Navigating Between the Scylla and Charybdis of Prescribing Dietary Protein for Chronic Kidney Diseases

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Abstract

A fundamental clinical problem in treating patients with chronic kidney disease (CKD) is designing their diets: an excess of protein leads to the accumulation of uremic toxins, whereas a diet insufficient in protein could lead to loss of lean body mass. The benefits of dietary protein restriction include reducing the accumulation of metabolic waste products that can suppress appetite and stimulate muscle protein wasting. There also is a potential for slowing the loss of kidney function. Unfortunately, advanced CKD is strongly associated with a protein wasting syndrome that is directly correlated with morbidity and mortality. Fortunately, the mechanisms underlying negative responses to an excess of dietary protein, including the causes of the wasting syndrome, are beginning to be understood. We have examined how dietary protein influences the mechanisms causing protein wasting, and we propose a framework for approaching the variable dietary protein requirements in patients with CKD or end-stage kidney disease.

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INTRODUCTION

The optimal dietary protein intake of patients with chronic kidney disease (CKD) has proved a most intractable issue. For more than 135 years, it has been known that reducing protein intake will limit the severity of the uremic syndrome, but controversy still remains regarding whether reducing dietary protein will slow the progression of renal disease. Similarly, kidney disease has long been known to be associated with a wasting syndrome, but it remains difficult to prove that increasing protein intake improves this problem in such patients. The influence of the partial replacement of renal function with dialysis has added complexity to prescribing dietary protein. On the positive side, our understanding of the mechanisms underlying protein metabolism in renal disease has advanced. We examine the appropriateness of different levels of dietary protein in light of these mechanisms and provide a framework for dietary protein requirements in patients with CKD or end-stage kidney disease (ESKD).

DIETARY FACTORS INFLUENCE THE LOSS OF KIDNEY FUNCTION AND THE SEVERITY OF KIDNEY DISEASE

There are well established mechanisms whereby elements of the diet of a patient with CKD can affect the progression of renal insufficiency (**Table 1**). In addition to altering the rate of loss of kidney function, specific dietary constituents can influence the measurement of kidney function. The degree of kidney damage is generally assessed by evaluating the function of the kidneys in two ways: measuring the glomerular filtration rate (GFR) and estimating the rate of loss of clearance function. These are different tasks, and it must be kept in mind that the measurement of the GFR is definitely influenced by the diet: A meal containing a large amount of protein acutely and transiently raises the GFR by increasing blood flow and intraglomerular pressure, thereby stimulating filtration (44). In contrast, low-protein diets reduce the GFR. In this case, the glomerular hemodynamic adjustments do not reflect ongoing kidney damage; rather, they represent a physiologic adaptation to the diet (66).

Table 1 The influence of protein-rich diets on the progression of renal insufficiency

1) Changes in the measurement of the rate of loss of kidney function
A) An acute change in dietary protein causes a parallel change in measured glomerular filtration rate (GFR)
B) Creatinine production changes with dietary protein
1) An increase or decrease in protein intake reciprocally change serum creatinine or eGFR
2) The new steady state after changing the diet occurs in ~4 months
2) Protein-associated dietary factors affecting progression of chronic kidney disease (CKD)
A) Salt and hypertension
B) Uric acid and hypertension/inflammation
C) Phosphates and kidney injury
4) Direct effects of protein intake and progression of CKD
A) Net acid load and aldosterone/hypertrophy
B) Albuminuria/proteinuria via hyperfiltration
C) Protein-derived nephrotoxins (e.g., indoxyl sulfate)

Measuring GFR requires a substantial commitment by the patient and is expensive. Consequently, surrogates of GFR are widely used to monitor changes in kidney function. GFR estimates are principally based on serum creatinine or its transformations (e.g., 1/serum creatinine, eGFR). The underlying assumptions are that steady-state conditions are present and hence that creatinine production remains constant. Thus, an increase (or decrease) in serum creatinine in the steady state reflects a fall (or rise) in creatinine clearance and hence in GFR. The diet must be taken into account when interpreting GFR because dietary protein definitely changes creatinine production and therefore will affect this estimate of GFR independent of a true change in the degree of kidney damage. For example, a reduction in the intake of specific amino acids or protein decreases creatine and hence creatinine production (93). Reciprocal changes occur when protein intake increases because raising dietary protein increases creatinine production and therefore serum creatinine if kidney function is unchanged. Note that these responses add to short-term changes induced by the glomerular hemodynamics responses outlined above. Patients who continue to eat a large amount of protein or who consume a markedly protein-restricted diet will experience parallel changes in creatinine production and serum creatinine. Thus, serum creatinine mainly reflects the diet until a new steady state is achieved, and reaching the new steady state requires ~4 months. Therefore, a CKD patient who adopts a new diet with a lower protein intake while continuing to lose GFR will have a corresponding change in serum creatinine. But, after four months, when serum creatinine rises or eGFR decreases, the true rate of loss of GFR will be uncovered. In summary, when measuring GFR, the patient should be fasted or given a standard meal at least three hours before the measurement. The meal should be restricted in protein content. Secondly, the interpretation of GFR from surrogate markers based on serum creatinine requires knowledge of the diet because an increase in dietary protein will raise creatinine production, whereas a protein-restricted diet will lower it. Again, a change in dietary protein requires months to achieve a new steady state, but after four months have passed, a change in serum creatinine can be attributed to a reciprocal change in GFR.

When examining dietary constituents that directly influence the severity of kidney disease, it is important to remember that higher-protein diets are also generally higher in the content of sodium, uric acid precursors, and phosphorus, and they yield more acid. A particularly important factor in the diet of CKD patients is dietary salt because it influences blood pressure: An excess in dietary salt raises blood pressure whereas dietary salt restriction reduces it, which improves the effectiveness of antihypertensive

drugs (143, 144). Another dietary influence on the degree of kidney damage is uric acid production. In experimental models of CKD, a high serum uric acid raises blood pressure and is associated with more intense vascular inflammation (50). In patients with hypertension, reducing the serum uric acid level with allopurinol can lower blood pressure independent of antihypertensive medications (29). Population studies reveal that a high-protein diet is associated with an increase in the risk of raising serum uric acid and the development of gout (20). These associations are magnified in patients with CKD because of their limited ability to excrete uric acid. Attention to the diet can blunt this problem. A third diet-related factor that adversely affects kidney function is a high serum phosphorus concentration. When kidney function is impaired and the diet is rich in protein, serum phosphorus increases to raise the risk of developing secondary hyperparathyroidism and to accelerate the loss of GFR (79). Sodium, phosphorus, and uric acid are also associated with enhanced cardiovascular mortality in CKD (137).

In 1982, Brenner and colleagues (13) proposed that the progressive kidney damage of CKD is directly linked to an increase in glomerular hemodynamics or "hyperfiltration." They showed experimentally that hemodynamic changes associated with kidney damage were reduced by restricting dietary protein (13, 46, 97). Excess dietary protein will also increase proteinuria, a surrogate marker for the rate of progression of renal disease (114). The mechanism for increasing proteinuria includes hyperfiltration, but acid can also play a role because a high-protein diet contains precursors of sulfates and phosphates, which increase the release of aldosterone (12, 36, 44). Notably, blocking aldosterone can reduce proteinuria (45). Acid loading may also promote progression of renal disease by increasing the degree of renal hypertrophy (34, 45).

