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Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism

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Protein energy wasting (PEW) is common in patients with chronic kidney disease (CKD) and is associated with adverse clinical outcomes, especially in individuals receiving maintenance dialysis therapy. A multitude of factors can affect the nutritional and metabolic status of CKD patients requiring a combination of therapeutic maneuvers to prevent or reverse protein and energy depletion. These include optimizing dietary nutrient intake, appropriate treatment of metabolic disturbances such as metabolic acidosis, systemic inflammation, and hormonal deficiencies, and prescribing optimized dialytic regimens. In patients where oral dietary intake from regular meals cannot maintain adequate nutritional status, nutritional supplementation, administered orally, enterally, or parenterally, is shown to be effective in replenishing protein and energy stores. In clinical practice, the advantages of oral nutritional supplements include proven efficacy, safety, and compliance. Anabolic strategies such as anabolic steroids, growth hormone, and exercise, in combination with nutritional supplementation or alone, have been shown to improve protein stores and represent potential additional approaches for the treatment of PEW. Appetite stimulants, anti-inflammatory interventions, and newer anabolic agents are emerging as novel therapies. While numerous epidemiological data suggest that an improvement in biomarkers of nutritional status is associated with improved survival, there are no large randomized clinical trials that have tested the effectiveness of nutritional interventions on mortality and morbidity.

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Among the many risk factors that affect outcomes of chronic kidney disease (CKD) patients, especially ones with end-stage renal disease (ESRD) and on maintenance dialysis, a state of metabolic and nutritional derangements, more aptly called *protein-energy wasting (PEW) of chronic kidney disease*, plays a major role.[1–3] Multiple studies now indicate that PEW is closely associated with major adverse clinical outcomes and results in increased rates of hospitalization and death in these patients.[4,5]

A significant number of factors affect nutritional and metabolic status in CKD, leading to multiple adverse consequences (Figure 1).[6] Accordingly, prevention and treatment of PEW of CKD should involve an integrated approach to limit protein and energy depletion, in addition to therapies that will avoid further losses and replenish already wasted stores.[7] This article aims to provide a broad approach for the management of PEW, with a specific emphasis on interventions targeted on etiological factors of PEW in CKD patients. The overarching aim is to describe methods to counteract the catabolic processes leading to PEW in CKD and provide means to treat the problem in patients already with PEW. In doing so, the rationale and

efficacy of nutritional interventions in CKD will also be discussed. This review is focused on stage 3–5 CKD and ESRD patients on maintenance dialysis, with literature selection and interpretation mostly based on the opinion of the authors and is not a systematic review of the literature.

PREVENTION OF PEW IN CKD

Dietary nutrient intake in CKD patients

A frequent and important cause of PEW in CKD patients, especially those on maintenance dialysis, is inadequate dietary protein and energy intake.[8–12] A major contributing factor to inadequate dietary intake in these patients is anorexia. Anorexia may develop as a result of retention of uremic toxins,[13] dialysis procedure, intercurrent illness, inflammation,[4,14] acidemia, and/or cardiovascular disease. Inadequate nutrient intake may also occur secondary to comorbid illness that affects gastrointestinal function, depression, poor socioeconomic situation, or early satiety feeling with peritoneal fluid infusion, and peritoneal glucose absorption in peritoneal dialysis (PD).[15,16] Furthermore, additional nutrient loss during dialysis such as amino acids, some peptides, blood, vitamins, trace elements, and glucose may further predispose these patients to an increased risk of PEW.[17,18]

Several strategies can be employed to prevent inadequate nutrient intake in CKD patients (Table 1). In clinically stable patients with stage 3–5 CKD who are not on dialysis, dietary protein and energy intakes of 0.6–0.8 g/kg of ideal body weight per day and 30–35 kcal/ kg of ideal body weight per day, respectively, are able to preserve their protein stores throughout the progression of kidney disease.[19–21] However, these levels should be adjusted when hypermetabolic conditions such as acute illness and hospitalizations occur. In ESRD patients on maintenance dialysis, there are additional protein catabolic stimuli such as the unavoidable loss of amino acids and albumin into the dialysate and the inflammatory stimulus associated with the dialysis procedure. Accordingly, the minimum protein and energy requirements for patients on maintenance hemo- and peritoneal dialysis are 1.2 g/kg of ideal body weight per day and 30–35 kcal/kg of ideal body weight per day based on physical activity level, respectively. Furthermore, it is important that at least 50% of the protein intake should be of high biological value. In elderly CKD patients who tend to lead a sedentary lifestyle, an energy intake of 30 kcal/kg body weight per day is acceptable. In addition to conventional strategies to improve dietary nutrient intake, monitored,

