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

Permalink
https://escholarship.org/uc/item/2z74w02k

Journal
Kidney international, 84(6)

ISSN
0085-2538

Authors
Ikizler, T Alp
Cano, Noel J
Franch, Harold
et al.

Publication Date
2013-12-01

DOI
10.1038/ki.2013.147

License
https://creativecommons.org/licenses/by/4.0/ 4.0

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

T. Alp Ikizler1, Noel J. Cano2, Harold Franch3, Denis Fouque4, Jonathan Himmelfarb5, Kamyar Kalantar-Zadeh6, Martin K. Kuhlmann7, Peter Stenvinkel8, Pieter TerWee9, Daniel Teta10, Angela Yee-Moon Wang11 and Christoph Wanner12

1Division of Nephrology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; 2CHU Clermont-Ferrand, Service de Nutrition, CRNH Auvergne, Clermont-Ferrand, France; 4Division of Nephrology, Department of Medicine, Emory University, Atlanta, Georgia, USA; 5Department of Nephrology, Hospital E.HERRIOT, Lyon, France; 6Division of Nephrology, Department of Medicine, University of California Irvine, Orange, California, USA; 7Division of Nephrology, Department of Medicine, Vivantes Klinikum im Friedrichshain, Berlin Germany; 8Department of Renal Medicine, Karolinska Institute, Huddinge University Hospital, Stockholm, Sweden; 9Department of Nephrology, Vrije University Medical Center, Amsterdam, The Netherlands; 10Department of Medicine, Service of Nephrology, University Hospital (CHUV), Lausanne, Switzerland; 11Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong, People’s Republic of China and 12Department of Medicine, Division of Nephrology, University of Wuerzburg, Wuerzburg, Germany

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.

Kidney International (2013) 84, 1096–1107; doi:10.1038/ki.2013.147; published online 22 May 2013

KEYWORDS: dialysis; malnutrition; metabolism; nutrition; supplementation

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,

---

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                       | > 1.2 g/kg/day                    | > 1.2 g/kg/day                        |
| Sodium              | 30–35 kcal/kg/day                      | 30–35 kcal/kg/day                 | 30–35 kcal/kg/day including kcal from dialysate |
| Potassium           | <1 mmol/kg if elevated                 | 80–100 mmol/day                   | 80–100 mmol/day                        |
| Phosphorus          | 800–1000 mg and binders if elevated    | 800–1000 mg and binders if elevated | Not usually an issue                   |

Greater than 50% of high biological value protein (that is, complete protein sources, containing the full spectrum of essential amino acids) is recommended.

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 m²).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 x/week in-center hemodialysis versus standard 3 x/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. Short daily dialysis, as compared with conventional HD, was associated with improved inflammatory status, and lower levels of interleukin 6 (IL-6) were observed following on-line hemodiafiltration as compared with conventional HD. 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. It has been reported that PD patients that are high transporters are more often inflamed than low transporters. Failed kidney transplants are an unrecognized cause of systemic inflammation in maintenance dialysis patients. Finally, there are also data to suggest that bowel bacteria overgrowth and pathologically altered bacterial flora may contribute to inflammation in ESRD patients.

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.\textsuperscript{53} The degree of insulin resistance and/or insulin deprivation seems to play the most critical role in this process.\textsuperscript{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.\textsuperscript{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.\textsuperscript{60}

Retained adipokines such as leptin, adiponectin, and visfatin in CKD may also contribute to PEW in CKD patients.\textsuperscript{61} This effect is accentuated in the setting of abdominal obesity. For example, although adiponectin has anti-inflammatory, anti-atherogenic, and insulin-sensitizing actions,\textsuperscript{62} experimental data suggest that adiponectin also promotes weight loss via increased energy expenditure.\textsuperscript{63} Elevated visfatin levels were associated with loss of appetite and low fasting serum amino acids in incident dialysis patients.\textsuperscript{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.\textsuperscript{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.\textsuperscript{67,68} Early recognition and treatment of depressive symptoms, which are common in CKD and ESRD and are linked to fatigue\textsuperscript{69} and an unwillingness to eat,\textsuperscript{70} are important components in the prevention of PEW.\textsuperscript{71-73}

