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Management of protein-energy wasting in non-dialysis-dependent chronic kidney disease: reconciling low protein intake with nutritional therapy^{1–4}

Csaba P Kovesdy, Joel D Kopple, and Kamyar Kalantar-Zadeh

ABSTRACT

Protein-energy wasting (PEW), characterized by a decline in body protein mass and energy reserves, including muscle and fat wasting and visceral protein pool contraction, is an underappreciated condition in early to moderate stages of chronic kidney disease (CKD) and a strong predictor of adverse outcomes. The prevalence of PEW in early to moderate CKD is ≥ 20 –25% and increases as CKD progresses, in part because of activation of proinflammatory cytokines combined with superimposed hypercatabolic states and declines in appetite. This anorexia leads to inadequate protein and energy intake, which may be reinforced by prescribed dietary restrictions and inadequate monitoring of the patient's nutritional status. Worsening uremia also renders CKD patients vulnerable to potentially deleterious effects of uncontrolled diets, including higher phosphorus and potassium burden. Uremic metabolites, some of which are anorexigenic and many of which are products of protein metabolism, can exert harmful effects, ranging from oxidative stress to endothelial dysfunction, nitric oxide disarrays, renal interstitial fibrosis, sarcopenia, and worsening proteinuria and kidney function. Given such complex pathways, nutritional interventions in CKD, when applied in concert with nonnutritional therapeutic approaches, encompass an array of strategies (such as dietary restrictions and supplementations) aimed at optimizing both patients' biochemical variables and their clinical outcomes. The applicability of many nutritional interventions and their effects on outcomes in patients with CKD with PEW has not been well studied. This article reviews the definitions and pathophysiology of PEW in patients with non-dialysis-dependent CKD, examines the current indications for various dietary modification strategies in patients with CKD (eg, manufactured protein-based supplements, amino acids and their keto acid or hydroxyacid analogues), discusses the rationale behind their potential use in patients with PEW, and highlights areas in need of further research. *Am J Clin Nutr* 2013;97:1163–77.

INTRODUCTION

Of the many various complications of chronic kidney disease (CKD)⁵, those involving protein-energy status not only have been shown to be some of the most powerful predictors of outcomes (1–3) but also have sparked an ongoing debate related to their management. Whereas there is broad agreement about the adverse prognostic significance of undernutrition, it remains

unclear to what extent the correction of undernourishment can improve clinical outcomes, especially in patients with non-dialysis-dependent (NDD) CKD. Furthermore, the role that overnutrition plays in the clinical outcome of patients with CKD also remains unclear. Obesity has been shown to be a risk factor for the development of kidney disease (4), but at the same time it has also been linked to greater survival in patients with virtually all stages of CKD (5–7). More clearly defined undesirable side effects of overnutrition include the development of hyperkalemia, hyperphosphatemia, sodium and volume overload, and an increase in uremic metabolic products and their various potential deleterious effects.

Whereas the short-term consequences of both abnormally low and high nutrient intakes are clear, it is less clear to what extent

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⁵ Abbreviations used: CKD, chronic kidney disease; DPI, daily protein intake; EAA, essential amino acid; eDPI, estimated daily protein intake; ESRD, end-stage renal disease; LPD, low-protein diet; MDRD, Modification of Diet in Renal Disease; MHD, maintenance hemodialysis; NDD, non-dialysis-dependent; PEW, protein-energy wasting; SVLPD, supplemented very-low-protein diet; UN, urea nitrogen; VLPD, very-low-protein diet.

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the long-term correction of these abnormalities can affect clinical outcomes, especially in NDD CKD. Furthermore, the design of nutritional interventions in patients with NDD CKD and protein-energy wasting (PEW) should consider the unique needs of these patients in terms of the amount and sources of their protein, energy, and other nutrient intakes and should balance these against the larger goals of such interventions applicable to all patients with NDD CKD, such as the amelioration of progression of CKD. The effect of most dietary interventions has not been specifically examined by properly powered randomized controlled trials in patients with NDD CKD and PEW, which makes it difficult to render evidence-based recommendations about proper nutritional goals and about the most ideal methods to achieve those in this vulnerable population. Therefore, it is of utmost importance that strategies for such interventions are developed with attention to the underlying pathophysiology and the potential benefits and risks of such interventions. This is particularly important with regard to the fine balance between the management of kidney disease progression while correcting a deficient protein-energy status.

In this review article we provide a brief overview of the nutritional needs of patients with NDD CKD, examine the pathophysiologic mechanisms underlying the development of PEW with a focus on NDD CKD, and discuss the various treatment strategies involving manipulation of protein and energy intakes that one could use to optimize outcomes.

PROTEIN AND OTHER NUTRIENT INTAKES IN CKD

The dietary protein requirements of nonnephrotic adult CKD patients who do not have superimposed catabolic illnesses appear to be similar to those of normal healthy individuals. Nonpregnant, nonlactating healthy adults appear to have a dietary protein need reported to be, on average, $\sim 0.6 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$. This refers to protein of unselected or mixed biological value. The FAO/WHO and Food and Nutrition Board of the National Academy of Sciences have added 33% to this average protein intake to obtain the safe intake (8). This is the genesis of the Recommended Dietary Allowance for healthy adults of $0.8 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$. For stable (eg, nonnephrotic, noninflamed/noncatabolic) NDD-CKD patients, the recommended so-called low-protein diet (LPD) provides $0.60\text{--}0.80 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, which represents sufficient protein intake—especially because the diet prescription includes the stipulation that $\geq 50\%$ of the protein should be of high biological value (9). Similarly, the so-called supplemented very-low-protein diet (SVLPD) also provides $\sim 0.3 \text{ g protein of any quality} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ with $\sim 0.28 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ of a mixture of the 9 essential amino acids (EAAs) or of some EAAs (10, 11) and keto acid and hydroxyacid analogues of the other EAAs (12). Thus, the SVLPD also provides an intake similar to $0.6 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, but the quality of the protein and keto acid/EAA mix is much higher. However, because a diet restricted to $0.6 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ is 25% below the recommended $0.8 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, the term “LPD” has generally been used to describe it. It can be argued that giving 25% less protein on a long-term basis might eventually compromise nutritional status, especially if such patients may have episodic conditions for which they would require higher amounts of protein, such as during infections or other hypercatabolic states. These considerations have resulted in the emergence of a camp in the field of renal nutrition representing the opinion that an intake of

$0.6 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ needs to be supplemented by EAAs or their keto-analogues. Notwithstanding the theoretical possibility of benefits to this approach, there is currently no convincing evidence to support or refute it (*see* Protein supplementation).