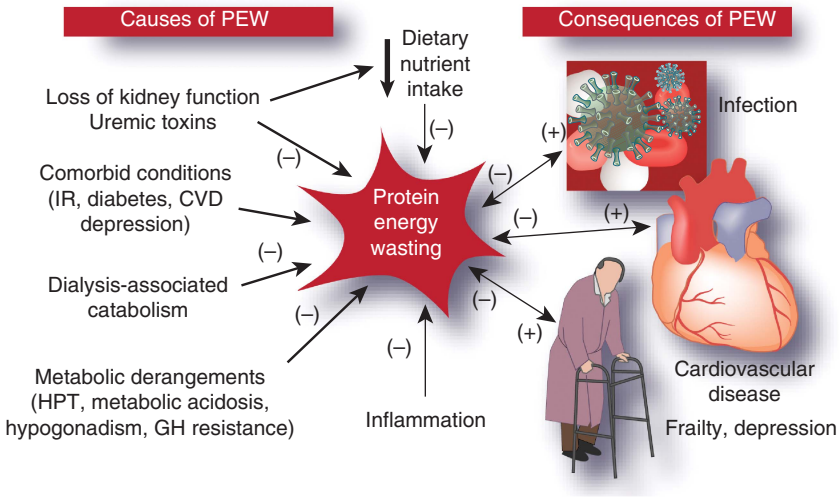

Figure 1 | The conceptual model for etiology and consequences of protein energy wasting (PEW) in chronic kidney disease. CVD, cardiovascular disease; GH, growth hormone; HPT, hyperparathyroidism; IR, insulin resistance.

Table 1 | Recommended minimum protein, energy, and mineral intakes for chronic kidney disease (CKD) and maintenance dialysis patients

	Nondialysis CKD	Hemodialysis	Peritoneal dialysis
Protein	0.6–0.8 g/kg/day Illness 1.0 g/kg	>1.2 g/kg/day	>1.2 g/kg/day Peritonitis >1.5 g/kg
Energy	30–35[a] kcal/kg/day	30–35[a] kcal/kg/day	30–35[a] kcal/kg/day including kcal from dialysate
Sodium	80–100 mmol/day	80–100 mmol/day	80–100 mmol/day
Potassium	<1 mmol/kg if elevated	<1 mmol/kg if elevated	Not usually an issue
Phosphorus	800–1000 mg and binders if elevated	800–1000 mg and binders if elevated	800–1000 mg and binders if elevated

Greater than 50% of high biological value protein (that is, complete protein sources, containing the full spectrum of essential amino acids) is recommended.
[a]Based on physical activity level. In sedentary elderly adults, recommended energy intake is 30 kcal/kg/day. All recommendations are based on ideal body weight. Regular follow-up supports compliance.

in-center provision of high-protein meals or supplements during hemodialysis is a feasible strategy and should be advocated in patients at risk.[22]

An important consideration regarding strategies to improve dietary protein intake in ESRD patients is the potential increase in the intake of several potentially harmful elements, especially phosphorus.[23] Although strictly limiting dietary phosphorus intake may indirectly lead to increased risk for PEW, allowing an unrestricted protein intake will undoubtedly increase phosphorus load. Epidemiologic data indicate that in maintenance hemodialysis (MHD) patients, a combination of decreased serum phosphorus and increased protein intake had the best outcomes, whereas a combination of low serum phosphorus and protein intake had the worst outcomes.[24] Therefore, dietary recommendations to improve protein intake should take into account the phosphorus content of the specific protein sources and other phosphorus-containing nutrients. An increase in serum phosphorus, especially following an increase in protein intake, is usually modest and may be primarily due to phosphorus contained in additives/preservatives from processed food.[25,26] In that context, a small randomized clinical trial (RCT) indicated that the source of protein (that is, vegetarian diet leading lower serum phosphorus levels) has a significant effect on phosphorus homeostasis in patients with CKD.[27]

Renal replacement therapy

Dialysis adequacy has long been viewed as a cornerstone among measures to prevent and treat PEW in maintenance dialysis patients, and a minimum dose of dialysis has been recommended to maintain optimal dietary nutrient intake. On the other hand, studies directly evaluating the effect of increased dialysis dose on nutritional parameters are scarce. The results of the National Cooperative Dialysis Study showed an association between lower protein intake and higher time-averaged urea concentrations, suggesting a relationship between underdialysis and anorexia.[28] These subjects also had poor clinical outcomes. Several subsequent studies suggested that protein nitrogen appearance is dependent on the type and the dose of dialysis.[29,30] In anuric PD patients, increasing the dialysis dose has also been shown to improve dietary intake and nutritional status.[31] However, these retrospective and/or cross-sectional studies did not definitively show a cause and effect relationship between dose of dialysis and nutrition. In the HEMO study, the higher delivered dose of dialysis (eKt/V 1.53 ± 0.09) neither prevented nor reversed the decline of several indices of nutritional status in prevalent MHD patients as compared with conventional dose of dialysis (eKt/V 1.16 ± 0.08). In PD patients, the ADEMEX trial did not show a significant difference in nutritional markers between subjects randomized to control versus high clearance (peritoneal creatinine clearance value of 60 l/week per $1.73\ m^2$).[32] Thus, it can be concluded that what is currently considered adequate dialysis in various guidelines is sufficient to preserve the nutritional status. Increasing dialysis dose beyond these targets has not been shown to improve the nutritional status any further.