Dietary factors most directly increase the risk of uremic toxin-induced damage to the kidney. Most nitrogen-containing toxins generated by the metabolism of amino acids accumulate because of impaired excretion. For example, the level of indoxyl sulfate, a metabolite of the essential amino acid tryptophan, rises when kidney function is lost, and higher levels are associated with complications of kidney disease (147). When a protein-restricted diet was instituted and combined with an absorbent of indoxyl sulfate, the circulating level of this compound fell and uremic symptoms improved in patients with CKD; the progressive loss of GFR also slowed (99).

ASSESSING THE INFLUENCE OF THE DIET ON THE PROGRESSION OF CHRONIC KIDNEY DISEASE

The foregoing discussion indicates that restricting dietary protein (and/or phosphates) might limit damage and prevent the loss of kidney function. As early as the 1930s, Chanutin and colleagues examined this possibility experimentally and demonstrated that restricting dietary protein protected rat models of CKD against progressive kidney damage (17, 18). Specifically, they found that restricting dietary protein reduced histologic damage and blood pressure while improving the survival of rats with CKD (13, 46, 97). These experimental results were consistent with reports about small numbers of patients with CKD who benefited from dietary protein restriction (80, 94). But when the influence of low-protein diets on the progression of CKD was tested in larger numbers of patients, more questions were raised than were answered.

In interpreting results from clinical trials, one depends heavily on information obtained from the best-quality, large randomized-controlled trials (RCTs) or meta-analyses; less weight is placed on information from prospective, controlled clinical trials. Results from retrospective trials, case reports, or expert opinion are the least-reliable sources. Fouque et al. (33) used these criteria to examine reports published from 1974 to 2006. More than 50 low-quality studies were considered to be too small in size or to be uncontrolled and thus were eliminated.

The remaining nine RCTs and four meta-analyses were examined to determine the influence of dietary protein on changes in kidney function in patients with established CKD. In many studies, the end point was "renal death," the occurrence of death, the need to start dialysis, or a specified decrease in GFR (almost always 50%) during the study. In most studies, actual protein intake was calculated from a reliable method based on urea nitrogen excretion (78, 81).

Randomized Clinical Trials of Nondiabetic Patients

Rosman et al. reported results from 247 patients after two or four years of protein-restricted diets (113). Actual protein intake was 0.90 to 0.95 g/kg/d in patients with GFR values between 30 and 60 mL/min and 0.7 to 0.8 g/kg/d when GFR values were between 10 and 30 mL/min. Control patients had an unrestricted diet. After two years, the rate of loss of GFR was significantly slowed in patients on the protein-restricted diet (patients with polycystic kidney disease did not experience the same benefits). After four years, renal death was markedly improved in those assigned to the more restricted dietary protein.

Williams and colleagues (146) studied 95 British patients with CKD for 18 months after randomly assigning them to receive a diet of 0.6 g protein/kg/day and 800 mg/day phosphate or a diet of 1000 mg/day phosphate plus phosphate binders and unrestricted dietary protein; a third group received no dietary protein or phosphate restriction. Adherence to the prescribed dietary protein averaged 0.7, 1.02, and 1.14 g protein/kg/day/day. Daily phosphorus intakes were estimated at 815, 1000, and 1400 mg, respectively. The authors found no differences in the rate of loss of creatinine clearance or in the commencement of dialysis therapy. The small study size and the use of creatinine clearance greatly limit the conclusions that can be based on the results.

Ihle et al. (49) studied 72 Australian patients with advanced CKD for 18 months (initial GFR <15 ml/min). The patients were randomly assigned to an unrestricted diet or to only 0.4 g protein/kg/day. The actual amount of protein eaten was 0.9 or 0.6 g/kg/day. The outcome was evaluated from measurements of GFR. On average, there was no loss of GFR in the low-protein diet group, and fewer patients progressed to dialysis when compared with results from the unrestricted diet group ($p < 0.005$). The authors concluded that moderate dietary protein restriction exerts a beneficial effect on the progression of CKD.

The Northern Italian Cooperative Study Group reported on 456 CKD patients studied during two years of observation in an RCT (70). Patients were assigned to a control diet of 1.0 g protein/kg/day or to a diet containing 0.6 g protein/kg/day; both diets included at least 30 calories/kg/day. The control group ate 0.90 g protein/kg/day, and the low-protein group ate 0.78 g/kg/day. There was a large overlap in the amount of dietary protein ingested by the two groups. The results indicated that "renal survival" was only slightly different; fewer patients in the low-protein diet group reached the predetermined endpoint ($p = 0.059$).

Malvy et al. (73) studied a different diet: restriction to 0.3 g protein/kg/day plus a supplement of ketoacid precursors of essential amino acids (Ketosteril, 0.17 g/kg/day). The control patients were prescribed 0.65 g protein/kg/day to provide the minimum daily protein requirement. Fifty patients with CKD (creatinine clearance ≤20 mL/min) were evaluated for differences in the progression to dialysis or to a creatinine clearance <5 mL/min/1.73 m^2. It was concluded that renal survival was not different between the two groups; however, only 25 patients in each group were studied. Interestingly, the patients with the most advanced initial loss of kidney function (GFR <15 mL/min/1.73 m^2) had a nine-month half life associated with the 0.6 g protein/kg/day diet before reaching dialysis. The half life to the same endpoint for those given the more restrictive diet was 21 months.

Mircescu et al. (87) prescribed a severely protein-restricted diet (0.3 g protein/kg/day

plus a ketoacid supplement) and compared results with those from patients assigned to the minimum daily protein requirement (0.60 g protein/kg/day). The results of their study of 53 nondiabetic patients with stage IV CKD revealed that the ketoacid-based diet increased serum bicarbonate and calcium while reducing blood urea nitrogen and serum phosphorus. There was no difference in the average of changes in serum creatinine. However, after 48 weeks, significantly fewer patients eating the ketoacid diet required dialysis (4%) in comparison with those on the low-protein diet (27%; $p = 0.01$).

Cianciaruso et al. (21) studied 423 patients with advanced CKD who were randomly assigned to a diet containing either 0.8 or 0.55 g protein/kg/day. During the 18 months of the trial, actual protein intakes were 0.92 versus 0.72 g protein/kg/day, respectively. In the 212 patients assigned to the low-protein diet, nine progressed to dialysis or had a doubling of the serum creatinine (i.e., a renal death). Those assigned to moderate protein restriction included 13 who experienced renal deaths (p = NS).

The Modification of Diet in Renal Disease (MDRD) study, sponsored by the National Institutes of Health and the largest study to date, examined more than 800 randomly assigned patients for an average of 2.2 years. Low-protein diets and strict blood pressure control were evaluated while GFR was measured repeatedly (57). In Study A (GFR 25 to 55 mL/min/1.73 m^2), the prescribed diets consisted of 1.4 g protein/kg/day compared with 0.6 protein/kg/day. In Study B (GFR 13 to 24 mL/min/1.73 m^2), patients were prescribed a diet with 0.6 g protein/kg/day or 0.3 g protein/kg/day plus a ketoacid supplement. No difference in the overall rates of GFR decline was detected in the two Study A groups. The low-protein diet was associated with a faster decline in GFR initially; this was attributed to hemodynamic changes rather than to progressive kidney damage. In Study B, the loss of GFR was somewhat slower in patients prescribed the 0.46 g protein/kg/day diet plus ketoacids than in patients prescribed the diet containing 0.60 g protein/kg/day ($p = 0.07$). It was initially concluded that low-protein diets did not slow progression. Unfortunately, the conclusion prompted some to suggest that dialysis should be started early to avoid complications of CKD (84). The suggestion was discarded when reports demonstrated that starting dialysis early did not reduce mortality (7, 134).