Finally, low circulating levels of vitamin D,\textsuperscript{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.\textsuperscript{75} Vitamin D and/or parathyroid hormone have long been considered contributors to PEW,\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{149} | 15 | RCT: ONS versus control groups | 105  | † Albumin, transferrin, bone density |
| Allman et al.\textsuperscript{150} | 21 | RCT: ONS versus control groups | 180  | † BW, LBM                      |
| Tietze et al.\textsuperscript{151} | 19 | RCT, crossover, ONS versus control periods | 120  | † BW, arm muscle circumference |
| Eustace et al.\textsuperscript{152} | 47 | RCT: ONS versus control groups | 90   | † Albumin, grip strength, SF12 mental health |
| Hiroshige et al.\textsuperscript{153} | 44 | RCT, crossover, ONS versus control periods | 180  | † DEI, DPI, fat mass, fat-free mass, albumin |
| Sharma et al.\textsuperscript{154} | 40 | RCT: ONS versus control groups | 30   | † Albumin                      |
| Leon et al.\textsuperscript{155} | 180 | RCT: ONS versus control groups | 365  | † DEI, DPI, albumin             |
| Cano et al.\textsuperscript{156} | 186 | RCT: ONS versus ONS + IDPN groups | 365  | † nPNA, BMI, albumin, prealbumin in both groups |
| Fouque et al.\textsuperscript{157} | 86 | RCT: ONS versus control groups | 90   | † DEI, DPI, SGA, QOL           |
| Moretti et al.\textsuperscript{158} | 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.

---

TA Ikizler et al.: Prevention and treatment of PEW in CKD patients

Kidney International (2013) 84, 1096–1107
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 supplemenations 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. 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 efficacies 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. 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. 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. 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. 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.

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

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

Abbreviations: AMC, arm muscle circumference; 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; TSF, 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.
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 PEW14–16 and the amount of nutrients received,15 diabetic patients showing an altered response to nutritional support in terms of serum albumin5 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 trials97–106 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 strength110 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 patients116,117 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, 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, improves muscle oxidative capacity, and increases the number of satellite cells necessary for the regeneration of muscle fibers. Despite the proven efficacy of long-term resistance exercise as an anabolic intervention in otherwise healthy elderly and certain chronic disease states, 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. 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.

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. 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. 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 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. 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.

Resistance exercise may attenuate inflammatory state in CKD patients but these results were not confirmed in MHD patients. In a murine model of CKD, myostatin inhibition by antymyostatin peptide not only suppressed IL-6 and tumor necrosis factor but also prevented muscle atrophy. Nutritional antioxidants, long-chain omega-3 fatty acids, and cholecalciferol are shown to have anti-inflammatory effects 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.

Pentoxifylline is a drug with anti-inflammatory properties. 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. Etanercept, a tumor necrosis factor receptor antagonist, was tested in a small number of MHD patients for a period of over 44-weeks. 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-1 receptor antagonist for 4 weeks in chronically inflamed MHD patients resulted in significant improvements in C-reactive protein and IL-6 levels 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. 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. In certain cases, a targeted approach using specific nutrients such as essential amino acids or branched-chain amino acid supplements have been shown to improve both nutrient intakes and nutritional status. 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. 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.