Dialysis membrane characteristics might have important implications in nutritional management of MHD patients. Middle molecules, such as β2-microglobulin, are more efficiently removed by high-flux dialyzers than low-flux dialyzers, although in the HEMO trial most nutritional parameters studied did not differ between the two groups.[33] In the European MPO trial, the effects of high-flux versus low-flux dialysis were studied in incident MHD patients. Although there was no difference for the patient group as a whole, there was a nominally significant survival benefit in patients with baseline serum albumin levels < 40 g/l (prespecified analysis) and with diabetes mellitus (*post hoc* analysis) randomized to high-flux dialysis.[34]

The effects of an increase in dialysis frequency on various outcome measures are reported in nonrandomized studies and suggest that daily dialysis increases appetite, protein and energy intake, body weight after hemodialysis, interdialytic weight gain, serum albumin, normalized protein nitrogen appearance, and serum cholesterol.[35] However, the results of the FHN trial indicate no appreciable difference in nutritional markers between subjects randomized to 6×/week in-center hemodialysis versus standard 3×/week in-center hemodialysis.[36] Hemodiafiltration has also been promoted as an efficient method for the removal of uremic toxins; however, no randomized prospective studies are available on the effects of hemodiafiltration on nutritional parameters.[37]

Metabolic acidosis

Metabolic acidosis, a common abnormality in patients with progressive CKD, promotes PEW by increasing muscle protein catabolism via suppression of insulin/insulin growth factor-1 signaling and activation of the ubiquitin–proteasome system.[38] In addition, acidosis stimulates the oxidation of essential amino acids and therefore raises protein requirements for MHD patients.[39] There are a number of studies indicating improvement in nutritional status with oral bicarbonate supplementation.[40] Metabolic studies in PD patients showed that correction of a low serum bicarbonate concentration will downregulate muscle proteolysis, although no appreciable effect is observed in net protein synthesis.[41] In an RCT in 134 patients with stage 4 CKD where serum bicarbonate was increased to 24 mmol/l dietary protein and energy intake, mid-arm muscle circumference and serum albumin improved and progression of CKD was slowed over 2 years compared with maintaining a serum bicarbonate level of 20 mmol/l.[40] An RCT in continuous ambulatory peritoneal dialysis patients showed similar nutritional benefits except for serum albumin.[42] Accordingly, a steady-state serum bicarbonate level should be > 22 mmol/l in PD patients. Predialysis bicarbonate reflects protein intake in adequately dialyzed MHD patients. To avoid alkalosis after hemodialysis, which associates with adverse outcomes in epidemiological studies,[43] we recommend a predialysis goal of 22–24 mmol/l in MHD patients with PEW.

Systemic inflammation

Emerging evidence suggests that inflammation is a major driving force for the uremic phenotype, which commonly includes both premature cardiovascular disease and PEW. Although much information has been gained regarding the etiology and effects of persistent uremic inflammation in CKD, little knowledge is available with regard to its treatment. The initial step for treatment of persistent inflammation should be elimination of etiological factors such as the use of central hemodialysis catheters in MHD patients.[44] Short daily dialysis, as compared with conventional HD, was associated with improved inflammatory status,[45] and lower levels of interleukin 6 (IL-6) were observed following on-line hemodiafiltration as compared with conventional HD.[46] As the dialysis procedure *per se* might stimulate the immune system, proinflammatory effects of dialysis membranes and fluids should also be taken into account in maintenance dialysis patients. Overall, dialysis prescription may have a significant impact on systemic inflammation. Appropriate management of fluid status might improve systemic inflammation in ESRD patients. Volume overload leads to immunoactivation and increased cytokine production via bacterial or endotoxin translocation.[47] It has been reported that PD patients that are high transporters are more often inflamed than low transporters.[48,49] Failed kidney transplants are an unrecognized cause of systemic inflammation in maintenance dialysis patients.[50] Finally, there are also data to suggest that bowel bacteria overgrowth and pathologically altered bacterial flora may contribute to inflammation in ESRD patients.[51,52]

Comorbidities in CKD

CKD patients often have other comorbid diseases that can adversely affect their nutritional status. Patients with CKD

