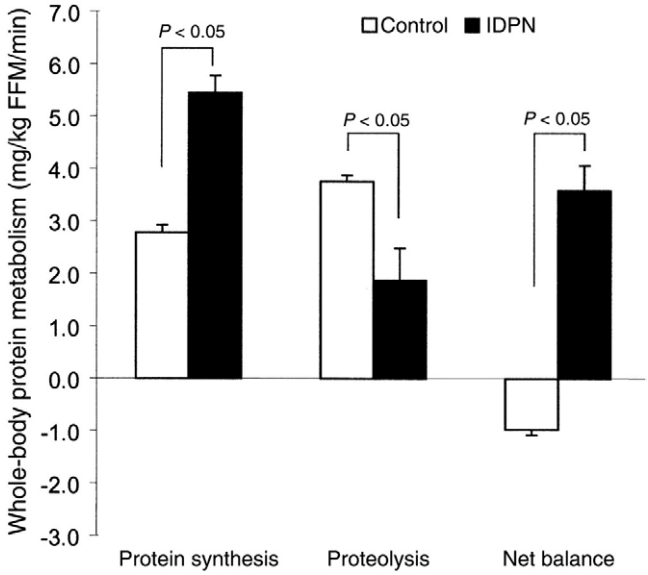

Figure 2 Whole-body protein components during hemodialysis, comparing control (□) and IDPN (■). FFM, fat-free mass. Units are in milligrams per kilogram of FFM per minute. Significant differences were observed for all components of whole-body protein homeostasis during this period. There were no differences during predialysis or postdialysis periods. Reprinted with permission from the American Society for Clinical Investigation.[92]

hesitancy for the use of this potentially beneficial treatment. Nonetheless, by using stable isotope infusion techniques we have been able to measure directly specific components of protein and energy metabolism in CHD after administration of IDPN.[92] We performed a randomized cross-over study in which all the patients were studied with and without IDPN (IDPN and control protocols). The results showed that IDPN promoted a 96% increase in whole-body protein synthesis and a 50% decrease in whole-body proteolysis compared with the control protocol (Fig 2). In addition, IDPN provided significantly higher forearm muscle protein synthesis compared with control (260%). Although there were no differences in forearm muscle proteolysis between protocols, the net result was a change from negative (muscle loss) to positive (muscle accretion) balance during IDPN administration. This suggests that IDPN provides adequate amino acids to replenish the extracellular pool sufficiently enough to increase muscle protein synthesis, during a state in which significant amounts of amino acids are being lost into the dialysate, inducing net protein anabolism both for visceral and somatic protein stores.

More recently, Veeneman et al[217] reported the effects of feeding during hemodialysis on whole-body protein balance. The feeding was in the form of yogurt, cream, and protein-enriched milk powder, given as 6 equal portions during the hemodialysis procedure and on a nondialysis day. Their results showed that consumption of a protein- and energy-enriched meals during hemodialysis resulted in a positive protein balance to the same extent as on a nondialysis day (Fig 3). The investigators did not assess skeletal muscle protein balance in this study.

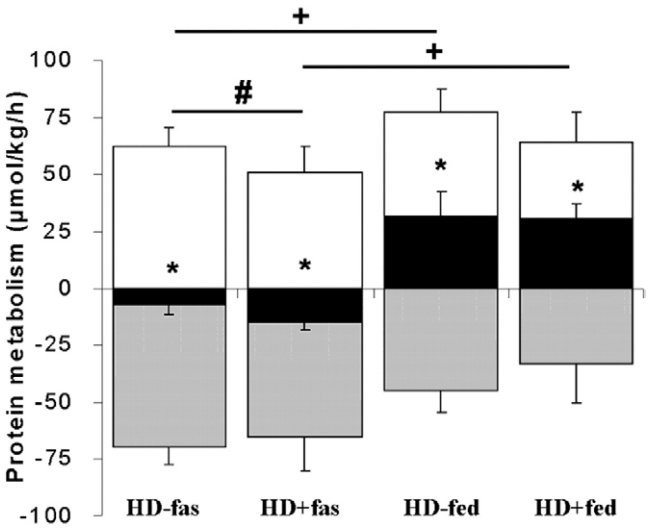

Figure 3 Summary of whole-body protein breakdown ([GRAPHICS]), synthesis (□), and protein balance (■) under all experimental conditions. *Whole-body protein balance significantly different from 0. ⁺Whole-body protein balance significantly different between fasting and feeding. #Whole-body protein balance significantly different between the hemodialysis (HD)+ and HD-protocols. Reprinted with permission from the American Physiological Society.[217]