Another important aspect of nutritional intake is the content of other nutrients and chemicals in the ingested foods. Restrictions of other components of the diet are often implemented in CKD patients because of the presence of such underlying comorbid conditions as diabetes mellitus or hypertension or because of an increased risk of hyperphosphatemia, hyperkalemia, negative calcium balance or sodium, and water retention. The long-term effects of dietary restrictions to prevent or to treat these complications are largely unknown and may have unintended consequences, including an inadvertent lowering of the amount of protein intake with worsening PEW. The wisdom of implementing dietary restrictions in the elderly based on extrapolations from general population guidelines has recently been questioned because of the uncertain benefits and potential harm caused by such strategies (13, 14). Some of the arguments against such restrictions could apply to patients with NDD CKD—a population in which the elderly are overrepresented. Recent evaluations of diets containing equivalent amounts of protein, but from different sources, indicate that vegetarian diets administered to NDD-CKD patients resulted in a decrease in proteinuria (15, 16) and in serum concentrations of phosphorus (16, 17), parathyroid hormone, and fibroblast growth factor-23 (17). Although the effects of such strategies on clinical outcomes in NDD-CKD patients are unclear, higher amounts of dietary phosphorus (18) and potassium (19) in patients with end-stage renal disease (ESRD) have been associated with increased mortality, and maintenance hemodialysis (MHD) patients who increased their protein intake at the same time that their serum phosphorus decreased had the greatest survival (20). It is unclear whether similar associations would be present in patients with earlier stages of CKD.

Finally, a crucial aspect of nutrient intake is the amount of energy ingested. Neutral or positive nitrogen balance normally requires adequate energy intake, and a low energy intake may directly cause protein wasting (21). On the basis of published studies, it is recommended that the daily energy intake in NDD-CKD patients should be $\sim 35 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ for those aged $< 60 \text{ y}$ and $30 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ for those aged $\geq 60 \text{ y}$ (9, 21). These recommendations for energy intake may be modified when examination of an individual patient's daily energy expenditure indicates a different energy requirement. The issue of energy intake becomes especially important when dietary protein restriction is prescribed (*see* Protein restriction).

PEW IN CKD

To differentiate various causes and consequences of the wasting syndrome in CKD, it is important to systematically define what is meant by the designation “protein-energy malnutrition” (22) or “uremic malnutrition” (23). A workable definition of protein-energy malnutrition was advanced by Kalantar-Zadeh et al in 2003 (1) as “the state of decreased body pools of protein with or without fat depletion or a state of diminished functional capacity, caused at least partly by inadequate nutrient intake relative to nutrient demand and/or which is improved by nutritional repletion.” We believe that this definition is applicable across all stages of CKD. The term “PEW” was developed in recognition that not all causes of wasting are due to inadequate nutrient intake or increased

TABLE 1

Potential causes of protein-energy wasting in patients with non-dialysis-dependent chronic kidney disease¹

A. Inadequate nutrient intake
a. Anorexia ² caused by
Uremic toxicity
Impaired gastric emptying (eg, diabetic gastroparesis)
Inflammation with or without apparent comorbid conditions ²
Hormonal derangements (eg, elevated serum leptin, low serum ghrelin)
Emotional and/or psychological disorders
b. Poor adherence to the following prescribed dietary restrictions ³
Low- and very-low-protein diet
Low energy intake
Low-potassium and low-phosphate regimens
Low-salt diet with restricted fluid (to control edema)
Low-fat diet (such as DASH diet)
Low-carbohydrate diet for glycemic control (eg, in patients with diabetes)
c. Social-economic constraints: poverty, inadequate dietary support
Physical incapacity: inability to acquire or prepare food or to eat or digest foods
Poor dentition and/or severe gum disease
Neurologic disorders (eg, after cerebrovascular accidents with deglutition disorders)
B. Moderate or severe proteinuria (eg, >10 g/d)
C. Hypercatabolism caused by comorbid illnesses
Cardiovascular diseases ²
Diabetic complications
Infection and/or sepsis ²
Other comorbid conditions ²
D. Hypercatabolism associated with the uremic milieu
Negative protein balance
Negative energy balance
Endocrine disorders of renal failure
Resistance to insulin
Resistance to growth hormone and/or IGF-1
Increased serum concentrations of or sensitivity to glucagon
Hyperparathyroidism
E. Acidemia due to metabolic acidosis
F. Others
Concurrent blood losses

¹ DASH, Dietary Approaches to Stop Hypertension; IGF-1, insulin-like growth factor-1.

² Usually if not always associated with inflammation.

³ Adherence to the following diets should not engender protein-energy malnutrition or protein-energy wasting. Patients who are unable to ingest the diets in their entirety may have inadequate protein and particularly energy intakes.

nutrient losses (eg, from proteinuria or dialysate losses of amino acids, peptides, and protein). PEW is defined as abnormally low levels or excessive losses of body protein mass and energy reserves. Causes of PEW include inadequate nutrient intake, increased nutrient losses, inflammation, oxidant stress, carbonyl stress, disorders of anabolic or catabolic hormones, and acidemia. Thus, protein-energy malnutrition is usually an important component of PEW (24). PEW is engendered when the body's need for protein or energy fuels or both cannot be met by the regular diet. The different causes of PEW in CKD patients are listed in **Table 1**. The list of suggested methods used for diagnosing PEW in CKD patients is shown in **Table 2**. The PEW Consensus Conference suggested that "at least 3 out of the 4" listed categories in **Table 2**

(and at least one test in ≥ 3 of the 4 selected categories) must be positive to satisfy the diagnosis of PEW. Optimally, each criterion should be documented on ≥ 3 occasions, preferably ~ 2 –4 wk apart (24).

When CKD reaches stages 4 and 5, a decline in protein and energy intakes is often accompanied by worsening protein-energy status (**Figure 1**) (25, 26). As a result, PEW is more common in the later stages of CKD. In a recent study of 1220 NDD-CKD patients, 45% of subjects had a serum albumin concentration < 3.6 g/dL and 22% of subjects had a serum albumin concentration of < 3.4 g/dL. Furthermore, the probability of PEW (defined as the presence of ≥ 2 of 3 biochemical markers of PEW) significantly and linearly increased with lower estimated glomerular filtration rates (**Figure 2**) (3). In another study, by Lawson et al (27), 20% of 50 NDD-CKD patients with serum creatinine > 1.7 mg/dL had mild to moderate PEW, and 8% had severe PEW. Other similar studies in NDD-CKD patients, by Campbell et al ($n = 56$) (28) and Sanches et al ($n = 122$) (29), estimated the prevalence of PEW to be $\sim 18\%$.