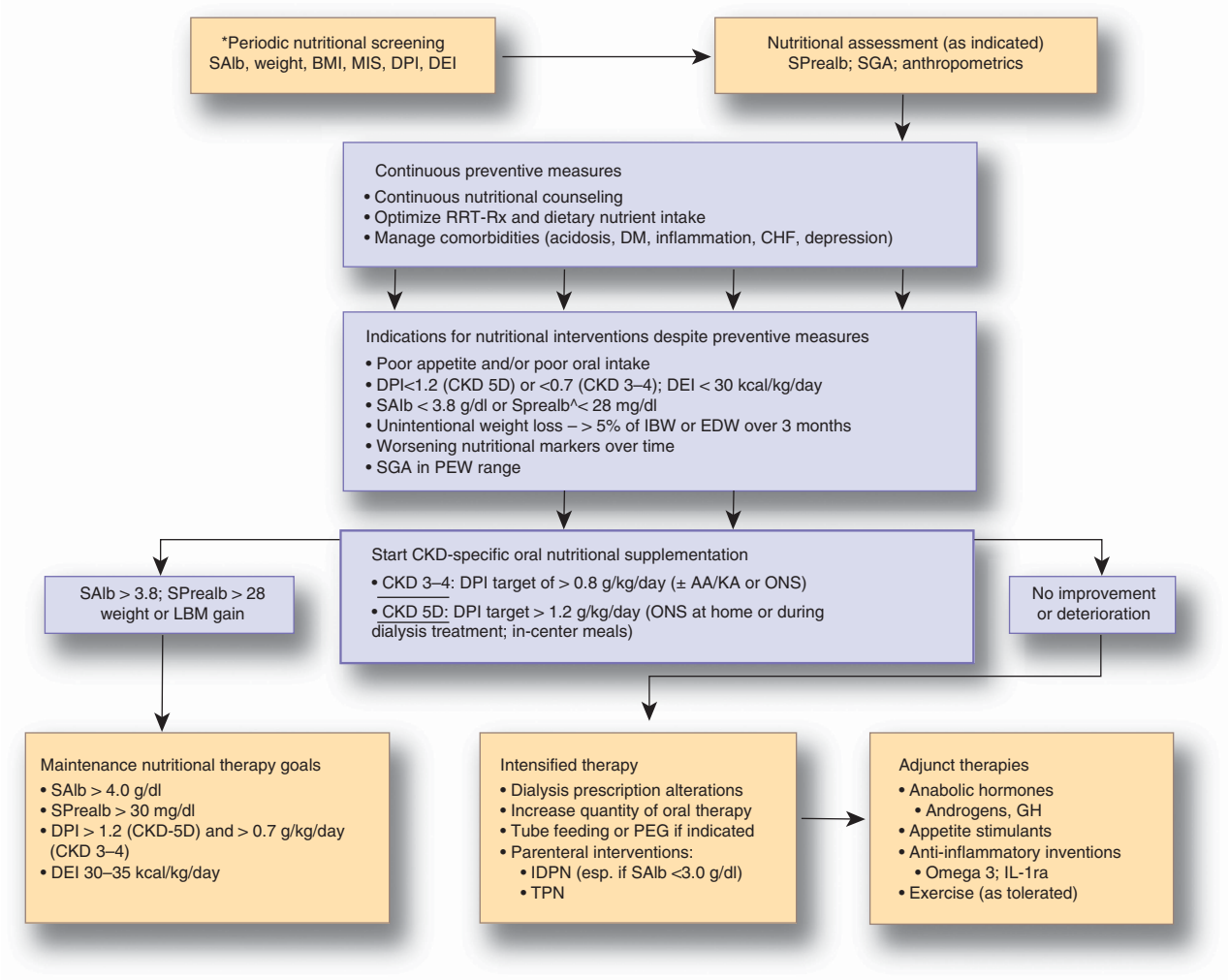

Figure 2 | Proposed algorithm for nutritional management and support in patients with chronic kidney disease. *Minimum every 3 months, monthly screening recommended. ^Only for ESRD patients without residual renal function. AA/KA, amino acid/keto acid; BMI, body mass index; CHF, congestive heart failure; CKD, chronic kidney disease; DEI, dietary energy intake; DM, diabetes mellitus; DPI, dietary protein intake; EDW, estimated dry weight; GH, growth hormone; IBW, ideal body weight; IDPN, intradialytic parenteral nutrition; IL-1ra, interleukin-1 receptor antagonist; LBM, lean body mass; MIS, malnutrition–inflammation score; ONS, oral nutritional supplement; PEG, percutaneous endoscopic gastrostomy; PEW, protein energy wasting; RRT-Rx, renal replacement therapy prescription; SAlb, serum albumin (measured by bromocresol green); SGA, subjective global assessment; SPrealb, serum prealbumin; TPN, total parenteral nutrition.

secondary to diabetes mellitus have a higher incidence of PEW when compared with non-diabetes mellitus patients.[53] The degree of insulin resistance and/or insulin deprivation seems to play the most critical role in this process.[54–59] Insulin resistance is detectable in MHD patients even in the absence of severe obesity and is strongly associated with increased muscle protein breakdown, even after controlling for inflammation.[59] Appropriate management of diabetes and insulin resistance is important in preventing further loss of lean body mass (LBM) in maintenance dialysis patients. This is especially relevant to PD patients, who are exposed to 80–330 g of additional glucose from the dialysate.[60]

Retained adipokines such as leptin, adiponectin, and visfatin in CKD may also contribute to PEW in CKD patients.[61] This effect is accentuated in the setting of abdominal obesity. For example, although adiponectin has anti-inflammatory, anti-atherogenic, and insulin-sensitizing actions,[62] experimental data suggest that adiponectin also promotes weight loss via increased energy expenditure.[63] Elevated visfatin levels were associated with loss of appetite and low fasting serum amino acids in incident dialysis patients.[64]

On the other hand, in spite of the potential adverse consequences of obesity in earlier stages of CKD, there are several epidemiological studies indicating that higher body mass index, regardless of its etiology (that is, increased adiposity and/or LBM) is associated with significantly better survival in ESRD patients.[65,66] Although the exact mechanism(s) underlying this association have not been elucidated, one may interpret the observational data to a potentially beneficial effect of increasing the protein and energy intakes to levels higher than those required to maintain a neutral nitrogen balance alone. If weight gain is one potential outcome of an intervention, gain in LBM should be a part of it along with gain in fat mass.

