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Diets and enteral supplements for improving outcomes in chronic kidney disease

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Abstract

Protein-energy wasting (PEW), which is manifested by low serum levels of albumin or prealbumin, sarcopenia and weight loss, is one of the strongest predictors of mortality in patients with chronic kidney disease (CKD). Although PEW might be engendered by non-nutritional conditions, such as inflammation or other comorbidities, the question of causality does not refute the effectiveness of dietary interventions and nutritional support in improving outcomes in patients with CKD. The literature indicates that PEW can be mitigated or corrected with an appropriate diet and enteral nutritional support that targets dietary protein intake. In-center meals or oral supplements provided during dialysis therapy are feasible and inexpensive interventions that might improve survival and quality of life in patients with CKD. Dietary requirements and enteral nutritional support must also be considered in patients with CKD and diabetes mellitus, in patients undergoing peritoneal dialysis, renal transplant recipients, and in children with CKD. Adjunctive pharmacological therapies, such as appetite stimulants, anabolic hormones, and antioxidative or anti-inflammatory agents, might augment dietary interventions. Intraperitoneal or intradialytic parenteral nutrition should be considered for patients with PEW whenever enteral interventions are not possible or are ineffective. Controlled trials are needed to better assess the effectiveness of in-center meals and oral supplements.

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Competing interests

K. Kalantar-Zadeh declares an association with Abbott Nutrition, B. Braun, National Kidney Foundation, Novo Nordisk, NutrePletion, Pentec Health. N. J. Cano declares an association with Baxter, B. Braun, Danone, Fresenius Kabi, Nestlé. C. Chazot declares an association with Fresenius Medical Care. C. Kovesdy declares an association with Abbott Nutrition. R. Mak declares an association with Abbott. R. Mehrotra declares an association with Baxter Healthcare. P. Stenvinkel declares an association with Abbott. T. A. Ikizler declares an association with Abbott Nutrition, Abbott Renal Care, Fresenius Medical Care, Renal Advantage. See the article online for full details of the relationships. The other authors declare no competing interests.

Author contributions

All the authors researched data to include in the manuscript, contributed to discussion of content for the article, reviewed and edited the manuscript before submission, and revised the manuscript in response to the peer-reviewers' comments.

Introduction

Overnutrition is a major problem in the general population and a serious risk factor for developing metabolic syndrome, cardiovascular disease and chronic kidney disease (CKD), with a subsequent increase in risk of mortality. By contrast, in patients with CKD, and especially in those undergoing maintenance dialysis, the so-called uremic malnutrition[1] (also referred to as protein-energy wasting [PEW])[2] is by far the strongest risk factor for adverse outcomes and death;[3] surrogates of overnutrition such as obesity or hyperlipidemia seem, counterintuitively, to be associated with increased survival.[4] Similar associations have been described in individuals with other chronic disease states, such as respiratory failure and heart failure,[5,6] or in the elderly population.[7] In CKD and other chronic diseases that are associated with wasting syndrome, it is believed that pathophysiological pathways associated with malnutrition are killers in the short-term and render risk factors such as obesity or hypertension practically irrelevant with regard to their contribution to mortality. In other words, patients undergoing dialysis die of the short-term consequences of PEW and do not live long enough to die of risk factors associated with overnutrition. This 'time-discrepancy hypothesis'[8] suggests that, in a patient with CKD whose risk of short-term mortality is high, interventions that improve nutritional status and prevent or correct wasting and sarcopenia have the potential to save lives, as compared with conventional interventions such as treating hypercholesterolemia, hypertension or obesity. Indeed, two randomized, controlled trials have shown that lowering cholesterol in patients on dialysis with hyperlipidemia has no effect on survival.[9,10] A 10-year cohort study in 206 patients undergoing hemodialysis indicated that serum albumin concentration was far superior as a predictor of mortality than inflammatory markers or intima–media thickness of the common carotid artery.[11] PEW seems, therefore, to be a strong predictor of mortality in patients with CKD, and improving nutritional status by dietary and non dietary interventions could be an important step towards improving outcomes in CKD. In this Review, we will focus on the dietary and enteral management of CKD as an important component of patient care. Parenteral and non dietary interventions, including adjunctive therapies, are also mentioned briefly.