The earlier-mentioned studies clearly indicated that nutritional supplementation, both intravenously and orally, can compensate adequately the catabolic effects of the hemodialysis procedure. Although these studies did not specifically study the cellular and molecular mechanisms associated with these responses, it is likely that the increased plasma concentrations of amino acids is one of the critical components that drive the positive protein balance.[269,270] However, studies examining nutrient supplementation under many different conditions have shown that muscle protein stores are not determined by nutrient intake alone. Insulin action also plays an important role in controlling nutrient deposition. Insulin decreases circulating concentrations of glucose, amino acids, and lipids, and promotes inward cellular transport of glucose and amino acids, enhances glycogen synthesis, stimulates adipose cells to synthesize and store lipids, and promotes protein accretion.[271] Specifically, circulating insulin influences carbohydrate homeostasis by altering muscle glucose transport[272,273] and use,[274] and regulates protein dynamics by stimulating amino acid transport, promoting whole-body and muscle protein synthesis, and inhibiting proteolysis.[271] These effects are amplified when amino acid availability is increased simultaneously with insulin.[271] In the study by Pupim et al,[92] insulin concentration increased by approximately 4-fold when IDPN was administered. In overnight fasted normal subjects, an approximately 7-fold insulin increase with amino acid concentrations maintained near baseline values did not increase whole-body protein synthesis, but decreased proteolysis by 25% from basal conditions.[271] Increased insulin concentration and ample amino acid availability as a result of IDPN in the study by Pupim et al[92] decreased whole-body proteolysis by 50%, suggesting that the effects are likely the result of both increased amino acid availability and increased insulin action. Another indication that insulin plays a critical role in the metabolic response associated with nutritional supplementation were the observations during the posthemodialysis phase in this study by Pupim et al. Once the IDPN infusion was stopped, the insulin concentration decreased back to baseline values with a simultaneous reversal of the net protein balance to baseline levels.

A recent study by Lim et al[306] further substantiated the notion that insulin plays a critical role in the protein homeostasis and metabolic response to nutritional interventions in CHD patients. In this study, 9 CKD patients were studied before initiation of chronic hemodialysis, 7 of which were re-evaluated after initiation of CHD. The investigators performed whole-body metabolic studies on the same day under 4 different conditions: baseline (flux 1), low-dose insulin administration (flux 2), high-dose insulin administration (flux 3), and, finally, high-dose insulin administration plus intravenous amino acid supplementation (flux 4). Several kinetic indices were measured to estimate whole-body protein synthesis, breakdown, balance, and glucose disposal. Studies were performed with hyperinsulinemic-euglycemic clamps. The results showed that exogenous administration of insulin has comparable protein anabolic effects on CKD, CHD patients, and healthy subjects, which is a reduction in protein breakdown in the fasting state. When the investigators performed simultaneous infusion of insulin and amino acids they observed increased protein synthesis, resulting in positive leucine balance, compared with a negative balance during fasting both with and without insulin.

Daily (nondialytic) nutritional supplementation

Because of the magnitude of the catabolic processes leading to uremic malnutrition, dietary counseling alone fails to optimize dietary intake in certain subgroups of malnourished dialysis patients. For these patients, other forms of supplementation such as enteral (including oral protein, amino acid tablets and energy supplementation, nasogastric tubes, and percutaneous endoscopic gastroscopy or jejunostomy tubes) and IDPN can be considered. There are only a limited number of studies evaluating the efficacy of oral nutritional supplementation in dialysis patients, which show conflicting results.[275-277] Nevertheless, recent preliminary reports provided intriguing data regarding beneficial effects of oral nutritional supplementation in chronic dialysis patients. Eustace et al[278] reported that oral amino acid supplements significantly improved serum albumin concentration in CHD patients in a prospective, randomized, placebo-controlled pilot study. In a more recent study, Caglar et al[279] found that intradialytic oral nutritional supplementation improved several nutritional parameters (including serum albumin and serum prealbumin concentrations and SGA) in a large group of malnourished CHD patients.[279] Although provocative, these studies do not always clearly characterize a malnourished state, which might have influenced their results and contributed to the mixed results provided by the available data. The studies therefore can be considered as preliminary, with findings that warrant larger randomized clinical trials.