CKD patients are also likely to suffer from protein depletion because of associated gastrointestinal disturbances (for example, diabetic gastroparesis, nausea and vomiting, bacterial overgrowth in the gut, and pancreatic insufficiency). Appropriate management of these disturbances along with an emphasis on oral health, especially in the elderly, is critical to maintain optimal oral nutrient intake. Other factors such as uncontrolled hyperparathyroidism and cardiac cachexia are associated with systemic inflammation and increased energy expenditure and their appropriate management is necessary to prevent PEW.[67,68] Early recognition and treatment of depressive symptoms, which are common in CKD and ESRD and are linked to fatigue[69] and an unwillingness to eat,[70] are important components in the prevention of PEW.[71–73]

Finally, low circulating levels of vitamin D,[74] a decrease in klotho, and rise in fibroblast growth factor 23 importantly increase parathyroid hormone synthesis, thereby contributing to the development of secondary hyperparathyroidism.[75] Vitamin D and/or parathyroid hormone have long been considered contributors to PEW,[76] but the data remain inconclusive regarding the mechanism involved. As recent evidence show links between fibroblast growth factor 23 levels and inflammation in CKD,[77] it could be hypothesized that regulation of fibroblast growth factor 23 might prevent inflammation and hence PEW.

TREATMENT OF PEW IN CKD

Oral and enteral nutritional supplementation

In CKD patients where standard preventive measures are unable to diminish loss of protein and energy stores, nutritional supplementation is a suitable next step. Specific indications for starting nutritional interventions are depicted in Figure 2. Oral supplementation should be given two to three times a day, preferably 1 h after main meals or during dialysis for MHD patients. Oral supplementation can provide an additional 7–10 kcal/kg per day of energy and 0.3–0.4 g/kg per day of protein requiring a minimum spontaneous intake of 20 kcal/kg per day of energy and 0.4–0.8 g/kg per day of protein in order to meet the recommended dietary energy intake and dietary protein intake targets.

The efficacy of oral supplementation has been studied in multiple settings. In metabolic studies, intradialytic parenteral nutrition (IDPN) and oral nutrition supplementation resulted in positive whole-body net balance, as compared with neutral or negative balance in the control session.[78,79] Although the anabolic effects of parenteral supplementation dissipated in the postdialytic period, oral supplementation led to sustained anabolic effects.

Table 2 | Effects of oral nutritional supplements (ONS) on nutritional outcomes in MHD patients in randomized clinical trials

Reference	*n*	Design	Days	Nutritional significant effects
Acchiardo *et al.*[149]	15	RCT: ONS versus control groups	105	↑ Albumin, transferrin, bone density
Allman *et al.*[150]	21	RCT: ONS versus control groups	180	↑ BW, LBM
Tietze *et al.*[151]	19	RCT, crossover, ONS versus control periods	120	↑ BW, arm muscle circumference
Eustace *et al.*[152]	47	RCT: ONS versus control groups	90	↑ Albumin, grip strength, SF12 mental health
Hiroshige *et al.*[153]	44	RCT, crossover, ONS versus control periods	180	↑ DEI, DPI, fat mass, fat-free mass, albumin
Sharma *et al.*[154]	40	RCT: ONS versus control groups	30	↑ Albumin
Leon *et al.*[155]	180	RCT: ONS versus control groups	365	↑ DEI, DPI, albumin
Cano *et al.*[87]	186	RCT: ONS versus ONS + IDPN groups	365	↑ nPNA, BMI, albumin, prealbumin in both groups
Fouque *et al.*[156]	86	RCT: ONS versus control groups	90	↑ DEI, DPI, SGA, QOL
Moretti *et al.*[157]	49	RCT: ONS versus control groups	365	↑ nPNA, albumin

Abbreviations: BMI, body mass index; BW, body weight; DEI, dietary energy intake; DPI, dietary protein intake; IDPN, intradialytic parenteral nutrition; LBM, lean body mass; MHD, maintenance hemodialysis; nPNA, normalized protein nitrogen appearance; QOL, quality of life; RCT, randomized clinical trial; SGA, subjective global assessment.

Table 3 | Effects of IDPN on nutritional outcomes in MHD patients in RCTs

Reference	*n*	Design	Days	Nutritional significant effects
Guarnieri *et al.*[158]	18	RCT, 3 groups: control, and 2 groups with different AA solutions	60	↑ BW in treated patients
Cano *et al.*[159]	26	RCT: IDPN versus controls	90	↑ DEI, BW, AMC, TSF, serum albumin, prealbumin, creatinine
Navarro *et al.*[160]	17	RCT: IDPN versus controls	90	↑ TSF, serum albumin, nPCR
Cano *et al.*[161]	35	RCT: two IDPN groups differing by fat émulsions (olive vs. soya)	35	In the two groups:↑nPCR, serum albumin, prealbumin, creatinine
Cano *et al.*[87]	186	RCT: IDPN + ONS versus ONS	365	No advantage of IDPN addition to ONS ↑ nPNA, BMI, serum albumin, prealbumin in both groups

Abbreviations: AMC, arm muscle circumference; BMI, body mass index; BW, body weight; DEI, dietary energy intake; IDPN, intradialytic parenteral nutrition; MHD, maintenance hemodialysis; nPNA, normalized protein nitrogen appearance; ONS, oral nutritional supplements; RCT, randomized clinical trial; TSFT, triceps skinfold thickness.