DISCLOSURE
TAl: consultant for Abbott Renal Care, Abbott Nutrition, DSI, Baxter Renal, Amgen, Affymax, Fresenius Medical Care North America, Fresenius-Kabi, and Satellite Healthcare; NJC: research grants from Barry-Caillebaud, Baxter, B Braun, Danone, Fresenius Kabi, Lactalis, Nestlé, Nutricia, and Sanofi; HF: none; DF: consultant for Abbott Renal Care, Abbott Nutrition, Fresenius Kabi, and Danone; JH: consultant for Abbott Renal Care; KK-Z: consultant and/or speaker for Abbott Renal Care, Abbott Nutrition, Baxter Renal, Amgen, Fresenius-Kabi, Otsuka, and Shire; MKK: speaker for Fresenius, Gambo, Baxter Renal, Fresenius Kabi, Abbott, Sanofi, Amgen, and Shire, and advisory board: Fresenius Kabi and Abbott; PS: member of the scientific advisory board of Gambo and consultant for Abbott Renal Care and Takeda; PT: advisory board member of AMGEN and Baxter Renal; DT: consultant and/or speaker for Abbott Nutrition International, Fresenius Medical Care, Fresenius Kabi, and Shire; AY-MW: advisory board member, has received speaker fee and grant from Sanofi, speaker fee and grant from Baxter Renal, and speaker for Fresenius Kabi; CW: scientific advisory board of Reata and Baxter Renal, speaker for Abbott Renal Care, Amgen, Fresenius Medical Care, and Mitsubishi Pharma. The sponsor had no influence on writing of the manuscript.

ACKNOWLEDGMENTS
This work is a product of the International Society of Renal Nutrition and Metabolism Focus Group Meeting convened at Vancouver, Canada in 2011 during World Congress of Nephrology. The meeting was supported in part by an unrestricted grant from Abbott Nutrition to International Society of Renal Nutrition and Metabolism.

REFERENCES
1. Ikizler TA, Hakim RM. Nutrition in end-stage renal disease. Kidney Int 1996; 50: 343–357.
2. Kopple JD. Effect of nutrition on morbidity and mortality in maintenance dialysis patients. Am J Kidney Dis 1994; 24: 1002–1009.
3. Fouque D, Kalantar-Zadeh K, Kopple J et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int 2008; 73: 391–398.
4. Kalantar-Zadeh K, Block G, McAllister CJ et al. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. Am J Clin Nutr 2004; 80: 299–307.
5. (DOQI) NKFDOQIN. Clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis 2000; 35: 51–140.
6. Carrero JJ, Stenvinkel P, Cuppari L et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement. From the International Society of Renal Nutrition and Metabolism (ISRN); J Ren Nutr 2013; 23: 77–90.
7. Johansen KL, Painter PL, Sakkas GK et al. Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: a randomized, controlled trial. J Am Soc Nephrol 2006; 17: 2307–2314.
8. Rocco MV, Parandani L, Burrowes JD et al. Nutritional status in the HEMO Study cohort at baseline. Hemodialysis. Am J Kidney Dis 2002; 39: 245–256.
9. Klokpenborg WD, de Jong PE, Huisman RM. Low calorie intake in dialysis patients: an alternative explanation. Am J Kidney Dis 1999; 33: 1202–1204.
10. Thunberg SJ, Swamy AP, Cestro RV. Cross-sectional and longitudinal nutritional measurements in maintenance hemodialysis patients. Am J Clin Nutr 1981; 34: 2005–2012.
11. Schoenfeld PY, Henry RR, Laird NM et al. Assessment of nutritional status of the National Cooperative Dialysis Study population. Kidney Int Suppl 1983; 13: S80–S88.
12. Wang AX, Sanderson J, Sea MM et al. Important factors other than dialysis adequacy associated with inadequate dietary protein and energy intake in patients receiving maintenance peritoneal dialysis. Am J Clin Nutr 2003; 77: 834–841.
13. Anderstam B, Mamoun AH, Sodersten P et al. Middle-sized molecule fractions isolated from uremic ultrafiltrate and normal urine inhibit digestive behavior in the rat. J Am Soc Nephrol 1996; 7: 2453–2460.
14. McCarthy DO. Tumor necrosis factor alpha and interleukin-6 have differential effects on food intake and gastric emptying in fasted rats. Res Nurs Health 2000; 23: 222–228.
15. Wright M, Woodrow G, O’Brien S et al. Disturbed appetite patterns and nutrient intake in peritoneal dialysis patients. Perit Dial Int 2003; 23: 550–556.
16. Mamoun AH, Anderstam B, Sodersten P et al. Inference of peritoneal dialysis solutions with glucose and amino acids on ingestive behavior in rats. Kidney Int 1996; 49: 1276–1282.
17. Ikizler TA, Flakoll PJ, Parker RA et al. Amino acid and albumin losses during hemodialysis. Kidney Int 1994; 46: 830–837.
18. Combarnous F, Tetta C, Cellier CC et al. Albumin loss in on-line hemodiafiltration. Int J Artif Organs 2002; 25: 203–209.
19. Lim VS, Kopple JD. Protein metabolism in patients with chronic renal failure: role of uremia and dialysis. Kidney Int 2000; 58: 1–10.
20. Cano NJ, Aparicio M, Brunori G et al. ESPEN Guidelines on Parenteral Nutrition: adult renal failure. Clin Nutr 2009; 28: 401–414.
Review