Shortcomings of the MDRD study have been identified (31, 100). In the first four months of Study A, a sharp decrease in GFR in the protein-restricted group was related to a physiologic reduction in glomerular hemodynamics (see above). Subsequently, the loss of GFR was slowed. If the initial hemodynamic effect is eliminated, the rate of loss of GFR was significantly lower with the protein-restricted diet; this was supported by a smaller number of participants proceeding to dialysis ($p = 0.009$). Second, the measured rate of GFR loss was lower than predicted for the initial power analysis. Moreover, patients were randomly treated with angiotensin-converting enzyme inhibitors. This strategy was subsequently shown to slow progression of CKD. Both factors increased the number of patients that should have been studied in order to test the efficacy of low-protein diets adequately. Finally, the duration of the MDRD study was only 2.2 years. This is relevant when evaluating large-scale clinical trials [e.g., the Diabetes Control and Complications Trial revealed that after two years there was no decrease in albuminuria as a sign of kidney disease, but after four years, fewer patients assigned to strict blood glucose control developed microalbuminuria (130)]. Investigators have recognized these shortcomings and have undertaken secondary analyses of results from the MDRD study. The conclusions are certainly less robust than those reported in 1994 (57). The secondary analyses demonstrate that if the rate of loss of GFR is analyzed according to actual protein intake, the outcome was positive because the rate of decline in GFR was strongly related

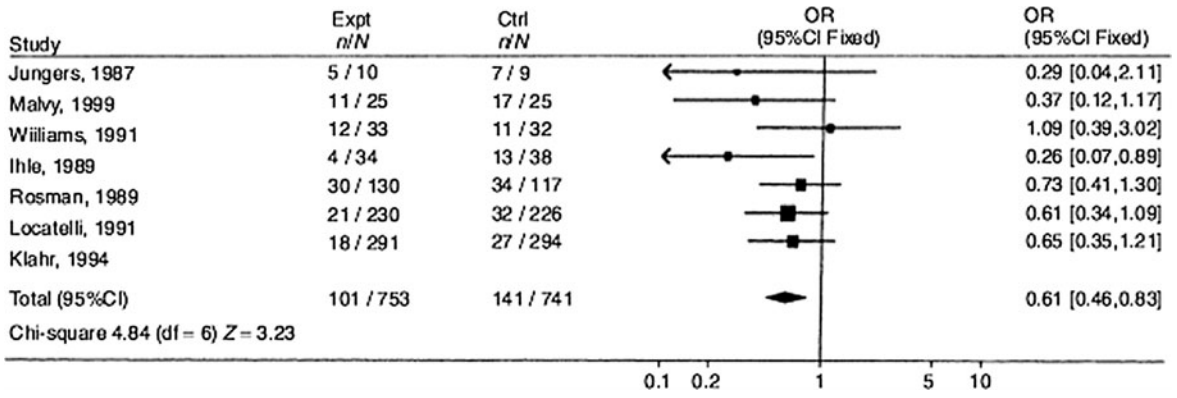

Figure 1

Meta-analysis of trials testing the influence of low-protein diets on loss of kidney function in patients with chronic kidney disease. A square denotes the odds ratio (treatment/control) obtained in individual trials; the diamond indicates the overall results of seven trials (95% CIs are represented by horizontal lines). Overall outcome or "common" odds ratio = 0.61 (95% CI: 0.46, 0.83; $p = 0.006$). See Reference 51 for Jungers et al. 1987 study. Ctrl, control; CI, confidence interval; df, degrees of freedom; expt, experiment; *n/N*, number of events/number of subjects; OR, odds ratio. Figure from Reference 33; used with permission.

to actual protein intake ($p = 0.011$) as was the number of patients progressing to dialysis or death ($p = 0.001$) (67). Specifically, reducing dietary protein by 0.2 g protein/kg/day slowed the loss of GFR by 1.15 mL/min/yr and reduced renal death by 49%.

Meta-Analyses

To increase the number of subjects studied when analyzing protein-restricted diets and progression to kidney failure, a series of meta-analyses have been conducted. The criterion analyzed in RCTs was renal death. The analyses were chosen to reduce biases and to increase the robustness of conclusions. In **Figure 1**, the impact of dietary manipulation on renal deaths is shown. Among more than 1400 patients (753 in protein-restricted dietary groups and 741 control patients assigned to a higher dietary protein), there was a 39% reduction in renal death ($p < 0.006$) for patients prescribed protein-restricted diets. In another meta analysis, results from more than 1900 patients indicated that assignment to the protein-restricted diet reduced the loss of GFR by 0.53 mL/min/yr ($p < 0.05$). Another type of analysis of these results has also been used (109). It can be calculated that the number of subjects who should be treated with a low-protein diet in order to prevent one renal death per year is 18 patients. This outcome is comparable to that calculated from the number of patients requiring statin therapy in order to observe a reduction in mortality when compared with a placebo (119).

Randomized Controlled Trials and Meta-Analyses of Patients with Diabetes and Chronic Kidney Disease

RCTs of low-protein diets and progression in patients with CKD and diabetes have the same problems as those encountered in studies of nondiabetic patients. These studies have been of short duration and hence renal deaths were infrequent. Second, instead of GFR measurements, surrogate criteria were often evaluated (e.g., changes in microalbuminuria, proteinuria, or creatinine clearance). Finally, administration of angiotensin-converting enzyme (ACE) inhibitors was not equally distributed in these trials, nor was blood pressure strictly comparable between groups. Regardless, the results are encouraging. Zeller

et al. (151) compared diets containing 1 g protein/kg/day with a diet of 0.6 g protein/kg/day in 36 patients with type 1 diabetes. The average follow-up was 35 months, and actual protein intakes were 1.08 and 0.72 g protein/kg/day, respectively. The protein-restricted diet led to substantial slowing of the loss of measured GFR ($p < 0.02$). The benefit was mainly present in the subgroup that had GFR values >45 mL/min.

The study with the longest duration was carried out in Denmark: Patients with type 1 diabetes and CKD were assigned to an unrestricted, control diet or to 0.6 g protein/kg/day and followed for four years (42). The actual protein intake was 1.02 g/kg/day in the control group versus 0.89 g/kg/day, a slight but significant difference. The authors found no difference in changes of proteinuria, but renal deaths were 36% lower in the protein-restricted group. When the results were adjusted for cardiovascular disease, the benefits of dietary restriction were even more significant ($p = 0.01$). Finally, a meta-analysis of the outcome of patients with CKD and diabetes revealed that dietary protein restriction improved the outcome by 44% ($p < 0.001$). In this case, the combined criteria of microalbuminuria and loss of renal function were analyzed (102).

Conclusion

Evidence from these trials supports the conclusion that diets containing the minimal daily requirement of 0.6 g protein/kg/day or the recommended daily allowance of 0.8 g protein/kg/day can reduce renal death in patients with CKD, especially in those with GFR values >15 ml/min. Since mortality was included in composite endpoints, the fact that patient survival improved suggests that such diets meet nutritional requirements. We conclude that the low-protein diets support survival of patients with CKD who are participating in trials, and they may slow the loss of kidney function. We recognize that the latter statement is controversial.