Table 4 | Implications of the results of randomized clinical trials using oral nutritional supplements or intradialytic parenteral nutrition in maintenance dialysis patients with protein energy wasting (PEW)

- The nutritional response to therapy is directly correlated with severity of PEW at baseline.
- The nutritional response to therapy is directly correlated with the amount of nutrients delivered.
- Underlying systemic inflammatory response does not hinder the beneficial effects of nutritional supplementation.
- Diabetic patients differ in their response to nutritional therapy and may require individualized prescription.
- The route of administration of nutritional supplementation (that is, oral or parenteral) does not have any significant effect on the response to therapy as long as equal and adequate amounts of protein and calories are provided.
- The optimal targets for dietary protein and energy intake in maintenance hemodialysis (MHD) patients is >1.2 g/kg/day and >35 kcal/kg/day, respectively.
- Routine nutritional markers such as serum albumin and prealbumin can be used as surrogate markers not only of nutritional status but also possibly of hospitalization, cardiovascular outcomes, and survival.

The studies designed to establish the benefits of oral nutritional supplementation on the long-term improvements of overall nutritional status of the MHD patients with PEW have yielded encouraging results. Table 2 provides a list of these studies along with their reported nutritional outcomes. The types of oral supplementations included regular meals during dialysis, oral supplementation taken at home or during dialysis, and oral amino acid tablets. The duration of the treatment ranged from 3 months to over a year. The beneficial nutritional effects of these supplements ranged from improvements in serum biomarkers such as albumin, prealbumin, and transferrin to gains in different body compartments such as weight and LBM. The effects were evident as early as within a month and were sustained in most if not all studies. There were also improvements in quality of life and physical functioning. In several of these studies, hospitalizations and death were reported but none of them had the statistical power to appropriately assess the efficacy of these interventions.

For patients who are unable to tolerate nutritional supplementation by mouth, nasogastric tubes, percutaneous endoscopic gastroscopy, or jejunostomy tubes can be considered.[20,80] Tube feeding is most often used in conditions such as severe anorexia, swallowing troubles secondary to neurologic or head and neck diseases, perioperative periods, and stress. The efficacy of oral and enteral supplementation on clinical (quality of life, complications, and mortality), biochemical (serum albumin and electrolyte levels), and nutritional (dietary intake and anthropometry) outcomes were examined in a meta-analysis.[81] The analysis included 18 studies (5 RCTs and 13 non-RCTs) and suggested that nutritional support significantly increased total (energy and protein) intake and serum albumin concentration on average by 0.23 g/dl, with no adverse effects on electrolyte status (serum phosphate and potassium).

Although provocative, the aforementioned studies can only be considered as preliminary evidence, especially in terms of clinical outcomes such as hospitalization and death. Two recent large-scale observational studies reported significant survival benefit in favor of hypoalbuminemic MHD patients receiving nutritional supplementation versus similarly matched controls.[82,83] Specifically, in a retrospective cohort study of 4289 matched pairs, death rates were 30.9% versus 37.3% in treated versus historically matched untreated groups, respectively.[82] In a prospective observational study, the effects of an oral nutritional supplementation (ONS) program performed as part of a disease management plan were reported in 276 MHD patients who received supplements versus 194 MHD patients who did not receive ONS because they were deemed inappropriate or refused.[83] ONS use was associated with higher serum albumin and lower hospitalization at 1 year, but there was no significant reduction in mortality risk. Although these studies had limitations of retrospective design, convenience sampling, and residual confounding from unmeasured variables, they highlight the potentially beneficial effects of this strategy in clinical practice.

Intradialytic parenteral nutrition

Although the gastrointestinal route is the preferred choice for nutritional supplementation, parenteral provision of nutrients, especially during the HD procedure, has been shown to be a safe and convenient approach for individuals who cannot tolerate oral or enteral administration of nutrients. Multiple studies including several RCTs showed evidence for nutritional improvements with the use of IDPN in MHD patients with overt PEW (Table 3). These studies are very heterogeneous in relation to the number of subjects, the nutritional status of patients at baseline, the composition of IDPN solutions, the treatment duration, and the criteria taken into account for IDPN evaluation.[84,85] The high cost of IDPN therapy and the regulatory concerns remain the greatest barriers to performing adequately powered clinical trials.[86]

In the largest and arguably best-executed nutritional intervention study in MHD patients with PEW (FINE study), 186 MHD patients with PEW were enrolled and received either IDPN plus ONS or ONS alone.[87] For ethical reasons, no control group was considered. Similar improvements of nutritional parameters were observed in the two groups over 2 years and there were no differences in rates of hospitalization or death. The clinically relevant conclusions that can be driven from the FINE study or other RCTs using IDPN or ONS are listed in Table 4 and include the direct correlation between response to nutritional supplementation and the severity of PEW[14–16] and the amount of nutrients received,[15] diabetic patients showing an altered response to nutritional support in terms of serum albumin[5] and the observation that inflammatory status does not significantly affect the response to nutritional support.[5,19,20]

Similar studies using amino acid dialysate (AAD) as a nutritional intervention in PD patients with PEW have also provided conflicting results. Two metabolic studies have indicated beneficial effects of AAD whereas long-term RCTs did not show a conclusive nutritional improvement through such a strategy in PD patients.[88–90] Of interest, the most significant improvements were observed in hypoalbuminemic PD patients.[89] It should also be noted that an increase in serum urea concentrations associated with exacerbation of uremic symptoms, as well as metabolic acidosis, remains a potential complication of AAD.[91] Overall, AAD remains to be a viable option in PD patients with PEW who cannot tolerate or are not suitable for PO and other enteral supplements.