The mechanisms underlying the development of PEW in NDD CKD are complex (**Figure 3**). An important factor in the genesis of PEW is latent or manifest anorexia, which can develop as a result of increases in anorexigenic hormones (30) and activation of proinflammatory cytokines and lead to insufficient protein and energy intakes. Further aggravating PEW are the catabolic effects of various metabolic abnormalities (such as inflammation, increased concentrations and/or activities of catabolic hormones,

TABLE 2

Methods of evaluation for diagnosis of protein-energy wasting in patients with non-dialysis-dependent chronic kidney disease¹

1. Nutritional intake
Direct: dietary recalls and diaries, food-frequency questionnaires
Indirect: based on urea nitrogen appearance (eg, 24-h urinary urea collection)
2. Body mass and composition
Weight-based measures: BMI, weight-for-height, edema-free fat-free weight
Skin and muscle anthropometric measurements: skinfold thickness, extremity muscle mass
Total-body elements: total-body potassium, total-body nitrogen
Imaging, energy-beam, or electrical current methods: DXA, BIA, NIR, CT, MRI
Body-density methods: underwater weighing, air-displacement methods
3. Indexes or scales
Subjective global assessment: conventional or modified for renal failure
Malnutrition-Inflammation Score
4. Laboratory measurements
Visceral proteins (negative acute phase reactants also affected by nutrient intake): serum albumin, prealbumin, transferrin
Lipids: cholesterol, triglycerides, other lipids and lipoproteins
Indicators of muscle mass and/or meat or protein intake: serum creatinine, urea
Growth factors: IGF-I, leptin
Peripheral blood cell count: lymphocyte count
Proinflammatory cytokines: serum CRP, TNF- α , IL-6

¹ BIA, bioelectrical impedance analysis; CRP, C-reactive protein; CT, computer tomography; DXA, dual-energy X-ray photon absorptiometry; IGF-I, insulin-like growth factor-I; NIR, near-infrared interactance.

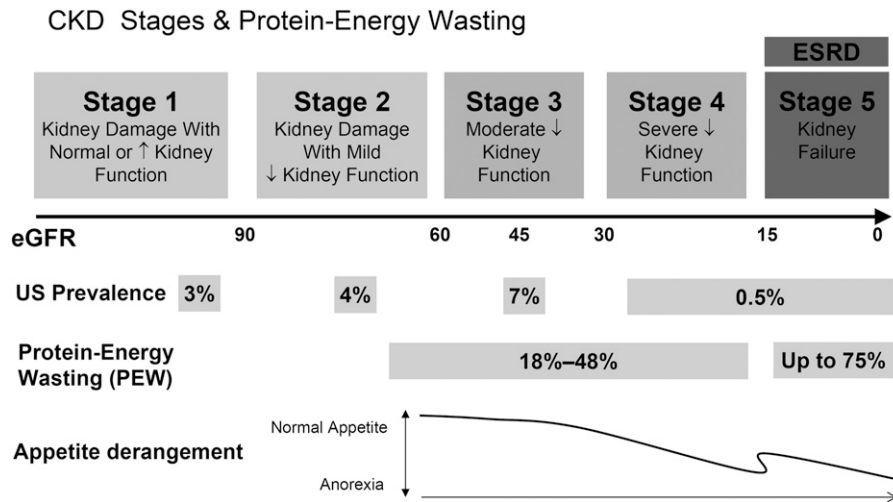


FIGURE 1. Schematic representation of the development of protein-energy wasting with advancing stages of chronic kidney disease. The appetite derangement component was reproduced with permission from reference 130. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ↑, increased; ↓, decreased.

decreased concentrations and/or resistance to anabolic hormones, metabolic acidemia, vitamin D deficiency, and abnormal glucose and insulin homeostasis) (Figure 3) (30).

In summary, PEW is common in CKD patients, and develops as a result of a complex series of interrelated mechanisms, which may or may not include an inadequate ingested protein intake. This results in changes in both the quality and the quantity of nutrient intake and the development of other catabolic or antianabolic events. The clinical effects of these changes in CKD have not been fully elucidated, but studies in chronic dialysis patients suggest that they are linked to adverse consequences. Thus, dietary therapy in NDD-CKD patients should be designed with an appreciation of the potential long-term clinical effects of such treatment.

MODIFICATION OF PROTEIN INTAKE: EFFECT ON CLINICAL OUTCOMES

Protein supplementation

One of the proximate causes of PEW in CKD and ESRD is a decrease in protein and energy intakes (Figure 3) (31, 32), which may be associated with increased mortality, at least in ESRD patients receiving renal replacement therapy (33, 34). As mentioned above, current nutritional guidelines (9) recommend the intake of $\sim 0.60 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ for non-nephrotic patients with stage 3–5 NDD-CKD. The goals of this recommended intake are to prevent the development of PEW, to prevent or mitigate uremic toxicity, and possibly to retard the rate of CKD progression. Adherence to the prescribed daily protein intake (DPI) in clinically stable NDD-CKD patients can be estimated by using 24-h urea nitrogen (UN), where 1 g UN represents 6.25 g protein and a non-UN excretion of $30 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ (35) along with urinary protein losses of $>5 \text{ g/d}$.

$$\text{eDPI (g/d)} = 6.25 \times \text{UN} + 0.03 \times \text{body weight (kg)} + \text{proteinuria (g/d)} \quad (1)$$

Another equation developed to determine the estimated DPI (eDPI), which is based on large numbers of nitrogen balance studies, is as follows (36):

$$\text{eDPI (g/d)} = 7.525 \times [\text{UN (g nitrogen/d)}] + 10.9 \text{ g protein/d} \quad (2)$$

These equations assume that the patient is not hypercatabolic and that the patient has essentially equilibrated on his current protein intake. In Equation 2, the eDPI can be increased by $\sim 1 \text{ g/d}$ for each gram of urinary protein loss above 5 g/d. If the intake is $<0.6 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, or if there are other signs of PEW, dietary counseling should be provided to ensure that a proper amount and quality of protein and adequate energy and other nutrients are ingested. In cases when counseling is unsuccessful, nutritional supplementation with proteins of high biological value or their equivalents in the form of EAAs and keto acids can be considered. This may provide additional benefits with regard to better palatability and easier control over the biologic value of ingested food proteins and the amount of energy intake.

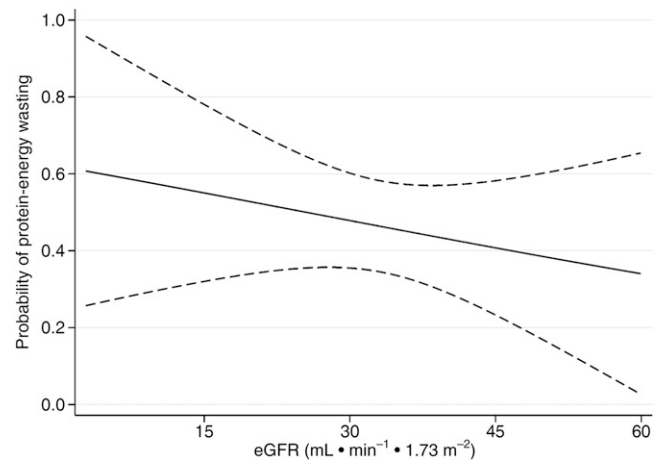


FIGURE 2. Probability (95% CI) of the presence of protein-energy wasting in patients with different eGFRs. Protein-energy wasting was defined as the presence of ≥ 2 of the following biochemical markers: serum albumin $<3.7 \text{ g/dL}$, percentage of lymphocytes in white blood cells $<22\%$, and white blood cell count $>7500/\text{mm}^3$. Values are based on data from Kovcsdy et al (3), assessed in 1220 patients with non-dialysis-dependent chronic kidney disease, obtained by using restricted splines. eGFR, estimated glomerular filtration rate.