PROTEIN-ENERGY WASTING IS ASSOCIATED WITH CARDIOVASCULAR DISEASE

One concern about using protein-restricted diets in unselected patients with CKD is whether the diet will worsen the risk of cardiovascular morbidity and mortality that is associated with loss of lean body mass. This is a concern because CKD is an important risk factor for the development of cardiovascular disease (CVD), independent of traditional risk factors (118). The risk of developing CVD rises precipitously as GFR falls, and it dominates clinical problems when there is advanced CKD. For example, the risk of CVD for a 20-year-old man with ESKD is roughly 100-fold higher than the risk in an age-matched nonkidney subject. The basis for this association is unclear because conventional risk factors do not explain the very high mortality rate of patients with ESKD, and interventions targeted at controlling conventional risk factors (e.g., statin therapy to lower low-density lipoprotein cholesterol or intensive blood pressure control) have not been effective in reducing the high mortality risk of patients with ESKD (60, 141). Even tight blood pressure control has not improved CVD outcomes when compared with less-intensive blood pressure control.

In patients with ESKD, an unexpected epidemiologic association that is affected by nutritional factors is the report of a negative correlation between conventional risk factors [e.g., serum total cholesterol or body mass index (BMI)] and mortality risk (53, 129). Interestingly, negative correlations also exist between BMI and serum cholesterol for the risk of mortality in patients with cancer, congestive heart failure, and chronic obstructive pulmonary disease. Reversal of the expected relationship between markers of body composition and mortality present in dialysis patients has been termed "reverse epidemiology" (55). But it is not clear if reverse epidemiology actually represents a unique pathophysiologic mechanism that overrides the expected relationship of obesity and increased risk of CVD (52). This is suggested because the time from the measurement

of the parameter (e.g., obesity, BMI, or serum cholesterol) to the endpoint of death was only one to five years, whereas the mortality rate of ESKD patients approaches 20% per year. Consequently, in any one-year period, a classic CVD risk factor would have a relatively small influence on mortality. If, however, beneficial mechanisms associated with obesity protected the patient during a short period of time, they would override the influence of standard CVD risk factors, making it appear that expected outcomes would not apply to the population (129). In this case, the subset of the dialysis population that expresses the protective mechanism should dominate mortality risks over a short time when compared to conventional pathophysiologic mechanisms.

Patients with CKD who are examined before reaching ESKD express many of the same relationships between abnormalities in body and plasma composition and the increase in mortality as do patients with ESKD [i.e., dialysis patients (62, 142)]. For example, results of the National Health and Nutrition Examination Survey III of the health status of Americans revealed that the risk of malnutrition (principally assessed as a low serum albumin) was increased in patients with stage IV CKD (GFR 15–29 ml/min) but not in those with stage III CKD (GFR 30–59 ml/min) (38). In the general population, markers of oxidative stress increase with higher values of BMI, whereas in patients with ESKD, the same markers start at much higher values but decrease in those with higher BMI values (30). Patients with CKD express levels of oxidative stress markers that are intermediate between those of patients with ESKD and the general population; in both populations, oxidative stress increases with BMI (109). Thus, mechanisms present in patients with ESKD could also be present in patients with CKD stages III or IV but to a more limited extent.

Definitions of Protein-Energy Wasting

Epidemiologic results from patients with ESKD suggest there is a major role of inflammation and loss of protein stores, and both abnormalities increase the risk that these patients will develop CVD (32). Suggested names for the constellation of problems in these patients include uremic malnutrition, renal cachexia, protein-energy malnutrition, malnutrition-inflammation atherosclerosis syndrome, or malnutrition-inflammation complex (or cachexia) syndrome. We prefer the term protein-energy wasting (PEW) (32). Cachexia is an alternate term more commonly associated with profound physiological, metabolic, psychological, and immunological disorders (28). We reserve cachexia to describe advanced stages of protein-energy wasting.

Why use one of these terms instead of simply labeling the patients as suffering from malnutrition? The main reason is that a diagnosis of malnutrition is often a misnomer and misleads those caring for the patient into concluding that the abnormalities result from too little protein in the diet (8). In fact, the definition of malnutrition in *Webster's College Dictionary* is a group of abnormalities that arise because of insufficient food intake or because there are improper proportions of nutrients in the diet (88). In children with kwashiorkor or in adults with true malnutrition, many of these abnormalities are reversed when dietary protein or nitrogen is provided (136). However, these problems are not reversed in patients with CKD or ESKD when they are given a protein/energy-rich diet, suggesting that more fundamental abnormalities prevent patients with kidney disease from effectively utilizing dietary nutrients (85). Second, inflammatory processes appear to cause many of the abnormalities ascribed to malnutrition in patients with kidney disease (16). For example, inflammation is associated with both protein catabolism and the development of anorexia, and presumably is linked to increased levels of catabolic cytokines (125). Third, loss of kidney function is associated with other comorbid conditions, including diabetes and congestive heart failure, and these are independently associated with protein wasting (38). Finally, mechanisms associated with the uremic syndrome impair protein and energy metabolism independent

of whether adequate nutrition is present (124). Mechanisms for this abnormality in kidney disease include metabolic acidosis, cellular resistance to insulin and insulin-like growth factor (IGF)-1, and an increase in the basal metabolic rate (36).

Definitions of syndromes may become popular with clinicians, but to be maximally useful, they must first be validated for sensitivity and specificity. There is no uniformly accepted definition of protein-energy wasting in patients with kidney disease (108). American and European guidelines for nutritional interventions include recommendations that measurements of Subjective Global Assessment (SGA) of nutrition be made repeatedly in dialysis patients. But major problems exist with SGA because it is based on subjective scoring, and no standardization techniques have been developed to establish the presence of protein-energy wasting (32, 108). Other scoring systems have been developed (but not validated) and are somewhat more quantitative (108). Because of these problems and other factors, an expert panel from the International Society of Renal Nutrition and Metabolism (ISRNM) proposed a working definition of protein wasting. To improve the ease of clinical use, markers were chosen to include those commonly used in many countries. The ISRNM definition of PEW is based on four categories: biochemical criteria, loss of fat mass or weight, loss of muscle mass, and low protein or energy intakes (**Table 2**). Having abnormalities in three of four categories is sufficient for the diagnosis, but at least one biochemical indicator should be included for a clinical diagnosis of PEW. Serial measurements over time should be collected, along with body mass criteria obtained over a six-month period. Problems with the definition include difficulty in measuring muscle mass reliably in hemodialysis patients. Inaccurate estimates of lean body mass (e.g., with Dexa scanning) are compounded by changes in body water that are associated with dialysis (9). But an advantage in examining patients with ESKD is that protein intake can be estimated monthly or more frequently using urea nitrogen kinetic measurements. On the other hand, food frequency questionnaires conducted repeatedly are not reliable in dialysis patients (58, 32). Clearly, these recommendations need further validation (32).

A comparison of these criteria with those recently proposed for the presence of cachexia (**Table 2**) illustrates that certain similarities exist (28). Cachexia is defined as weight loss plus three other positive markers from five categories: biochemical, muscle strength, fatigue, anorexia, or low lean body mass. These diagnostic abnormalities place emphasis on weight, biochemical abnormalities, and lean body mass, criteria similar to those of the ISRNM recommendations (32) except that the cachexia definition focuses more on the disability caused by the wasting process. In addition, the biochemical criteria for cachexia include a lower level for serum albumin than in the protein-energy wasting in kidney disease recommendation (3.2 versus 3.8 mg/dl, respectively). Finally, criteria for inflammation and anemia are confounded for results from patients with ESKD because of erythropoetin deficiency and the high levels of inflammatory markers triggered by the dialysis process.