In the meantime, as a practical measure, oral nutritional supplementation should be attempted in malnourished dialysis patients if the problems that could be responsible for reducing nutrition intake cannot be resolved.

Similar studies using amino acid dialysate (AAD) as a nutritional intervention in malnourished PD patients also have provided conflicting results. Jones et al[280] have reported benefit from AAD, with increases in serum transferrin and total protein concentrations and a tendency of plasma amino acid profiles toward normal levels with 1 or 2 exchanges of AAD. Of interest, there were significant improvements in serum albumin and prealbumin concentrations in malnourished PD patients, particularly in those who had serum albumin concentrations in the lowest tertile.[280] It also should be noted that an increase in BUN concentration associated with exacerbation of uremic symptoms and metabolic acidosis remains a complication of AAD.[281] These results are consistent with reports suggesting that these interventions are most useful in dialysis patients with severe uremic malnutrition.

Overall, the available evidence suggests that IDPN, intradialytic oral nutrition, and AAD may be useful in the treatment of malnourished chronic dialysis patients and offers an alternative method of nutritional intervention in dialysis patients in whom oral or enteral intake cannot be maintained. However, available data support the limited number of long-term prospective studies reporting beneficial effects of IDPN and AAD in ESRD patients. Furthermore, there are no data to show that aggressive nutritional supplementation through the gastrointestinal tract is inferior to parenteral supplementation in dialysis patients. Until a controlled study comparing various forms of nutritional supplementation in similar patient groups is completed, one should be cautious in choosing very costly nutritional interventions. In the meantime, large-scale, well-designed nutritional intervention trials evaluating clinical outcomes (including nutritional status) in chronic dialysis patients with overt uremic malnutrition are needed.

Growth factors

As previously mentioned, growth hormone and its major mediator, IGF-1, have several anabolic properties. With the availability of recombinant forms of these agents, recombinant human growth hormone (rhGH) has been used in multiple patient populations at pharmacologic doses to promote net anabolism.[187] Consequently, with the recognition of alterations in the growth hormone–IGF-1 axis in ESRD patients, rhGH has been proposed as a potential anabolic agent in this patient population.[282] Several animal studies have suggested that rhGH induces a net anabolic action in uremic rats and also improves food use.[283] Furthermore, a preliminary short-term study in CHD patients by Ziegler et al[284] showed a decrease of predialysis BUN concentrations by approximately 25% and a significant reduction in net urea generation and polymerase chain reaction with rhGH administration.

Similar net anabolic actions of rhGH also have been observed in CAPD patients. In a controlled prospective study by Ikizler et al,[285] rhGH treatment was shown to induce a substantial (29%) decrease in net urea generation in 10 CAPD patients. Interestingly, these changes were associated with concurrent statistically significant decreases in serum potassium and phosphorus concentrations, and an increase in serum creatinine concentrations, suggestive of a net anabolic process in muscle mass. In a subsequent analysis of amino acid profiles of the same patients, the net anabolic processes induced by rhGH reflected a shift in amino acid metabolism toward peripheral muscle tissues.[285]

Because IGF-1 is the major mediator of growth hormone action, recombinant human IGF-1 also has been proposed as an anabolic agent. Preliminary nitrogen balance studies in CAPD patients are consistent with this hypothesis, however, the side-effect profile of this agent, at least as observed in CKD patients, may impede its widespread use at this time.[286-287] Interestingly, the combined use of these agents in healthy patients seems to provide the most efficient anabolic action with the least side-effect profile.[287] It is not yet known whether the long-term use of these agents in malnourished CHD and CAPD patients would result in improved nutritional parameter and hence better outcomes. Nevertheless, such studies should be encouraged in these patient populations.