Results from the RISCADIV study. Nephrol Dial Transplant 2008; 23: 2337–2343.

Niebauer J, Volk HD, Kemp M et al. Endotoxin and immune activation in chronic heart failure: a prospective cohort study. Lancet 1999; 353: 1838–1842.

Carrero JJ, Axelsson J, Avesani CM et al. Being an inflamed peritoneal dialysis patient - a Dante's journey. Contrib Nephrol 2006; 150: 144–151.

Cordeiro AC, Carrero JJ, Abensur H et al. Systemic and local inflammation in peritoneal dialysis: mechanisms, biomarkers and effects on outcome. Contrib Nephrol 2009; 163: 132–139.

Lopez JM, Perales L, Jofre R et al. Presence of a failed kidney transplant in patients who are on hemodialysis is associated with chronic inflammatory state and erythropoietin resistance. J Am Soc Nephrol 2004; 15: 2494–2501.

Aguilera A, Gonzalez-Espinoza L, Codocoro R et al. Bowl bacterial overgrowth as another cause of malnutrition, inflammation, and atherosclerosis syndrome in peritoneal dialysis patients. Adv Perit Dial 2010; 26: 130–136.

Vazni ND. CKD impairs barrier function and alters microbial flora of the intestine: a major link to inflammation and uremic toxicity. Curr Opin Nephrol Hypertens 2012; 21: 587–592.

Cano NJ, Roth H, Aparicio M et al. Malnutrition in hemodialysis diabetic patients: evaluation and prognostic influence. Kidney Int 2002; 62: 593–601.

Degener SM, Sundell MB, Siew ED et al. Insulin resistance and protein metabolism in chronic hemodialysis patients. J Ren Nutr 2013; 23: e59-e66.

Siew ED, Ikizler TA. Determinants of insulin resistance and its effects on protein metabolism in patients with advanced chronic kidney disease. Contrib Nephrol 2008; 161: 138–144.

Flakoll PJ, Carlson M, Cherrington AC. Physiological action of insulin. In: Leroith DTS, Olefsky J (eds) Diabetes Mellitus: A Fundamental and Clinical Text, 2nd edn. Williams & Wilkins: Philadelphia, PA, 2000: 146–161.

Pupim LB, Flakoll PJ, Majchrzak KM et al. Increased muscle protein breakdown in chronic hemodialysis patients with type 2 diabetes mellitus. Kidney Int 2005; 68: 1857–1865.

Pupim LB, Heimburger O, Qureshi AR et al. Accelerated lean body mass loss in incident chronic dialysis patients with diabetes mellitus. Kidney Int 2005; 68: 2368–2374.

Pupim LB, Majchrzak KM et al. Inteinsic insulin resistance is associated with skeletal muscle protein breakdown in non-diabetic chronic hemodialysis patients. Kidney Int 2007; 71: 146–152.

Grotdstein GP, Blumenkranz MJ, Kopple JD et al. Glucose absorption during continuous ambulatory peritoneal dialysis. Kidney Int 1981; 19: 564–567.

Carrero JJ, Cordeiro AC, Lindholm B et al. The emerging pleiotropic role of adipokines in the uremic phenotype. Curr Opin Nephrol Hypertens 2010; 19: 37–42.