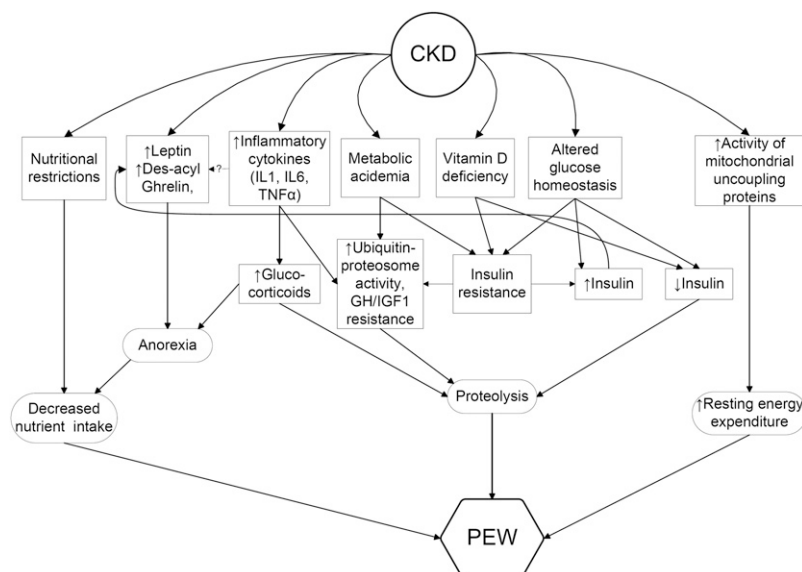


FIGURE 3. Mechanisms of action leading to the development of PEW in CKD. CKD, chronic kidney disease; GH, growth hormone; IGF-I, insulin-like growth factor-1; PEW, protein-energy wasting; ↑, increased; ↓, decreased.

As an example, when a supplement providing high biological value protein is ingested, the biological value of the protein in the normal foods ingested becomes less important; therefore, the patient will have a greater variety of foods from which to select.

Protein supplementation by a variety of different methods has been shown to be effective for improving markers of PEW (for a review, *see* reference 37). Importantly, data suggest that optimal dietary protein intake can improve PEW irrespective of its etiology in patients with a variety of chronic disease states, such as in cancer cachexia, even though inadequate nutritional intake may play a lesser causal role in this condition, and the malignant disease itself and the associated high concentrations of proinflammatory cytokines may be more prominent causal factors for the cachexia (38). However, a positive effect on biochemical or other measures of PEW may not in itself translate to better clinical outcomes. Prospective, nonrandomized studies in MHD patients have described greater survival in patients receiving oral (39) and parenteral nutritional supplements (40). MHD patients who show a favorable nutritional response to dietary or parenteral nutrition interventions are also reported to show improved survival (41). It is unclear whether these results can be extrapolated to NDD-CKD populations, and, to the best of our knowledge, no randomized controlled clinical trials have been conducted in any population of chronically ill patients to test the hypothesis that protein supplementation can be beneficial beyond simply improving PEW.

It is broadly agreed that for NDD-CKD patients whose spontaneous dietary protein intake is less than the recommended $0.60\text{--}0.80\text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, it is beneficial to implement dietary interventions that will increase protein intake to this level (*see* below for the types of interventions that may supplement protein intake). Furthermore, even a DPI of $0.6\text{--}0.8\text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ could be inadequate in patients with hypercatabolic states. It is much less clear that increasing protein intake above these goals is beneficial in clinically stable nonhypercatabolic patients. Increasing protein intake in patients with PEW as a means to promote anabolism and faster rebuilding of body protein and muscle stores may appear intuitively appealing, even in those

patients who are not acutely catabolic (eg, after an acute illness, in the recovery phase). However, the added anabolic value of supplemental proteins or protein equivalents diminishes with increasing baseline intakes (42–44); hence, it is unclear to what extent supplementation to achieve intakes $>0.6\text{--}0.8\text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ would be useful. In acutely catabolic patients, higher protein intakes appear reasonable; however, it is unclear what the actual amount of the DPI should be, even in these patients. It has been suggested that a DPI as high as $1.5\text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ may be beneficial in elderly patients (14) and that the recommended DPI in CKD patients with superimposed acute kidney injury should be $\sim 1.5\text{--}2.5\text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, depending on the severity of acute kidney injury, the presence of underlying catabolic diseases, and the presence or absence of renal replacement therapy (45). In comparison, the recommended DPI in maintenance dialysis patients is $\sim 1.2\text{--}1.3\text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ (9). Although none of these analogous conditions provide definite information on the optimal DPI for NDD-CKD patients with impending or actual PEW, they may provide some guidance to this end, especially when the clinical circumstances are well defined. Finally, it is also unclear what the best source of supplemental protein should be for patients with NDD CKD and PEW; these possibilities include proteins of high biological value, EAAs, or keto-analogues; however, there is a paucity of head-to-head comparisons of their use for the treatment of PEW. It is possible that protein sources rich in branched-chain amino acids (especially leucine and isoleucine) or their keto-analogues could be more beneficial by virtue of their anabolic or anti-catabolic effects (46–51).

Complicating the uncertainty surrounding the proper amounts and types and the clinical effects of protein supplements is the concern about potential negative effects of high protein intakes (Table 3). The glomerular filtration rate is affected by protein intake through effects on afferent arteriole dilatation and the functioning of the glomerular basement membrane; hence, high protein intake can result in glomerular hyperfiltration and worsening proteinuria—issues that are especially relevant for NDD-CKD patients (52–54). Furthermore, the accumulation in blood

and tissues of various protein breakdown products as a result of decreasing kidney function can result in uremic toxicity, the uremic syndrome (at least in patients with stage 4–5 CKD), and such untoward metabolic effects as oxidative stress, altered endothelial function, reduced nitric oxide production, and insulin resistance (55).

Examination of these open questions in properly designed and conducted clinical trials is essential before one can arrive at definitive opinions for or against the supplementation of protein (or its equivalents) above the $0.6\text{--}0.8\text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ level in patients with NDD-CKD and PEW. Until then we suggest individualizing these decisions based on a patient's catabolic status and other clinical and financial considerations.

Restriction of protein intake: beneficial or risky?