Appetite stimulants

Because anorexia sometimes is not treatable easily by measures such as increased dialysis dose, the use of appetite stimulants is a promising and tempting component of a comprehensive therapy for uremic malnutrition. Examples of pharmacologic agents that may stimulate appetite include megestrol acetate, dronabinol, cyproheptadine, melatonin, and thalidomide. However, most of these drugs have not been studied, at least systematically, in the CKD population. The most extensively studied drug is megestrol acetate, a steroid-like progestogen used for the treatment of breast cancer, which caused increased appetite and weight gain as an unexpected side effect.[288] In elderly men, the orexigenic and weight-gaining effects of megestrol acetate have been attributed recently to its anticytokine effects via reduced levels of interleukin-6 and tumor necrosis factor (TNF)-α.[289] Interestingly, associated with the increased appetite, body weight, and quality of life, the weight gain mainly was caused by increased fat but not lean body mass.[290] Moreover, megestrol acetate has been associated with important side effects that remain to be evaluated in detail including hypogonadism, impotence, and an increased risk for thromboembolism. Therefore, although megestrol acetate has been shown to stimulate appetite[291,292] and induce small increases in serum albumin levels in pilot studies in dialysis patients,[293] large-scale prospective studies are needed to assess whether these drugs are of value as an adjunctive nutritional therapy in all stages of CKD.[291,294,295] To the best of our knowledge, no studies have been performed to study the appetite-stimulating and weight-gain effects of dronabinol, cyproheptadine, melatonin, and thalidomide in CKD patients.

Anti-inflammatory Interventions

With the understanding that chronic inflammation is an important catabolic factor, new strategies aimed at blocking the adverse effects of inflammation have been proposed in mul-

tiple patient populations. At present, there are few studies in CKD patients evaluating the use of anti-inflammatory interventions to ameliorate the adverse effects of chronic inflammation on nutritional status. The goal of such anti-inflammatory therapy is to selectively block, inhibit, decrease production, or increase degradation of proinflammatory substances, while avoiding compromise of host defenses. For example, 3 months of therapy with thalidomide, a drug with inhibitory effects on TNF-α production,[296-298] on COX-2 expression,[299,300] and TNF-α mRNA levels,[301,302] significantly improved muscle mass in acquired immune deficiency syndrome patients, in a double-blind, placebo-controlled clinical trial.[303] Whether this or another anti-inflammatory drugs would be helpful in terms of improving uremic malnutrition is to be determined by potential future studies.

Transplant patients

As is the case with other aspects of nutrition in transplant patients, the prevention and/or the treatment of malnutrition has not been studied in detail. However, one can propose that such interventions should include avoiding unnecessary or excessive use of catabolic agents, particularly in patients with frequent acute rejection episodes in their early transplant stages. For patients with chronic rejection, it is crucial not to delay the initiation of chronic dialysis and provision of an efficient tapering of corticosteroid doses. It is a common experience that most transplant patients who are initiated on chronic dialysis are still on chronic corticosteroid therapy, which for most patients is unnecessary.

It is clear that much work is needed in this patient population with regard to nutrition. Therefore, studies that evaluate the importance of nutrition in transplant patients with acute and chronic rejection should be encouraged. Finally, the importance and efficacy of rhGH in pediatric uremic and transplant patients have been highlighted by several studies.[304,305]

Summary

In summary, it is evident that uremic malnutrition is highly prevalent in CKD and chronic dialysis patients, and is present to some extent in some transplant patients. Uremic malnutrition is related clearly to multiple factors encountered during the predialysis stage and during chronic dialysis therapy. A body of evidence highlights the existence of a relationship between malnutrition and outcome in this patient population. Several preliminary studies suggest that interventions to improve the poor nutritional status of uremic patients may improve the expected outcome in these patients, although their long-term efficacy is not well established. It therefore is important to emphasize that uremic malnutrition is a major comorbid condition in the ESRD population and that all efforts should be made in trying to better understand and effectively treat these conditions to improve not only mortality but also quality of life of chronically uremic patients.

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