Protein-Energy Wasting Is Not Malnutrition

A low value of serum albumin has been touted as a major predictor of mortality in dialysis patients (71). As discussed above, the relationship between serum albumin and mortality is more complicated than a simple decrease in dietary protein. Although we do not dismiss the evidence that anorexia occurs in patients with advanced CKD and in patients with ESKD, we do not believe that anorexia alone is the major determinant of a low albumin. First, in other conditions, serum albumin is scarcely related to dietary factors: In patients with anorexia nervosa, a disorder that clearly arises from too little protein and too few calories in the diet, serum albumin is virtually normal, even in patients who have lost 30% or more of their lean body mass (121). Second, a low serum albumin value in patients with CKD or ESKD is more

Table 2 Definitions of protein-energy wasting

A. International Society of Renal Nutrition and Metabolism Criteria for Protein-Energy Wasting (32)

At least three of the four listed categories (and at least one test in the selected category) must be satisfied for the diagnosis of kidney disease–related protein-energy wasting. Optimally, each criterion should be documented on at least three occasions, preferably two to four weeks apart.

Serum chemistry

1) Serum albumin <3.8 g/dl (bromocresol green)
2) Serum prealbumin (transthyretin) <30 mg/dl (healthy levels may vary according to glomerular filtration rate (GFR) level for maintenance dialysis patients)
3) Serum cholesterol <100 mg/dl

Body mass

1) Body mass index <22 kg/m2 (under 65 years), <23 kg/m2 (>65 years)
2) Unintentional weight loss over time: 5% over 3 months or 10% over 6 months
3) Total body fat percentage <10%

Muscle mass

1) Muscle wasting: muscle mass reduced 5% over 3 months or 10% over 6 months
2) Reduced mid-arm muscle circumference area (>10% of reduction in relation to fiftieth percentile of reference population)
3) Creatinine appearance

Dietary intake

1) Unintentional low dietary protein intake: <0.80 g/kg/day for at least 2 months for dialysis patients or <0.6 g/kg/day for patients chronic kidney disease stages 2 to 5
2) Unintentional low dietary energy intake: <25 Kcal/kg/day for at least 2 months

B. Cachexia Society Guidelines (28)

Weight loss of at least 5% in 12 months or less in the presence of underlying illness or body mass index less than 20 and at least three of the following criteria:

1) Decreased muscle strength
2) Fatigue
3) Anorexia
4) Low free body mass index
5) Abnormal biochemistry
   a. Increased inflammatory markers: C-reactive protein >5.0 mg/dl or IL-6 >4.0 pg/ml
   b. Anemia: hemoglobin <12 g/dl
   c. Low serum albumin: <3.2 g/dl

closely linked to metabolic abnormalities. Two abnormalities associated with advanced CKD cause hypoalbuminemia. Zimmermann et al. reported that there was approximately a five-fold increase in death associated with high circulating values of C-reactive protein (CRP) in dialysis patients (153). For poorly understood reasons, inflammatory processes are common in patients with ESKD or CKD; they have much higher circulating levels of acute phase-reactant proteins in comparison with the general population (109). The hemodialysis procedure per se is associated with a rise in inflammatory cytokines that is probably related to stimulation of blood cells by the dialysis membrane. The use of temporary hemodialysis catheters or peritoneal dialysis catheters is associated with higher levels of acute phase-reactant proteins (and by implication, inflammation), providing an explanation for the inflammation present in patients with kidney disease (48). In addition, patients with CKD and ESKD frequently suffer from comorbid conditions that are associated with inflammation, particularly congestive heart failure and diabetes mellitus (32). Finally, patients with kidney disease frequently suffer transient, intercurrent catabolic illnesses (e.g., catheter infections, volume overload) that elicit inflammatory responses and a decrease in nutrient intake.

Beyond epidemiologic associations, there is evidence that inflammation causes hypoalbuminemia. In 2004, Don & Kaysen (26)

examined the determinants of hypoalbuminemia in 364 hemodialysis patients over six months and found that the blood CRP level was inversely correlated with serum albumin. In investigating mechanisms to explain this result, Kaysen et al. studied patients participating in the National Institutes of Health's multicenter Hemodialysis (HEMO) Study of stable hemodialysis patients. The patients were monitored sequentially for changes in serum albumin and acute phase-reactant proteins. Kaysen et al. (56) found that a rise in blood levels of ceruloplasmin or alpha-1 acid glycoprotein in one month was predictably followed by a decrease in serum albumin in the subsequent month. This relationship was not present when another acute phase-reactant protein, namely CRP, was studied. This type of evidence suggests that inflammation rather than decreased protein intake plays a major role in identifying causes for hypoalbuminemia in patients with ESKD, particularly since Kaysen et al. (56) found there was a minimal influence of variations in dietary protein linked to a decrease in serum albumin.

Another factor that influences serum albumin in patients with kidney disease is metabolic acidosis. In part, the mechanism involves changes in albumin synthesis, as indicated in a report by Ballmer et al. (4) that inducing metabolic acidosis in normal adults by giving NH_4Cl suppressed albumin synthesis. In a longer-term study, Movilli and colleagues (96) studied hemodialysis patients over eight months while they corrected metabolic acidosis by administering sodium bicarbonate. At the end of the study, the serum albumin was significantly higher. This study emphasizes the adverse effects of acidosis on protein metabolism in patients with kidney disease (see below).

Undoubtedly, an inadequate intake of protein or calories does influence of a decrease in lean body mass in patients with ESKD (32). For example, the dietary protein intake of dialysis patients was assessed by measuring urea kinetics and normalizing the results per kg of body weight (i.e., the so-called normalized nitrogen appearance, or nPCR). The patients had an improved survival when the protein intake was 1.0 to 1.4 g/kg/day over 18 months in comparison with patients consuming more or less protein (120). The importance of preventing deterioration of lean body mass has been repeatedly emphasized. One report indicated that an unintentional loss of as little as 1% to 2% of body weight within a two-year period was associated with an increased risk of mortality (54). Other analyses have suggested that a higher serum creatinine is associated with decreased mortality in patients with ESKD. The explanation was based on the fact that creatine is contained predominately in muscle, so an increase in serum creatinine could reflect more creatine and hence more muscle mass (71). This presumes that creatinine removal is constant with each dialysis. Although the conclusion that a higher lean body mass is beneficial has some rationale, there are problems with accepting the conclusion that patients with higher levels of serum creatinine have more lean body mass. First, the removal of creatinine during dialysis can vary because of differences in blood flow, the duration of the dialysis, etc. Second, in patients with advanced kidney disease, creatinine is metabolized, representing another factor that changes the serum level (91).