Growth hormone

Growth failure is a dominant feature of children with CKD. There is an acquired growth hormone (GH) resistance, which is not completely restored by transplantation.[92,93] Recombinant human GH, an approved treatment of short stature in pediatric CKD patients,[94–96] leads to improved growth, confirming that recombinant human GH could overcome GH resistance. In adults with CKD, resistance to GH may be responsible for the premature decline in body composition. A number of detailed metabolic studies and prospective randomized trials[97–106] provide convincing direct or indirect evidence for anabolic responses and improved biomarkers and LBM in maintenance dialysis patients. In a large multicenter RCT, significant decreases were observed in C-reactive protein and homocysteine levels along with increases in serum high-density lipoprotein cholesterol and transferrin levels in hypoalbuminemic MHD patients.[107] Unfortunately, this large RCT was prematurely terminated because of slow recruitment, without the ability to assess the effects of Recombinant human GH on hospitalization or death.

Anabolic steroids

Anabolic steroids stimulate net muscle protein synthesis by inducing mRNA expression of skeletal muscle androgen receptor, and increasing the intracellular pool of amino acids derived from protein degradation.[108,109] Administration of supraphysiologic doses of testosterone, especially when combined with strength training, increases fat-free mass and muscle size and strength[110] in patients with burns,[111] chronic obstructive pulmonary disease,[112] cancer,[113] and HIV infection.[114] A short-term study in an elderly population suggested beneficial effects of testosterone replacement therapy in modifying some specific cardiovascular risk factors such as insulin resistance, abdominal obesity, dyslipidemia, and inflammation.[115] Testosterone deficiency is highly common in male MHD patients[116,117] and is associated with increased mortality risk. Several RCTs performed in MHD patients showed significant increases in both anthropometric and biochemical parameters including body weight, body mass index, skinfold, mid-arm muscle circumference, and serum levels of total protein, prealbumin, and transferrin with nandrolone decanoate treatment.[118–120] MHD patients who received nandrolone decanoate for 3 months gained an average of 3.1 ± 2.2 kg of LBM. No consistent effect of nandrolone decanoate was demonstrated on physical functioning in several studies and high-dose nandrolone decanoate (100 mg/week) was intolerable in females because of its virilizing effects.[121,122] Studies in non-CKD cohorts have reported complications including cardiomyopathy, hepatocellular carcinoma, reduction in high-density lipoprotein levels, hypercoagulation, irregular menses, virilization and hirsutism in women, testicular atrophy, and infertility in men and occasional sudden death.[109] Thus, the use anabolic steroids should be limited to 6 months.

Exercise

Abnormalities in muscle function, exercise performance, and physical activity abnormalities begin in the early stages of CKD, and decline dramatically as ESRD develops.[123,124] In ESRD, there are metabolic and structural muscle abnormalities with reductions in oxidative capacity and type 1 fibers with associated decrease in muscular endurance.[125,126] Although a number of studies have examined the effects of

cardiopulmonary fitness training in ESRD patients,[127] relatively few studies have examined the role of exercise training on stimulating the muscle growth. Exercise in CKD increases muscle content of insulin growth factor-1 and insulin growth factor-II mRNAs,[128] improves muscle oxidative capacity,[129] and increases the number of satellite cells necessary for the regeneration of muscle fibers.[130] Despite the proven efficacy of long-term resistance exercise as an anabolic intervention in otherwise healthy elderly and certain chronic disease states,[131,132] studies in ESRD patients have not demonstrated consistent long-term improvements in markers of muscle mass and have resulted in a limited increase in LBM or improvements in muscle structure only detectable by very precise methods such as magnetic resonance imaging or computed tomography.[7,128,133,134] Several metabolic studies have suggested the beneficial effects of combining exercise with nutritional supplementation, although one RCT did not show further benefits of additional resistance exercise on long-term (6-month) somatic protein accretion above and beyond nutritional supplementation alone.[134,135]

Collectively, the available data indicate that the presumed beneficial effects of exercise such as improvements in muscle quality and quantity, strength, and physical functioning are not consistently observed in ESRD patients. The possible explanations for the limited efficacy of exercise in CKD patients include the limitations of methods to assess body composition, inadequate intensity and/or duration of exercise, and the lack of understanding the actual metabolic and morphologic abnormalities related to PEW in the setting of advanced CKD.

Emerging therapies for treatment of PEW in CKD

Appetite stimulants. Examples of pharmacologic agents that may stimulate appetite include megestrol acetate, dronabinol, cyproheptadine, melatonin, thalidomide, and ghrelin. Most of these drugs have not been studied systematically in MHD patients with PEW but have been used in other catabolic illnesses such as breast cancer.[136] In elderly men, the orexigenic and weight gaining effects of megestrol acetate have been attributed to its anticytokine effects via reduced levels of IL-6 and tumor necrosis factor-α.[136] The increase in appetite was associated with an increase in weight gain, primarily fat mass accrual. Moreover, megestrol acetate has been associated with the side effects including hypogonadism, impotence, and increased risk of thromboembolism. In MHD patients, megestrol acetate can stimulate appetite and induce small increases in serum albumin and weight[137] but large-scale prospective studies are needed to assess whether these drugs provide adjunctive nutritional therapy for MHD or CKD patients.