Drechsler C, Krane V, Winkler K et al. Changes in adipocine and the risk of sudden death, stroke, myocardial infarction, and mortality in hemodialysis patients. Kidney Int 2009; 76: 567–575.

Qi Y, Takahashi N, Hileman SM et al. Effects of increasing delivered dialysis treatment to malnourished peritoneal dialysis patients. Kidney Int 2000; 57: 1743–1754.

Paniagua R, Amato D, Vonesh E et al. Analysis of the effects of increasing delivered dialysis treatment to malnourished peritoneal dialysis patients. Kidney Int 2000; 57: 1307–1312.

Eknayan G, Beck GJ, Cheung AK et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 2002; 347: 2010–2019.

Locatelli F, Martin-Malo A, Hannedouche T et al. Effect of membrane permeability on survival of hemodialysis patients. J Am Soc Nephrol 2009; 20: 645–654.

Pierrotas A, McFarlane P, Chan CT et al. Daily hemodialysis 2006. State of the art. Minerva Urol Nefrol 2006; 58: 99–115.

Chertow GM, Levin NW, Beck GJ et al. In-center hemodialysis six times per week versus three times per week. N Engl J Med 2010; 363: 2287–2300.

Locatelli F, Manzoni C, Del Vecchio L et al. Recent trials on hemodiafiltration. Contrib Nephrol 2011; 171: 92–100.

Bailey JL, Wang X, England BK et al. The acidosis of chronic renal failure activates muscle proteolysis in rats by augmenting transcription of genes encoding proteins of the ATP-dependent ubiquitin-proteasome pathway. J Clin Invest 1997; 99: 1447–1453.

Graham KA, Reaich D, Channon SM et al. Correction of acidosis in hemodialysis decreases whole body protein degradation. J Am Soc Nephrol 1997; 8: 632–637.

de Brito-Asthurst I, Varagunam M, Raftrey MJ et al. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol 2009; 20: 2075–2084.

Pickering WP, Price SR, Bircher G et al. Nutrition in CAPD: serum bicarbonate and the ubiquitin-proteasome system in muscle. Kidney Int 2002; 61: 1286–1292.

Stein A, Moorhouse J, Iles-Smith H et al. Role of an improvement in acid-base status and nutrition in CAPD patients. Kidney Int 1997; 52: 1089–1095.

Wu DY, Shinaberger CS, Regidor DL et al. Association between serum bicarbonate and death in hemodialysis patients: is it better to be acidic or alkalotic? Clin J Am Soc Nephrol 2006; 1: 70–78.

Goldstein SL, Ikizler TA, Zappitelli M et al. Non-infected hemodialysis catheters are associated with increased inflammation compared to arteriovenous fistulas. Kidney Int 2009; 76: 1063–1069.

Ayus JC, Mizani MR, Achinger SG et al. Effects of short daily versus conventional hemodialysis on left ventricular hypertrophy and inflammatory markers: a prospective, controlled study. J Am Soc Nephrol 2005; 16: 2779–2786.

Panichi V, Rizza GM, Paolotti S et al. Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies.
11. Kimmel PL, Peterson RA, Weilkh KL et al. Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. Kidney Int 2000; 57: 2093–2098.

22. Riebeseboks R, Naua KJ, Honig A et al. The association of depressive symptoms with survival in a Dutch cohort of patients with end-stage renal disease. Nephrol Dial Transplant 2010; 25: 231–236.

33. Nagler EV, Webster AC, Vanholer R et al. Antidepressants for depression in stage 3–5 chronic kidney disease: a systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP). Nephrol Dial Transplant 2012; 27: 3736–3745.

24. Cuppari L, Garcia-Lopes MG. Hypovitaminosis D in chronic kidney disease patients: prevalence and treatment. J Ren Nutr 2009; 19: 38–43.

35. Martin A, David V, Quares M. Regulation and function of the FGFR3/Klotho endocrine pathways. Physiol Rev 2012; 92: 131–155.