Uremic Toxicity Includes Impaired Appetite

The causes of protein-energy wasting in uremia can be broken down into those that typically cause anorexia and those that cause muscle wasting. Uremic toxicity is due in large part to the retention of small-molecular-weight compounds derived from dietary protein. The blood urea nitrogen is a surrogate for retention of these toxins, including the retention of acid, sodium and phosphates, small peptides, and protein-bound compounds (middle-molecule toxins), plus alterations in endocrine function. As discussed below, it appears that the factors that influence appetite largely arise from small toxins and peptides that are derived from metabolism of dietary protein plus are hormones released during responses to eating (6). For this reason, an excess of dietary protein can

cause anorexia in patients with advanced CKD and suggests why the appetite can improve with adequate dialysis treatment. Unfortunately, the mechanism is not simple. Some factors responsible for muscle wasting (such as acidosis) are improved with dialysis, whereas others (such as inflammatory cytokines) are actually worsened by dialysis. Thus, anorexia may improve with dialysis, but this does not mean that loss of protein stores is reversed. In fact, the prevalence of protein energy wasting actually increases when patients are treated by dialysis.

What are the toxins? Toxic mediators derived from dietary protein include urea, which can form cyanates that modify terminal amino groups of peptides and proteins, and the amide groups of lysine-forming carbonyl groups on proteins (63). There also is accumulation of arginine metabolites, asymmetric dimethyl arginine and ornithine, which are associated with loss of appetite in rodent models of kidney disease (74, 75). Similarly decreasing the blood levels of indoxyl sulfate, a metabolite of tryptophan, is associated with improved food intake (98). However, indoxyl sulfate was lowered by a resin, and the resin could have removed other toxins capable of depressing appetite, illustrating the complexity of these pathways.

Another potential anorexiogenic mechanism that is not closely linked to dietary protein is accumulation of molecules arising from peripheral tissues (e.g., leptin) and those that are present in the central nervous system (e.g., melanocortin) (19). Leptin suppresses neural pathways that cause hunger, including neurons that produce neuropeptide Y and agouti-related peptide (72). A decline in leptin levels stimulates appetite, whereas an increase in leptin suppresses appetite. The latter response has been partially overcome by the administration of ghrelin a mouse model of CKD (24). Interestingly, plasma ghrelin levels rise in patients with CKD, a response that could partially offset leptin-induced hypothalamic signaling (104). Consequently, even though leptin levels are elevated, the extent to which leptin and ghrelin are responsible for the anorexia and weight loss that accompany uremia remains to be determined. Leptin also activates hypothalamic nuclei that regulate sympathetic nervous activity. This is relevant because an increase in sympathetic activity has been proposed as a factor causing the increased basal energy requirements of uremic patients (23, 128).

Influence of a Low-Protein Diet in Chronic Kidney Disease

Based on available reports, it is unclear whether a lower lean body mass is causally linked to mortality or is merely a marker of an underlying disease process that decreases protein intake and increases mortality. Available information suggests that CKD patients who do not have acidosis or complicating illnesses can adapt normally to dietary protein restriction (89). Specifically, normal adults activate adaptive responses to dietary protein restriction by progressively decreasing the irreversible destruction of amino acids; hence, there is decreased production of nitrogen-containing waste products. But this initial adaptive response has limits, and when the limit is reached, another adaptive mechanism is activated, namely a decrease in the degradation of protein and at least some stimulation of protein synthesis (95). Together, these adaptive responses act to prevent loss of body protein stores by improving the balance between nitrogen intake and nitrogen excretion (i.e., protein balance). Patients with CKD that is uncomplicated by a catabolic illness or condition that causes protein losses (e.g., a febrile illness or glucocorticoid therapy) activate the same mechanisms, ensuring adaptation to dietary protein restriction with an improved protein balance (2, 39, 133, 139). Interestingly, the same adaptive responses are activated in nephrotic patients given a protein-restricted diet (77). It is not known if these adaptive responses occur in patients with ESKD and whether they would be sufficiently effective to prevent excessive catabolism.

There are no randomized trials of the influence of protein intake and mortality in patients with kidney disease, but the MDRD

study did include nondiabetic patients with stage III or IV CKD (57). Patients randomized to the lower protein intake in the MDRD study had an improvement in serum albumin and a small loss of lean body mass based on changes in anthropomorphic measurements or body weight (61). Long-term follow up of the patients after the end of the study showed no difference in mortality between the normal and protein-restricted groups (67, 86). Presumably, adaptive responses of patients with CKD were sufficient to prevent protein-energy wasting despite a reduced protein intake. The low mortality rate of patients in the MDRD study may be attributable at least in part to the entry criteria for the study; patients with known wasting diseases were excluded from the investigations (57). It is our opinion that the comorbidities, occurring so commonly in patients with CKD, contribute greatly to the protein-energy wasting present in so many of the epidemiologic assessments. In short, low-protein diets are safe in CKD patients who do not have comorbidities. This conclusion is similar to that provided in the National Kidney Foundation's Disease Outcomes Quality Initiatives nutrition guidelines (1).

MECHANISMS BLOCKING THE ADAPTIVE RESPONSES TO DIETARY PROTEIN RESTRICTION

One consequence of CKD or ESKD is metabolic acidosis that blunts or blocks the adaptive responses to dietary protein restriction. In rodent models of CKD, it was shown that acidosis stimulates the breakdown of essential amino acids, thereby blocking the initial adaptive response to a decrease in dietary protein (43). Acidosis also stimulates the breakdown of muscle protein, blunting the second adaptive response (37, 83). Similar results have been demonstrated in studies of predialysis CKD patients with metabolic acidosis as well as in patients with ESKD who are being treated by hemodialysis or CAPD (40, 41, 110). Other abnormalities induced by CKD also stimulate the breakdown of muscle protein, contributing to loss of muscle mass, fatigue, abnormalities in protein stores, etc.

In animal models of CKD, the abnormalities in cellular metabolism that cause loss of muscle mass include two common pathways. First, the loss of muscle mass is principally related to the acceleration of protein degradation in muscle and specifically to activation of the ubiquitin-proteasome system (UPS). Notably, the UPS is also activated in other conditions that cause muscle wasting (see below). Second, the UPS is activated by impaired function of the insulin/IGF-1 signaling pathway (**Figure 2**).

The UPS is involved in the regulation of many cellular functions because it degrades transcription factors and proteins regulating the cell cycle and proteins with short half lives as well as the bulk of proteins in all cells, including muscle (92, 112). In muscle, two specific E3 ubiquitin ligases, Atrogin-1 and MuRF1, are key mediators of the increase in muscle protein breakdown (10). In CKD models, evidence for activation of the UPS includes an increase in Atrogin-1 expression and accelerated proteolytic activity that is blocked by an inhibitor of the proteasome; transcription of components of the UPS is also increased (3). Similar events occur in other catabolic conditions including experimental sepsis, starvation, diabetes, denervation, and cancer (5, 90, 106, 131, 140, 148, 149). Evidence for activation of the UPS also has been demonstrated in patients with kidney failure, trauma, cancer, and sepsis (76, 105, 132, 145).

The breakdown of muscle protein in these catabolic conditions requires more than an increase in UPS activity because it has only limited ability to degrade the complex structure of muscle, including actomyosin or myofibrils (122). In contrast, actin or myosin are rapidly degraded by the UPS, indicating that another proteolytic system cleaves the complex structure of actomyosin or myofibrils to produce substrates for the UPS. We found that the other protease activity can be attributed to caspase-3.

It is activated in muscle of rodents with CKD or acute diabetes and cleaves actomyosin to products degraded in the UPS to form peptides (27). The peptides generated are converted to amino acids by intracellular peptidases in muscle (64).