Ghrelin is an orexigenic peptide released primarily from the stomach that increases appetite and adjusts both short- and long-term energy balance. Although elevated ghrelin levels have been documented in CKD, subcutaneous ghrelin administration resulted in several-fold increases in plasma ghrelin concentration and improvements in short-term energy intake in maintenance dialysis patients with mild to moderate PEW.[138] In addition to its direct orexigenic effects, ghrelin administration has been reported to inhibit sympathetic nerve activity and inflammatory response, and improve left ventricular function and exercise capacity, making it a good candidate for treatment of anorexic ESRD patients.

Anti-inflammatory interventions. When comorbidities and potential dialysis-related causes of inflammation have been evaluated and appropriately treated, other anti-inflammatory treatment strategies could be considered in maintenance dialysis patients who are persistently inflamed. Such interventions can be indirect, such as exercise, antioxidative, and/or bioecological strategies, or with direct effects such as targeted anticytokine therapies.[139]

Resistance exercise may attenuate inflammatory state in CKD patients but these results were not confirmed in MHD patients[140,141] In a murine model of CKD, myostatin inhibition by antimyostatin peptibody not only suppressed IL-6 and tumor necrosis factor but also prevented muscle atrophy.[142] Nutritional antioxidants, long-chain omega-3 fatty acids, and cholecalciferol are shown to have anti-inflammatory effects[143] similar to statins, angiotensin-converting enzyme inhibitors, or peroxisome proliferator-activated receptor-γ agonists. However, whether these effects can translate into improvements in nutritional markers in CKD patients remains to be demonstrated. Several other compounds might possess anti-inflammatory properties (that is, catechins in green tea extract, resveratrol, curcumin, and pomegranate juice). The effect of these compounds in the setting of CKD needs further studies.[139]

Pentoxifylline is a drug with anti-inflammatory properties.[144] Its administration in CKD patients has been shown to improve protein breakdown along with an incremental anabolic effect when combined with a balanced amino acid mixture.[145] Etanercept, a tumor necrosis factor receptor antagonist, was tested in a small number of MHD patients for a period of over 44-weeks.[146] Although there were encouraging positive effects on serum albumin and prealbumin levels compared with the placebo group with no occurrence of adverse events, the etanercept treatment did not result in significant changes in serum C-reactive protein and IL-6. Finally, administration of IL-1receptor antagonist for 4 weeks in chronically inflamed MHD patients resulted in significant improvements in C-reactive protein and IL-6 levels,[147] along with a tendency for serum albumin, serum prealbumin, and LBM to increase. These results indicate the need for larger-scale studies examining the efficacy and safety of anticytokine therapies as nutritional interventions in CKD patients.

AN INTEGRATIVE APPROACH FOR PREVENTION AND TREATMENT OF PEW IN CKD: SUMMARY AND RECOMMENDATIONS

Because of its metabolic and functional importance in whole-body homeostasis, preservation of muscle mass is the

ultimate goal in the management of PEW in CKD patients. In normal conditions, apart from genetic determinants, protein anabolism is determined by nutrient availability, especially amino acids, and a greater ratio of anabolic to the catabolic hormones, that is, insulin, androgens, growth factors, and catecholamines. In CKD and ESRD patients, where a number of catabolic signals dominate, it is critical to maintain a dietary protein and energy intake relative to needs. Preemptive treatment of concurrent conditions that contribute to catabolism, such as metabolic acidosis, insulin resistance, and systemic inflammation, is of paramount importance for the prevention of development PEW. A holistic approach to dialytic prescription is necessary to avoid the adverse nutritional side effects of uremic toxin retention. Nonconventional dialytic strategies may remove the necessity for overrestrictive diets in maintenance dialysis patients leading to improved nutritional status.[38] When supplemental nutrition is indicated, it is crucial to take into account all the determinants of body and muscle mass: protein and energy content, exercise, anabolizing hormones, antioxidants and antiinflammatory nutrients or drugs, and other specific nutrients.[38] In certain cases, a targeted approach using specific nutrients such as essential amino acids[36] or branched-chain amino acid supplements have been shown to improve both nutrient intakes and nutritional status.[37] Strategies to improve anabolic signaling pathways such as insulin or growth hormone through pharmacological (that is, recombinant human GH or androgens) and nonpharmacological (that is, exercise or anti-inflammatory nutrients) means are promising interventions to increase muscle mass in maintenance dialysis patients.[44,45,46] Finally, it is important to assess the impact of nutritional supplements not only in terms of changes in nutritional parameters, but to translate these observations to potential improvements in hospitalization, mortality, and cost effectiveness. The potential complications of nutritional interventions are minimal, if any, especially for the ones targeted for prevention. In addition to the number of deaths and hospitalizations that can be prevented by improvements in nutritional status, the predicted financial gains greatly overcome any cost associated with readily available nutritional interventions for CKD and ESRD patients.[148]

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