Stage 3–5 CKD patients often spontaneously ingest excessive and unhealthy quantities of various nutrients, including sodium, phosphorus, and sometimes potassium. These undesirable intakes can be eliminated by carefully controlling the composition of the diet. A reduced protein intake can result in the alleviation of uremic symptoms; possibly better control of hyperparathyroidism, hyperphosphatemia, and hyperkalemia; reduction of proteinuria; and possibly slower progression of kidney failure (56). On the basis of these considerations, therapeutic protein restriction has been used to treat some or all of these complications in a controlled manner. Most studies that have examined the effects of protein-restricted diets have examined patients with stage 3–5 NDD CKD because they appear to be most likely to benefit from them. The Modification of Diet in Renal Disease (MDRD) Study was the largest randomized prospective study that examined the effects of protein and phosphorus restriction on the progression of CKD. The main findings of the MDRD Study were negative (12), but subsequent reanalyses of its results suggest that patients who were prescribed a diet with $0.58\text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ and lower phosphorus intakes, as compared with the diet providing $1.3\text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, experienced significantly less loss of kidney function after the first 4 mo of implementation of the intervention (57). Furthermore, when other risk factors of progressive CKD were accounted for, a lower protein intake was associated with a 29% lower risk of CKD progression and no added benefit from keto acid supplements (58). Subsequent meta-analyses of smaller randomized controlled trials also indicated benefits toward renal protection from LPDs (59, 60).

Renal benefits aside, a main concern regarding restricted dietary protein intakes is the development of PEW with potential adverse consequences, such as an increased risk of death (Table 3). The MDRD Study detected small, but significant, decreases in protein and energy intakes and declines in some of the nutritional indexes over time, but no adverse effects on clinical outcomes (12, 61). Much evidence indicates that a carefully controlled LPD or SVLPD combined with adequate energy intake will likely prevent rather than promote PEW (21, 62–64). Correct implementation of protein-restricted diets (which includes careful attention to proper energy intake and to other nutrients, such as phosphorus, potassium, alkali, vitamins, and micronutrients) does not induce PEW. Nevertheless, PEW can develop if not all aspects of the protein-restricted diet are properly implemented or followed. Insufficient energy intake (especially with LPD, of

which 50% of the protein is of high biological value, which makes the provision of adequate energy sources difficult) is a common reason why LPDs may lead to the development of PEW. Consumption of primarily proteins of low biological value with the LPD (because of greater convenience or better palatability of foods containing low-quality protein) theoretically should also increase the risk of negative protein balance, although this has not been tested in CKD patients. One strategy to deal with this problem is to provide part of the LPD in the form of a prescribed supplement, which allows for easier implementation of proper energy intake (21) and ensures that sufficient amounts of EAAs or amino acid precursors (ie, in the form of EAAs or keto acids or hydroxyacid analogues of EAA) are ingested. Last but not least, it is important to stress that even a properly implemented LPD or SVLPD could aggravate PEW in patients who are catabolic, who have progressive CKD, or additional comorbidities such as chronic infections (eg, diabetic foot ulcers). In these groups of patients, a higher DPI might be necessary, and the utilization of various dietary interventions toward achieving these higher goals may be needed (*see* above).

Supplemented protein restriction

A strategy used to enhance the potential beneficial effects of a protein-restricted diet is to reduce protein intake to $\sim 0.3\text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ of mixed biological protein [very-low-protein diet (VLPD)] and provide a daily supplement of $\sim 0.28\text{ g/kg}$ of a combination of some EAAs and keto acids or hydroxyacid analogues of the other EAAs. These supplements of the VLPD are necessary to provide adequate total protein/amino acids and EAAs to meet a patient's nutritional needs; they may also possibly provide an anabolic stimulus (46–51) and are free of phosphorus compounds, which may have additional advantages given the association of hyperphosphatemia with CKD progression (65). Furthermore, the keto acid and hydroxyacid analogues provide EAA precursors without the nitrogen load from EAAs. Hence, these SVLPDs appear to generate less toxic metabolic products than similar amounts of protein from LPDs (66). These VLPDs, and LPDs in general, also appear to reduce proteinuria (56, 67).

As indicated above, because of the supplemental EAAs and keto acid/hydroxyacid analogues of EAAs, the food protein component of the SVLPDs does not need to be of high-quality protein. Therefore, it is easier and more palatable for many patients to ingest sufficient calories than with an LPD providing $0.60\text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, which requires $\sim 50\%$ of the protein to be of high biological value and which therefore may substantially limit the patients' food choices. In addition, it is easier to add high-calorie condiments to foods containing more low-quality protein (eg, butter, jelly, cream cheese, honey, frosting added to breads, pancakes, biscuits, and cakes). The MDRD Study (12) and a secondary analysis of this study (58) did not suggest a clear benefit from SVLPD as compared with the $0.60\text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, although there was a trend toward slower progression of kidney failure with the SVLPD. However, the SVLPD used in the MDRD Study may not have been ideal because the keto acid/EAA supplement contained a rather large amount of tryptophan which could have generated more nephrotoxic metabolites, particularly indoxyl sulfate (68, 69). Hence,

TABLE 3
Advantages, disadvantages, and questions surrounding the various interventions involving manipulation of protein intake in patients with non-dialysis-dependent chronic kidney disease¹

Intervention	Examples	Target population	Advantages	Disadvantages	Comments
Protein supplementation (CKD-specific; low K, P, and Na; low fluid; high biological value)	Oral or parenteral alimentation	Patients with or at risk of PEW	Improvement in PEW Control over amount of intake Relatively easy to implement	Cost Increased catabolic load with untoward consequences	Long-term risk/benefit, effect on clinical outcomes not defined
Protein supplementation + binders	Oral alimentation plus -Protein and/or -Phosphorus and/or -Potassium-binding resins	Patients with or at risk of PEW Patients with or at risk of progressive CKD Patients with or at risk of metabolic complications of high protein intake	Concomitantly addresses PEW and deleterious aspects of protein intake/catabolism Relatively easy to implement	Cost of some medications may be high Medication-related adverse effects Added pill burden Limited scope of each individual binder may leave some deleterious effects of protein intake and catabolism unaddressed	Long-term risk/benefit, effect on clinical outcomes not defined
Protein restriction	LPD	Patients with or at risk of progressive CKD Patients with or at risk of complications of high protein intake	Addresses all the deleterious effects of protein intake/catabolism	Risk of inducing or worsening PEW and consequent poor outcomes Cost of properly composed diet Requires considerable motivation and discipline on patient's part	Long-term risk/benefit, effect on clinical outcomes not defined
Protein restriction + supplements (CKD specific, <i>see above</i>)	LPD or VLPD with keto-analogue and/or amino acid supplementation	Patients with or at risk of progressive CKD Patients with, or at risk of metabolic complications of high protein intake Patients with or at risk of PEW	Concomitantly addresses PEW and deleterious aspects of protein catabolism	Resource-intensive (need for trained dietitian) Cost of properly composed diet and supplements Requires considerable motivation and discipline on patients' part Resource-intensive (need for trained dietitian)	Long-term risk/benefit, effect on clinical outcomes remains unclear

¹ CKD, chronic kidney disease; LPD, low-protein diet; PEW, protein-energy wasting; VLPD, very-low-protein diet.

it is possible that alternative keto acid/EAA supplements may be more effective at slowing the progression of CKD.