46. Akmal M, Masory SG, Gotein DA et al. Role of parathyroid hormone in the glucose intolerance of chronic renal failure. J Clin Invest 1985; 75: 1037–1044.

57. Munoz Mendoza J, Isakova T, Ricardo AC et al. Fibroblast growth factor 23 and inflammation in CKD. J Am Soc Nephrol 2012; 7: 1155–1162.

68. Tooneen KN, Kingma KN, Boer TS et al. Protein intake during hemodialysis maintains a positive whole body protein balance in chronic hemodialysis patients. Am J Physiol Endocrinol Metab 2003; 284: E954–E965.

79. Pupim LB, Majchrzak KM, Flakoll PJ et al. Intradialytic oral nutrition improves protein homeostasis in chronic hemodialysis patients with uncontrolled nutritional status. J Am Soc Nephrol 2006; 17: 3149–3157.

90. Cockram DR, Heslewood MK, Rodriguez M et al. Safety and tolerance of medical nutritional products as sole sources of nutrition in people on hemodialysis. J Ren Nutr 1998; 8: 25–33.

101. Stratton RJ, Bircher G, Fouque D et al. Multinutrient oral supplements and tube feeding in maintenance dialysis: a systematic review and meta-analysis. Am J Kidney Dis 2005; 46: 387–405.

112. Lacson E Jr, Wang W, Zebrowski B et al. Outcomes associated with intradialytic oral nutritional supplements in patients undergoing hemodialysis: a quality improvement report. Am J Kidney Dis 2012; 60: 591–600.

123. Cheu C, Pearson J, Dahlerus C et al. Association between oral nutritional supplementation and clinical outcomes among patients with ESRD. Clin J Am Soc Nephrol 2012; 8: 100–107.

134. Chertow GM, Ling J, Lew NL et al. The association of intradialytic parenteral nutrition with survival in hemodialysis patients. Am J Kidney Dis 1994; 24: 912–920.

145. Mortelmans AK, Duyv P, Vanderbroucke J et al. Intradialytic parenteral nutrition in malnourished hemodialysis patients: a prospective long-term study. J Parenter Enteral Nutr 1999; 23: 90–95.

156. McCann LM, Foulks CJ. Nutritional recommendations for patients undergoing continuous peritoneal dialysis. Semin Dial 1992; 5: 136–141.

167. Cano NJ, Fouque D, Roth H et al. Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: a 2-year multicenter, prospective, randomized study. J Am Soc Nephrol 2007; 18: 2583–2591.

178. Garibotti G, Sofia A, Canepa A et al. Acute effects of peritoneal dialysis with dialysates containing dextrose or dextrose and amino acids on protein anabolism in renal failure patients on automated peritoneal dialysis. Am J Kidney Dis 2010; 56: 4095–4103.

189. Fouque D, Garibott G, Barrea A, Russo R et al. Effects of recombinant human growth hormone on muscle protein turnover in malnourished hemodialysis patients. J Clin Invest 1997; 99: 97–105.

200. Iglesias P, Diez JJ, Fernandez-Reyes MJ et al. Recombinant human growth hormone therapy in malnourished dialysis patients: a randomized controlled study. Am J Kidney Dis 1998; 32: 454–463.

211. Johannsson G, Bengtsson BA, Ahlmen. Double-blind, placebo-controlled study of growth hormone treatment in elderly patients undergoing chronic hemodialysis: anabolic effect and functional improvement. Am J Kidney Dis 1999; 33: 709–717.

222. Hansen TB, Gram J, Jensen PB et al. Influence of growth hormone on weight and regional soft tissue composition in adult patients on hemodialysis. A double-blind, randomized, placebo-controlled study. Clin Nephrol 2000; 53: 99–107.

233. Feldt-Rasmussen B, Lange M, Suluwicz W et al. Growth hormone treatment during hemodialysis in a randomized trial improves nutrition, quality of life, and cardiovascular risk. J Am Soc Nephrol 2007; 18: 2161–2171.