The activity of caspase-3 can be detected because it forms a characteristic 14 kD fragment of actin, which accumulates in the insoluble fraction of muscle (27, 65, 123, 152). This index of caspase-3 activity also occurs in muscles of catabolic patients. We found that the density of the 14 kD actin fragment in muscle biopsies was highly correlated to the simultaneously measured rate of protein breakdown in patients who were undergoing hip replacement (150). The 14 kD actin fragment was also found in unburned muscle of patients who were recovering from serious burn injuries to other parts of their body. This finding supports our earlier studies of the systemic influence of burn injury in causing widespread protein wasting (22). Regarding CKD, dialysis patients engaging in endurance exercise training experienced a significant reduction in the density of the 14 kD actin fragment in their muscles. This beneficial response did not occur in patients trained in resistance exercise. Clearly, these results will have to be confirmed in other patients and in those with other types of catabolic injury. If they are confirmed, the presence of the actin fragment might be used as a biomarker of accelerated muscle protein breakdown.

There has been progress in identifying cellular triggers that activate proteolytic mechanisms in muscle (**Figure 2**). For example, caspase-3 and the UPS are stimulated in muscle when there is impaired insulin/IGF-1 signaling (65, 117, 126). This is important because impaired insulin signaling has been demonstrated in patients with relatively early CKD [i.e., serum creatinine >2.4 mg/dl (59)]. Several conditions associated with CKD also cause abnormalities in insulin/IGF-1 signaling, including inflammation, an increase in glucocorticoids production, and acidosis (25, 47, 83, 115, 116, 152).

Mechanisms Causing Inflammation-Induced Protein-Energy Wasting

Evidence of inflammation is commonly present in CKD and ESKD (103). The mechanisms responsible for the increase in cytokines in kidney patients and their impact on protein nutrition are unclear. However, inflammation does interfere with insulin/IGF-1 signaling and therefore could contribute to the muscle wasting present in CKD and ESKD (47, 115, 152). To evaluate how high levels of angiotensin II (Ang II) cause muscle wasting, we examined Ang II and the production of cytokines and acute phase-reactant proteins (152). In mice, Ang II increased the production of IL-6 and serum amyloid A, and they acted synergistically to stimulate SOC83 (suppressor of cytokine signaling). This in turn led to impaired insulin/IGF-1 signaling with activation of the UPS and caspase-3, resulting in muscle protein degradation (123, 152). These results further substantiate a new role for acute phase-reactant proteins, indicating they could augment responses to inflammatory cytokines rather than simply serving as an evidence of inflammation.

Interestingly, inflammatory cytokines fall in the middle molecule category of uremic toxins. As serum creatinine rises, circulating IL-6 levels increase; the IL-6 binding protein/receptor also increases (11, 101). The magnitude of the increase in circulating cytokines associated with kidney disease depends on the degree of inflammation and oxidative stress as well as the influence of dialysis, which increases inflammation.

Gluccocorticoids are another factor that may prevent normal metabolic adaptations to a reduced protein intake. This adverse effect of glucocorticoids could be due to their propensity to cause insulin resistance, in part by suppressing the activity of phosphatidylinositol 3-kinase, leading to impaired insulin/IGF-1 signaling (116). In addition, glucocorticoid production rises in models of CKD or type II diabetes, which are characterized by excessive protein catabolism (83). In patients with ESKD, the half-life of cortisol is twice normal, thereby

increasing the duration of the exposure of muscle to high cortisol levels (138). Acidosis also increases circulating glucorticoids due to a rise in ACTH; curiously, correcting the acidosis with dietary sodium bicarbonate does not eliminate the high glucocorticoid level (82). In patients with ESKD, hemodialysis induces significant increases in circulating ACTH and cortisol. This stimulation of glucocorticoid production is a presumably crucial factor in causing abnormalities in muscle protein metabolism (36).

DIETARY TREATMENT OF PROTEIN-ENERGY WASTING

RCTs are needed to uncover nutritional interventions that result in weight gain and then to determine if such diets also increase the survival of dialysis patients. However, the constellation of symptoms resulting in loss of protein stores in patients with kidney disease is not corrected by simply supplying more food to the patient, a point that emphasizes the need for new strategies. Most studies of nutritional support have involved hemodialysis patients who are given oral supplements three times a week at the dialysis session or who are given intravenous nutrition (intradialytic pareneteral nutrition; IDPN) during hemodialysis. The supplements have provided ample dietary protein (1.0–1.2 g/kg/day) and calories (30–35 g/kg/day) to maintain or build more muscle mass (1). Results of these strategies have been mixed: Younger patients with fewer comorbid conditions appear to maintain muscle mass, whereas others continue to suffer from PEW (15, 32). In one study, a supplement providing 500 kcal and 15 g protein was provided at each dialysis session in an RCT (127). The supplementation was associated with weight gain and an increase in serum albumin. A meta-analysis of all trials providing oral supplements suggested that serum albumin can improve in patients with severe protein-energy wasting (127).

The French Intradialytic Nutrition Evaluation Study recently reported findings from a randomized trial that assessed the effect of feeding regimens on mortality. It involved 186 hemodialysis patients randomly assigned to IDPN with 15.4 kcal and 0.6 g protein per kg per dialysis or to no IDPN support (14). Both groups had access to oral supplements that provided 5.8 kcal and 0.4 g protein per kg daily. The addition of IDPN to the oral supplements did not significantly improve nutritional parameters or survival, but there was an increase in body mass index and some increase in serum albumin and transthyretin levels. Overall, the study did not demonstrate a benefit for patients given IDPN plus oral supplements of calories and proteins. Interestingly, when transthyretin rose by more than 30 mg/l within three months, there was a decrease in the predicted two-year mortality. Although we agree with providing oral nutritional support for a dialysis patient with protein-energy wasting when the diet contains <0.8 g protein/day and 20 kcal/kg/day, evidence that it is beneficial is lacking.

Why is it so difficult to uncover a benefit of feeding dialysis patients who have protein-energy wasting? One reason is that the abnormalities causing protein-energy wasting do not arise from inadequate protein-energy intake. In short, improving the diet will not eliminate the catabolic stimulus. If the patient has an infected dialysis catheter, congestive heart failure, or elevated glucocorticoids, improving the diet will not overcome the problems. Consequently, protein-energy wasting presents diagnostic and therapeutic challenges: The cause of the inflammation, insulin resistance, or anorexia must be addressed before therapy is selected.

Careful studies of whole-body and muscle protein metabolism have documented that nutritional therapy has limits: Feeding regimens consistently increase whole-body protein synthesis but rarely show a significant improvement in whole-body nitrogen balance (68, 107). The increase in muscle protein synthesis induced by nutritional therapy is generally accompanied by an increase in muscle protein degradation, canceling protein synthesis and resulting in no improvement in muscle protein

balance. Moreover, administration of IDPN is associated with increased appearance of the 14 kDa actin fragment, which indicates that there is caspase 3-mediated degradation in muscle (107).

How does protein feeding induce muscle proteolysis? In normal adults, chronic feeding of an isocaloric protein-rich diet increases insulin, related at least in part to the induction of insulin resistance (69). Experimentally, acute intravenous infusion of amino acids or bathing isolated muscles in a high concentration of amino acids increases the insulin needed to increase glucose entry into cells (135). Just as with protein synthesis, individual amino acids can exert different degrees of insulin resistant: Leucine induces less insulin resistance than do other amino acids (135). Because insulin resistance stimulates muscle protein degradation by caspase-3 and the UPS, the link of excess diet protein and insulin resistance offers an explanation for a nonselective increase in proteolysis with intensive feeding.