Recent clinical trials of SVLPDs (**Table 4**) have shown stable or improved serum albumin concentrations (70–75) and only subtle decreases in lean body mass and fat mass, although one study indicated a significant decrease in bone mass over 2 y (76). These recent studies of SVLPDs appear to confirm a decrease in proteinuria (56, 67, 71, 72) and, in some studies, a less rapid progression of CKD (56, 72–75, 77). In one particularly intriguing multicenter prospective randomized trial, 112 elderly nondiabetic patients with advanced NDD CKD (glomerular filtration rate: 5–7 mL/min) were randomly assigned to receive a diet providing $35 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ and $0.3 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ supplemented with keto acids/EAAs, amino acids, and vitamins compared with starting regular dialysis therapy with higher protein intakes. Over a median follow-up of 26.5 mo, all-cause mortality rates were similar in the 2 groups, and hospitalization rates were higher in patients randomly assigned to dialysis therapy, which indicates that initiation of dialysis can be safely delayed in patients with advanced CKD by using a SVLPD (78). Similar effects were reported in a more recent single center trial that examined 207 nondiabetic patients with CKD stage 4, in which, over a defined period of time, fewer patients randomly assigned to an SVLPD initiated dialysis compared with patients randomly assigned to LPD (L Garneata, personal communication, 2012).

In observational studies that examined the long-term safety of SVLPDs in comparison with historical controls, patients previously exposed to such an intervention appeared to have low mortality rates after initiating hemodialysis or after undergoing renal transplantation (71, 79). No randomized controlled trials have examined the effect of SVLPDs on mortality rates; hence, the results of these observational studies can only be considered hypothesis generating and not proof that SVLPDs are neutral or beneficial in terms of mortality. The one exception may be a follow-up study of the MDRD Study that examined the incidence of ESRD and mortality after a long-term 10-y follow-up of patients enrolled in study B (low- compared with very-low-supplemented protein intakes). This study indicated no significant difference in the incidence of ESRD, but there was a significantly higher mortality rate (adjusted HR: 1.92; 95% CI: 1.15, 3.20) in patients randomly assigned to a supplemented very-low protein intake ($0.3 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ supplemented with $0.28 \text{ g keto acids/EAAs} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) (80). However, during the last ~ 7.8 y in this 10-y follow-up, the patients almost certainly had no access to the keto acid/EAA supplement, and there is also no information about their dietary intake, blood pressure control, or other aspects of their clinical condition during this period of time.

In summary, studies of SVLPD suggest a beneficial effect on kidney function and, in those with more advanced CKD, on clinical signs and symptoms, without the concomitant development of PEW. However, it is less clear whether an SVLPD can be used to treat established PEW. Hypothetically, this strategy could be applied to provide patients who have PEW and inadequate protein energy intake with sufficient high-quality protein equivalents to achieve the desired ($0.6\text{--}0.8 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ or higher; *see above*) intake, but the efficacy and safety of such a strategy requires examination in future clinical trials. Furthermore, some (but not all) opinion leaders suggest that a

mitigation of PEW risk may be possible by not limiting the DPI to $0.6 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, when applying dietary protein supplementation with EAAs or their keto-analogues, for the following reasons:

1) The suggested DPI of $0.6 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ provides only the minimum protein requirements, hence the suggestion by the Institute of Medicine to increase this amount by 33% to $0.8 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ for the healthy general population. (Currently the average DPI in the United States is $0.8\text{--}1.1 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$.)

2) Many patients with NDD CKD may have concurrent catabolic states, such as diabetic foot ulcers or other concomitant infections, that increase their risk of developing PEW with a DPI of $0.6 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ —the adequacy of which is predicated in a stable noncatabolic state.

3) Many CKD patients may have significant proteinuria ($\geq 5 \text{ g/d}$), which leads to significant protein losses.

4) Some CKD patients may experience bleeding (including extended menstruation in women) given worsening bleeding diathesis and platelet dysfunction in uremia, which leads to more protein loss.

5) Nausea, vomiting, and diarrhea may lead to additional losses of nutrients and protein in CKD patients.

Given the above considerations, there is an emerging paradigm in contemporary nephrology suggesting that the addition of protein with high biological value, EAAs, and/or their keto-analogues to a DPI of $0.6 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ may be beneficial, at least during those clinical conditions associated with increased nutrient needs. We have mixed opinions about this issue and believe that more evidence is needed before rendering judgment about this practice.

Other strategies to avoid deleterious effects of high protein intake

As mentioned above, CKD patients with established PEW or with acute or chronic catabolic illnesses—such as infection, vasculitis, or vascular insufficiency—may require a protein intake well above the goals recommended for stable non-nephrotic and noncatabolic patients. The current therapeutic approach for patients with acute catabolic conditions, such as those with acute kidney injury (81–84), consists mainly of enteral or parenteral nutrition, which are designed to increase protein and energy intakes. These techniques, on the other hand, have been less well studied in patients with PEW and NDD CKD, in whom the optimal amount of daily protein intake under these circumstances remains unclear. Strategies that use increased protein intakes (irrespective of the actual amount) raise concerns about the effects of high protein and energy intakes on uremic toxicity, other undesirable metabolic changes (eg, in the diabetic CKD patient), and potentially unfavorable changes in body composition and progression of kidney failure (Table 3).

We discussed above the possibility of providing additional protein-equivalent intakes in the form of high biological value protein supplements or specially formulated EAA or keto acid/EAA supplements and the pros and cons of such a strategy. An additional approach in CKD patients is to selectively prevent the absorption of toxic compounds derived from protein metabolism that contribute to progressive kidney disease and other undesirable effects. This therapeutic approach is still in its infancy,

TABLE 4 Recent studies that examined the effects of an LPD or a VLPD supplemented with amino acids and/or keto acids on various endpoints since the MDRD Study¹