244. Pupim LB, Flakoll PJ, Yu C et al. Recombinant human growth hormone improves muscle amino acid uptake and whole-body protein metabolism in chronic hemodialysis patients. Am J Clin Nutr 2005; 82: 1235–1243.

255. Guebre-Egziabher F, Juillard L, Boirie Y et al. Short-term administration of a combination of recombinant growth hormone and insulin-like growth factor-I induces anabolism in maintenance hemodialysis. J Clin Endocrinol Metab 2009; 94: 2299–2305.

266. Kopple JD, Cheung AK, Christiansen JS et al. OPPORTUNITYtrade;: a large-scale randomized clinical trial of growth hormone in hemodialysis patients. Nephrol Dial Transplant 2011; 26: 4095–4103.

277. Fouque D, Guebre-Egziabher F, Laville M. Advances in anabolic interventions for malnourished dialysis patients. J Ren Nutr 2003; 13: 161–165.

288. Orr R, Fiatarone Singh M. The anabolic androgenic steroid oxandrolone in the treatment of wasting and cachectic disorders: review of efficacy and safety. Drugs 2004; 64: 725–750.

299. Bhasin S, Storer TW, Berman N et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996; 335: 1–7.

300. Basaria S, Wahlsom JT, Dobs AS. Clinical review 138: Anabolic-androgenic steroid therapy in the treatment of chronic diseases. J Clin Endocrinol Metab 2001; 86: 5108–5117.

311. Creutzberg EC, Wouters EF, Mostert R et al. A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. Chest 2003; 124: 1733–1742.

322. Gullete NP, Hebbard G, Ziegler TR. Update on clinical trials of growth factors and anabolic steroids in cachexia and wasting. Am J Clin Nutr 2010; 91: 1143S–1147S.

333. Johns K, Beddall MJ, Corin RC. Anabolic steroids for the treatment of weight loss in HIV-infected individuals. Cochrane Database Syst Rev 2005; 4: CD005483.

344. Grunewald DA, Matsmoto AM. Testosterone supplementation therapy for older men: potential benefits and risks. J Am Geriatr Soc 2003; 51: 101–115; discussion 15.

355. Gungor O, Kiricelli F, Carrero JJ et al. Endogenous testosterone and mortality in male hemodialysis patients: is it the result of aging? Clin J Am Soc Nephrol 2010; 5: 2018–2023.

366. Carrero JJ, Stenveinkel P. The vulnerable man: impact of testosterone deficiency on the urological phenotype. Nephrol Dial Transplant 2012; 27: 4030–4041.
118. Barton Pai A, Chretien C, Lau AH. The effects of nandrolone decanoate on nutritional parameters in hemodialysis patients. Clin Nephrol 2002; 58: 38-46.

119. Navarro JV, Mora C, Macia M et al. Randomized prospective comparison between erythropoietin and androgens in CAPD patients. Kidney Int 2002; 61: 1537–1544.

120. Gascon A, Belvis JJ, Berisa F et al. Nandrolone decanoate is a good alternative for the treatment of anemia in elderly male patients on hemodialysis. Geriatr Nephrol Urol 1999; 9: 67–72.

121. Macdonald JH, Marcora SM, Jibani MM et al. Progressive exercise for muscle wasting of chronic diseases. J Am Soc Nephrol 2002; 13: 1059–1068. J phase II dose-finding study. Nephron Clin Pract 2007; 105: c125-c135.

122. Johansen KL, Mulligan K, Schambelan M. Anabolic effects of nandrolone decanoate in patients receiving dialysis: a randomized controlled trial. JAMA 1999; 281: 1275–1281.

123. Kurella Tamura M, Covinsky KE, Chertow GM et al. Functional status of elderly adults before and after initiation of dialysis. N Engl J Med 2009; 361: 1539–1547.

124. Leikis MJ, McKenna MJ, Petersen AC et al. Exercise performance falls over time in patients with chronic kidney disease despite maintenance of hemoglobin concentration. Clin J Am Soc Nephrol 2006; 1: 488-495.