It appears that an increase in protein degradation is an integral part of muscle responses to the delivery of amino acids. It has been proposed that the rise in muscle protein degradation in response to feeding is part of normal muscle protein turnover (35). In fact, protein feeding could be required for remodeling and restoring proteins by selectively degrading substituted or misfolded protein and damaged mitochondria. Clearly, the clinical benefit of an adequate protein intake can be explained by the removal of oxidized (and, likely, nitrosoylated and glycosolylated) proteins by increased degradation. If this hypothesis is correct, feeding actually refreshes muscle proteins to improve muscle function, permitting more physical activity. The benefit extends to visceral protein stores, as an improvement in gut and immune function reduces inflammation (127). Overfeeding of protein, however, does not produce additional benefits because excess protein could increase insulin resistance, protein nitrosylation, and mitochondrial oxidative stress.

A disappointing implication of the scheme whereby feeding increases muscle proteolysis is that muscle will not improve by feeding alone. Feeding plus exercise, on the other hand, increases muscle protein synthesis and decreases muscle protein breakdown, leading to efficient muscle cell growth (i.e., hypertrophy) (111). This is possible because exercise reduces insulin resistance and improves muscle mitochondrial function with reduced tissue oxidation. Investigation of the influence of exercise training used in conjunction with well-designed feeding strategies (to avoid excess waste product accumulation) could lead to an integrated approach to improve muscle function and mass even in hemodialysis patients (**Figure 3**).

CONCLUSION

Our understanding of protein nutrition in CKD will always be guided by balancing the benefits of adequate protein and calorie intakes with the toxicity caused by excessive intakes. Clearly, patients with CKD need adequate calories and exercise to make the most effective use of dietary protein. Prescribing the level of dietary protein for patients with CKD is therefore difficult. Patients with CKD without inflammatory or wasting benefit the most from a protein-restricted diet, as advised by the k/DOQI clinical nutrition guidelines (1). Our best guess is that patients with CKD who have evidence of protein-energy wasting should be supplied a higher protein intake until their underlying disorder is diagnosed and corrected. After they recover, a lower-protein diet will be needed. Patients with ESKD require a higher protein intake in part because of inflammatory responses to dialysis. Future studies that integrate protein and calorie requirements should include physical activity as a tool to improve muscle function. There is a pressing need for understanding how to block or suppress the underlying mechanisms that cause protein-energy wasting in patients with kidney disease. These strategies must not interfere with the normal adaptive mechanisms that are required to improve nutritional status.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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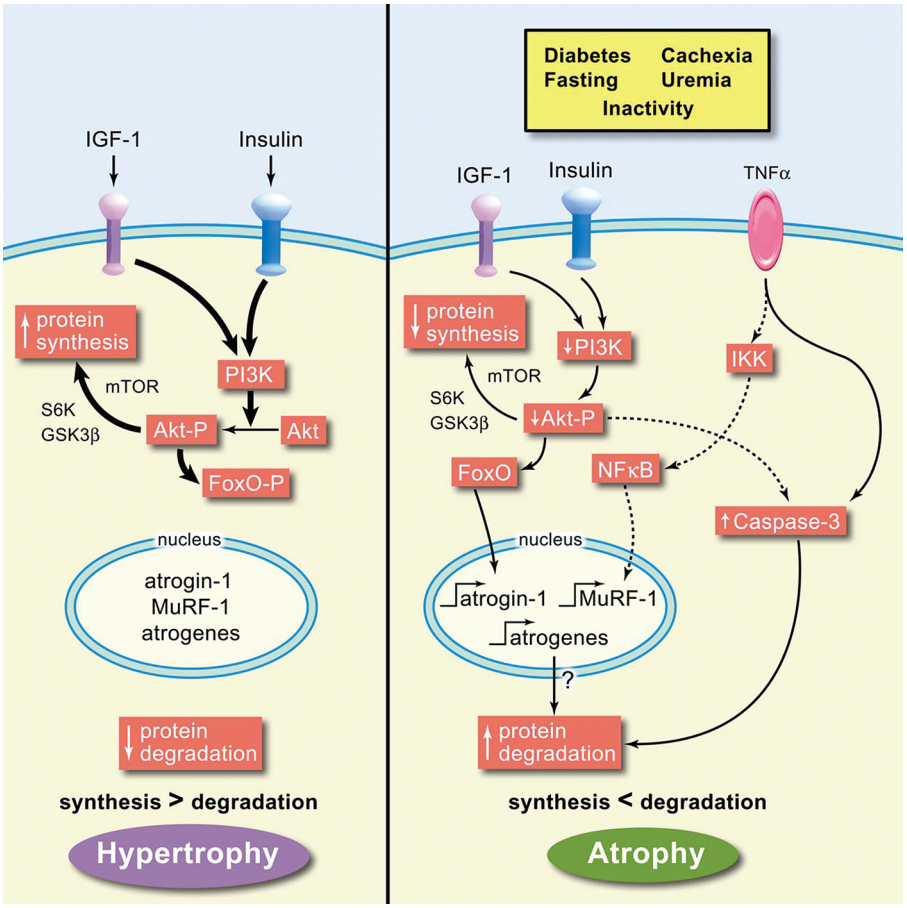

Figure 2

The influence of insulin/insulin-like growth factor (IGF)-1 signaling on skeletal muscle protein synthesis and protein degradation. Protein synthesis in muscle rises with insulin/IGF1 signaling while proteolysis remains dormant (*left panel*). With insulin/IGF-1 resistance or inflammatory cytokines, activation of caspase-3 in muscle to cleave myofibrillary protein and stimulation of atrogenes to express Atrogin-1 and MurF1 leads to increased proteolysis via the ubiquitin/proteasome system (*right panel*). Published with permission from the *Journal of the American Society of Nephrology*.

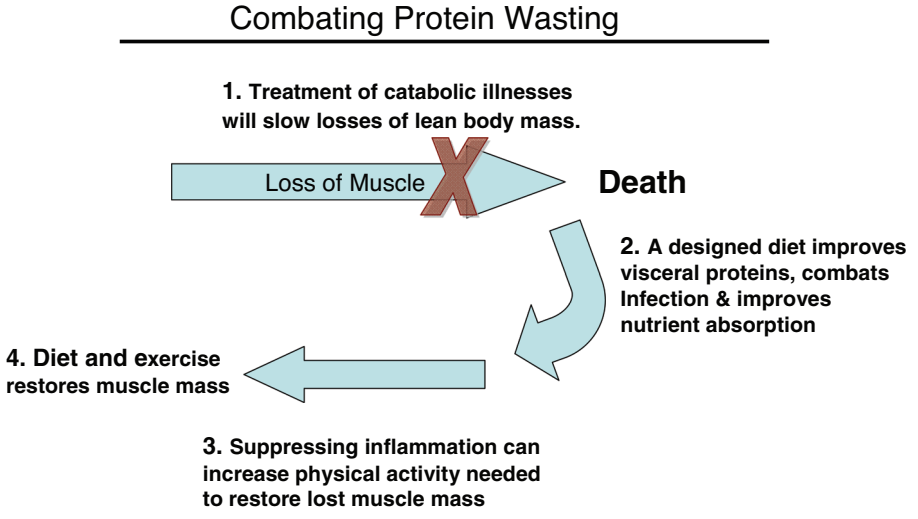

Figure 3

Factors influencing the recovery from protein-energy wasting.

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Errata

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