Study	Patients	Intervention	Outcome	Follow-up	Results	Comment
Aparicio et al, 2000 (71)	256 with advanced CKD (eGFR: 13.1 ± 4.1)	0.3 g protein, 35 kcal, and 5–7 mg inorganic phosphorus per kg per day supplemented with essential AAs, keto-analogues, calcium carbonate, iron, and multivitamins	Nutritional markers at end of SVLPD; mortality after initiation of dialysis or after transplantation, after discontinuation of SVLPD	Median: 22.5 mo of SVLPD Median: 54 mo of dialysis	No significant change in serum albumin and BMI; significant decrease in proteinuria. Mortality was not associated with any of the nutritional variables at the end of the SVLPD	Mortality was assessed in observational study that followed intervention with SLVPD. Interventional study was an uncontrolled, single-arm study that assessed the effects of SVLPD on nutritional variables. Only 14 deaths.
Brunori et al, 2007 (78)	112 Italian uremic patients without diabetes >70 y of age, GFR 5–7 mL/min	SVLPD (0.3 g protein, 35 kcal, supplemented with keto-analogues, AAs, and vitamins) compared with dialysis	Mortality, hospitalization, and metabolic markers	Median: 26.5 mo	Mortality rate was not different between the 2 groups; hospitalization rate was higher in the dialysis group	Randomized, controlled, open-label multicenter study
Chang et al, 2009 (77)	120 patients with CKD stages 3 and 4	LPD for 6 mo followed by LPD + keto-analogues for 6 mo	Slopes of eGFR	12 mo	Slopes improved during the LPD + keto-analogue period compared with the LPD-alone period	Observational study; goals of LPD were not achieved
Chauveau et al, 1999 (70)	10 patients with advanced CKD (GFR: 13.2 ± 4.8)	SVLPD (0.3 g protein/kg per day supplemented with AAs and keto-analogues)	Biochemical and anthropometric (DXA) nutritional markers	12 mo	Biochemical markers remained stable; anthropometric markers worsened (decrease in lean body mass and increased fat mass)	Observational study; small number of patients
Chauveau et al, 2003 (76)	13 patients with advanced CKD (GFR 15 ± 5)	SVLPD (0.3 g protein/kg per day of protein supplemented with AAs and keto-analogues)	Measured GFR, nutritional status, and body composition (DXA)	24 mo	Stable GFR, albumin, prealbumin, fat mass; lean body mass initially decreased then increased; bone mass decreased significantly	Observational study; small number of patients
Chauveau et al, 2007 (56)	220 patients with advanced CKD	SVLPD	Change in proteinuria, measured GFR	24 mo	Significant decrease in proteinuria after SVLPD; slope of GFR improved in patients with ≥50% decrease in proteinuria	Observational study
Chauveau et al, 2009 (79)	203 patients with CKD	SVLPD for a mean duration of 33.1 mo	All-cause mortality	10 y of dialysis or after transplantation after SVLPD was discontinued	Mortality rates similar to those of historical controls; mortality was not associated with the duration of SVLPD	Observational study
Di Iorio et al, 2009 (67)	32 patients	VLPD compared with LPD	Change in proteinuria and AGE	6 mo in each treatment arm	Significant reduction in proteinuria and in serum AGE level after VLPD	Randomized, controlled crossover study

(Continued)

TABLE 4 (Continued)

Study	Patients	Intervention	Outcome	Follow-up	Results	Comment
Jiang et al, 2009 (128)	60 patients receiving peritoneal dialysis	LPD compared with SLPD (LPD + keto acids) compared with HPD	Residual renal function and nutritional markers	12 mo	Nutritional status was stable in all 3 groups; residual renal function stable in SLPD group and decreased in the LPD and the HPD groups	Patients had no evidence of protein-energy wasting at the start of the study
Mircescu et al, 2007 (129)	53 nondiabetic patients with eGFR <30	SVLPD (0.3 g vegetable proteins/kg per day supplemented with keto-analogues) compared with LPD	Biochemical markers, eGFR, and incidence of renal replacement therapy	48 wk	Decreased retention of uremic waste products and stable nutritional variables with SVLPD; decreased progression of CKD with SVLPD (lower incidence of renal replacement therapy and more favorable slope of eGFR)	Open-label, single-center study. Patients had no evidence of protein-energy wasting at baseline and were selected based on expectation to comply with instructions.
Montes-Delgado et al, 1998 (75)	33 patients with CKD	LPD compared with LPD + a low-protein and hypercaloric supplement	Nutritional status and renal function	6 mo	Better nutritional status, better treatment compliance, and less progression of CKD in the supplemented group	Small study; only 22 patients completed the 6 mo of follow-up
Prakash et al, 2004 (74)	34 patients with advanced CKD	LPD (0.6 g protein/kg per day) + placebo compared with SVLPD (0.3 g protein/kg per day + keto-analogues)	Changes in GFR and renal and nutritional variables	9 mo	Stable BMI; nutritional variables, and GFR in the SVLPD group and worsening nutritional variables and GFR in the LPD group	Prospective, randomized, double-blind, placebo-controlled single-center trial
Teplan et al, 2001 (72)	105 patients with creatinine clearance of 22–36 mL/min	LPD + rhuEPO + keto acids compared with LPD + rhuEPO compared with LPD	Progression of CKD and nutritional markers	3 y	The LPD + rhuEPO + keto acids group showed slower progression of CKD and favorable metabolic and nutritional variables	Role of rhuEPO unclear
Zakar, 2001 (73)	181 predialysis CKD and 42 dialysis patients	Predialysis: 0.5–0.6 g protein/kg per day + keto acid; dialysis: 1.2 g protein/kg per day + keto acid	Metabolic variables and progression of CKD (1/serum creatinine slopes)	18 mo	Favorable progression of CKD in predialysis patients; improved nutritional variables in both groups	Uncontrolled design

¹ AA, amino acid; AGE, advanced glycation end products; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HPD, high-protein diet; LPD, low-protein diet; MDRD, Modification of Diet in Renal Disease; rhuEPO, recombinant human erythropoietin; SLPD, supplemented low-protein diet; SVLPD, supplemented very-low-protein diet; VLPD, very-low-protein diet.

although some progress in this field has been made. Several such potentially toxic components or metabolic products of high-protein diets have been identified. These include phosphorus and potassium (as briefly mentioned earlier), but compounds derived from the breakdown of protein and amino acids (many of which can be grouped under the term “uremic toxins”) have also been found to exert direct toxic effects. Uremic toxins linked directly or indirectly to the intestinal absorption of digested protein include indoles, phenols, cresol, urea, guanidines, and middle molecules, some of which have been linked to such deleterious processes as increased oxidative stress (85), inflammation (86, 87), vascular (88–90) and renal (68, 69) toxicity, and increased mortality (90–94). Another uremic toxin associated with high protein intake is the hydrogen ion (engendering metabolic acidemia), which, in addition to accelerating the progression of kidney failure, has been implicated in bone resorption and osteopenia, muscle protein catabolism, multiple endocrine disorders, increased serum concentrations of proinflammatory cytokines, inflammation, increased β_2 -microglobulin production, and hypertriglyceridemia (95–108). Administration of alkali has been shown to improve PEW (100, 109–112) and bone disease and to slow the progression of chronic kidney failure (113–115). Its examination in larger clinical trials is awaited.

Interventions aimed at selectively lowering the concentrations of uremic toxins include the administration of binder medications, such as phosphate binders and potassium binding resins (only occasionally needed). Another such compound, AST-120 (Kremezin; Kureha), is an activated charcoal binder that lowers

serum indoxyl sulfate concentrations in animal models (116–119) and humans (120, 121). In animal models of renal insufficiency, AST-120 has ameliorated renal interstitial fibrosis (122), glomerular sclerosis and proteinuria (123), and endothelial dysfunction (117) and has increased urinary nitric oxide concentrations. AST-120 was shown to be effective in slowing the progression of renal failure in CKD patients in small clinical trials in Japan (124–126). However, the efficacy and safety of AST-120 in the treatment of progressive CKD was examined in 2 larger randomized clinical trials in the United States (clinicaltrials.gov: NCT00500682, NCT00501046, and Evaluating Prevention of Progression in CKD-1 and -2) without finding a benefit in the primary endpoints of the studies (127). It remains to be determined whether such a binder-based strategy, which has been primarily studied as a renoprotective therapy, can be used to allow NDD-CKD patients to safely ingest higher amounts of dietary proteins to treat PEW.