125. Ikizler TA, Himmelfarb J. Muscle wasting in kidney disease: let’s get physical. J Am Soc Nephrol 2006; 17: 2097–2098.

126. Kopple JD, Storer T, Casburi R. Impaired exercise capacity and exercise training in maintenance hemodialysis patients. J Ren Nutr 2005; 15: 44-48.

127. Painter P, Johansen KL. Improving physical functioning: time to be a part of routine care. Am J Kidney Dis 2006; 48: 167-170.

128. Koppell JD, Wang H, Casburi R et al. Exercise in maintenance hemodialysis patients induces transcriptional changes in genes favoring anabolic muscle. J Am Soc Nephrol 2007; 18: 2975–2986.

129. van den Ham EC, Koopman JP, Schols AM et al. The functional, metabolic, and anabolic responses to exercise training in renal transplant and maintenance hemodialysis patients. Transpl Int 2003; 16: 1058–1068. J phase II dose-finding study. Nephron Clin Pract 2007; 105: c125-c135.

130. Wang XH, Du J, Klein JD et al. Exercise ameliorates chronic kidney disease-induced defects in muscle protein metabolism and progenitor cell function. Kidney Int 2009; 76: 751–759.

131. Koopman R, van Loon LJ. Ageing, exercise, and muscle protein metabolism. J Appl Physiol 2009; 106: 2040-2048.

132. Zina EM, Yarasheski KE. Exercise treatment to counteract protein wasting of chronic diseases. Curr Opin Clin Nutr Metab Care 2003; 6: 87–93.

133. Cheema B, Abas H, Smith BC et al. Progressive exercise for anabolism in kidney disease (PEAK): a randomized, controlled trial. J Am Soc Nephrol 2011; 22: 437-442.

134. Macdonald JH, Marcora SM, Jibani MM et al. Progressive exercise for muscle wasting of chronic diseases. J Am Soc Nephrol 2002; 13: 1059–1068. J phase II dose-finding study. Nephron Clin Pract 2007; 105: c125-c135.

135. Wang XH, Du J, Klein JD et al. Exercise ameliorates chronic kidney disease-induced defects in muscle protein metabolism and progenitor cell function. Kidney Int 2009; 76: 751–759.

136. Koopman R, van Loon LJ. Ageing, exercise, and muscle protein metabolism. J Appl Physiol 2009; 106: 2040-2048.

137. Zina EM, Yarasheski KE. Exercise treatment to counteract protein wasting of chronic diseases. Curr Opin Clin Nutr Metab Care 2003; 6: 87–93.

138. Cheema B, Abas H, Smith BC et al. Progressive exercise for anabolism in kidney disease (PEAK): a randomized, controlled trial. J Am Soc Nephrol 2011; 22: 437-442.

139. Macdonald JH, Marcora SM, Jibani MM et al. Progressive exercise for muscle wasting of chronic diseases. J Am Soc Nephrol 2002; 13: 1059–1068. J phase II dose-finding study. Nephron Clin Pract 2007; 105: c125-c135.

140. Castaneda C, Gordon PL, Parker RC et al. Nandrolone decanoate is a good alternative for the treatment of anemia in elderly male patients on hemodialysis. Geriatr Nephrol Urol 1999; 9: 67–72.

141. Cheema BS, Abas H, Smith BC et al. Effect of resistance training during hemodialysis on circulating cytokines: a randomized controlled trial. European journal of applied physiology 2011; 111: 1437–1445.

142. Zhang L, Rajan V, Lin E et al. Pharmacological inhibition of myostatin suppresses systemic inflammation and muscle atrophy in mice with chronic kidney disease. FASEB J 2011; 25: 1653–1663.

143. Stenvinkel P. Can treating persistent inflammation limit protein energy supplementation in plasma amino acid concentrations and nutritional variables in non diabetic patients. Am J Clin Nutr 2000; 71: 765–773.

144. Cano N, Saito Y, Dupuy AM et al. Intradialytic parental nutrition: comparison of olive oil versus soybean oil-based lipid emulsions. Br J Nutr 2006; 95: 152-159.