PRACTICAL ASPECTS OF DIETARY TREATMENT OF PEW IN NDD-CKD

The implementation of the discussed various dietary treatment strategies for PEW in NDD-CKD also poses many practical challenges. Virtually all dietary interventions require significant efforts from the health care team, with the diagnostic evaluations, the dietary counseling, and the monitoring of treatment effects all being time consuming and labor intensive, and requiring

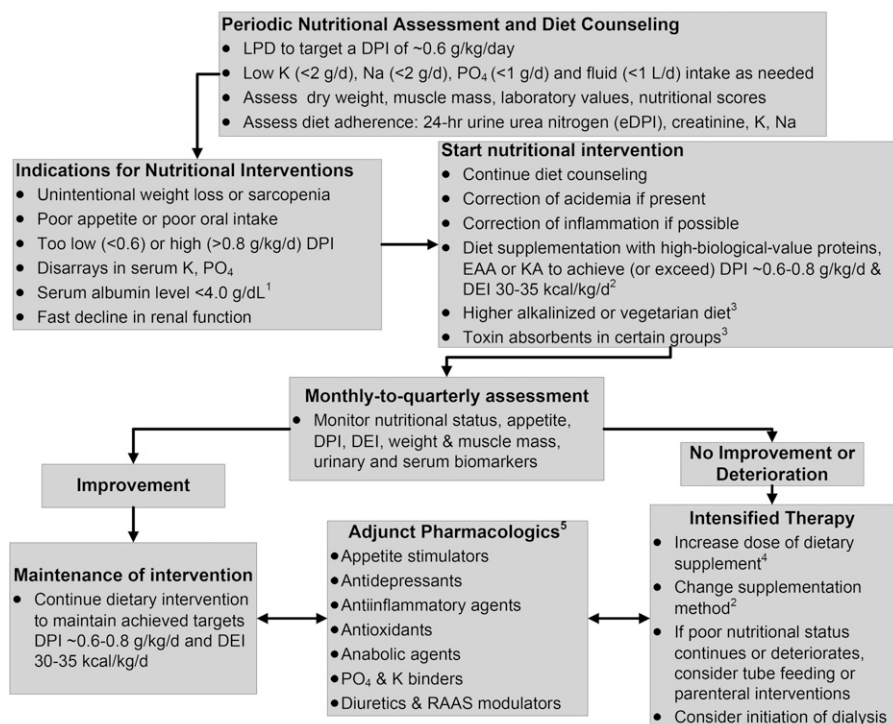


FIGURE 4. Suggested algorithm for clinical assessment and interventions aimed at assessing and treating PEW by manipulating protein intake in patients with chronic kidney disease. ¹Measured with bromocresol green method. ²Head-to-head comparisons of the different supplementation methods for the treatment of PEW are not available. Individual patient characteristics and tolerance of, adherence to, and affordability of specific supplementation methods should be considered. ³Efficacy and safety because treatment of PEW is not proven. ⁴Ideal amount of daily protein intake in PEW is unclear. ⁵Directed by specific clinical scenario. The efficacy and safety of PEW treatment in patients with non-dialysis-dependent chronic kidney disease is generally unproven. DEI, daily energy intake; DPI, dietary protein intake; EAA, essential amino acid; eDPI, estimated daily protein intake; KA, keto acid; LPD, low-protein diet; PEW, protein-energy wasting; RAAS, renin angiotensin aldosterone system.

expertise in an area that is often outside of the mainstream focus of most practicing nephrologists. The implementation of dietary interventions can be challenging to the patients too. Adherence to some of the prescribed diets can sometimes be difficult because of palatability, the effort it takes to ensure ongoing proper dietary preparation and intake of high biological value proteins and adequate amounts of calories, and the financial burden that strict dietary prescriptions may pose to some. Many of the foregoing clinical studies of dietary interventions were conducted in a rather controlled environment under supervision by highly trained personnel, where the diets or the various supplements may have been provided at no cost to the patients. The circumstances under which similar dietary interventions would have to be implemented in everyday clinical practice are often very different; hence, the development of strategies to increase adherence will remain a challenge to both health care workers and to the patients themselves, even if the costs for diets and for supplements are covered by funding agencies. Substantial resource allocation thus will be necessary for the successful implementation of the various dietary strategies, including the training and the deployment of proper numbers of renal dietitians. On the other hand, if these diets have a beneficial effect on outcomes, including the slowing of the progression of CKD and the treatment of PEW (with potentially beneficial downstream clinical effects), it might be argued that they actually reduce the cost of medical care and improve the quality of life and possibly the health and survival of CKD patients.

As mentioned above, the application of the various dietary interventions for the treatment of PEW has not been properly tested in randomized clinical trials, and advocacy for their use was based on extrapolations from studies that examined them for other clinical indications. However, because it is currently unlikely that there will be a head-to-head comparison of the various interventions for PEW in the foreseeable future (especially ones that examine hard clinical endpoints), we need to use the existing data and infer practical suggestions to improve patient care. A suggested therapeutic algorithm guiding the clinical implementation of protein intake strategies, based on currently available evidence and the authors' opinions, is depicted in **Figure 4**. Short of comparative effectiveness trials, decisions about which of the listed multiple potential interventions to implement should be determined by the amount of supportive data for one compared with the other (mainly regarding efficacy and safety in clinical trials), the feasibility and cost-effectiveness of each intervention (including cost coverage, ease of implementation, physician and patient preferences, and patient adherence), and the commercial availability of properly formulated agents for patients with NDD CKD. At this time, the effectiveness of each of the interventions can be assessed by using short-term surrogate endpoints such as biochemical markers of PEW, but more research is needed before any of them can be applied with confidence that their use will improve patient outcomes.

CONCLUSIONS

PEW is a powerful predictor of outcomes over the entire range of CKD and often can be alleviated by ensuring adequate protein and energy intake (37). Conversely, uncontrolled high protein intakes can have deleterious consequences, including biochemical imbalances such as hyperkalemia and hyperphosphatemia, and worsening oxidative stress, altered endothelial function,

nitric oxide production, insulin resistance, glomerular hyperfiltration, and uremic symptoms. Dietary interventions for PEW must both ensure adequate intakes of protein and energy and avoid deleterious effects of high protein intakes. These seemingly contradictory goals can only be achieved with careful attention to both the quantity and quality of ingested proteins and to the intake of other nutrients. Potential strategies to achieve these goals include supplementing the usual (or low) amount of protein in the diet with essential nutrients or supplements that are specifically designed for CKD patients (75) and/or prevention of the deleterious side effects of high dietary protein intakes (eg, binder medications and alkali). The effectiveness and safety of these strategies at improving patient outcomes will need to be confirmed in future studies.

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