PEW, mortality and albumin levels

Evidence indicates that surrogates of PEW, such as low serum levels of albumin or inadequate protein intake, correlate with mortality. Indeed, a low serum albumin concentration is by far the strongest predictor of poor outcomes and mortality, at least in patients on dialysis, when compared with any other risk factor,[12,13] including traditional risk factors (hypertension, hypercholesterolemia, diabetes mellitus, and obesity) or nonconventional risk factors (measures of anemia, mineral and bone surrogates, and dialysis modality).[3] The sensitivity of measuring serum levels of albumin to predict outcomes in patients with CKD is high, with a granularity of as little as 2 g/l or less (Figure 1).[14,15] In other words, a patient on dialysis with a baseline serum albumin concentration of 2 g/l above or below that of another patient with similar demographic features and comorbidities has a substantially decreased or increased risk of death, respectively.

The association between serum albumin levels and mortality is highly incremental and linear, and the mortality predictability of a serum albumin concentration of <40 g/l has virtually no cut-off level below which the association with death would cease or reverse.[14,15] This association is in sharp contrast to most other predictors of outcome in CKD, which have U-shaped or J-shaped survival associations. More importantly, changes in serum levels of albumin over time are associated with proportional and reciprocal alterations in the risk of mortality, in that an increase or decrease in serum albumin concentration of as little as 1 g/l over a period of a few months is associated with increased or decreased survival, respectively (Figure 2).[14] Similar predictors of mortality have been reported with

other nutritional markers, such as serum prealbumin concentration (<300 mg/l)[16,17] and a malnutrition–inflammation score of ≥5.[18] Nevertheless, measuring serum levels of albumin remains the simplest test that is readily available. Given all of the above, serum levels of albumin and prealbumin and other measures of nutritional status seem to be reliable indicators of performance measures in patients with CKD, especially if it can be shown that an increase in serum levels of albumin or prealbumin by feasible interventions would lead to an improvement in nutritional status and outcomes.

Hypoalbuminemia: marker of PEW or inflammation?—At any given time, approximately two-thirds of all patients on dialysis in the USA exhibit hypo albuminemia, that is, a serum albumin concentration of <40 g/l (based on the bromocresol green technique), which is used to diagnose PEW as suggested by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative.[19] Hypoalbuminemia is at least as prevalent in the early stages of CKD as in patients undergoing dialysis; a study of 1,220 patients with nondialysis-dependent CKD found that 74% of patients had a serum albumin concentration of <40 g/l, and 55% of patients had a concentration of <38 g/l.[20]

A low serum albumin concentration in patients with CKD could be related to non-nutritional conditions, such as inflammation, acute or chronic comorbidities or infectious events, and proteinuria, especially if residual renal function with marked proteinuria persists.[21] A study by de Mutsert *et al.*[22] reported that the mortality risk associated with low levels of albumin could partially be explained by levels of C-reactive protein, but less so by normalized protein catabolic rate or subjective global assessment. Indeed, anorectic patients who display no inflammation or cachexia may have normal serum levels of albumin.[23]

Although the debate continues as to whether low serum levels of albumin in patients with CKD are a surrogate of inadequate protein intake or other conditions related to PEW, such as inflammation or comorbidity,[21] there seems to be less disagreement regarding the consistent association of hypoalbuminemia with poor outcomes in dialysis patients and those with nondialysis-dependent CKD.[20] Reports indicate that patients attending dialysis clinics that provide superior care and have a good performance exhibit higher serum albumin levels and better survival rates than patients who attend clinics with an inferior performance.[12,24] Despite ongoing studies to determine whether serum albumin concentration is a nutritional marker or not, the actionability and responsiveness of serum albumin levels to nutritional interventions are far more relevant. Longevity has consistently been observed in those patients with CKD who have a better nutritional status, including larger muscle mass,[25,26] fat mass,[27] better appetite,[28,29] and higher protein intake.[30] One study has suggested that imposing dietary protein restrictions to control serum phosphorus levels might cause harm and increased mortality, especially if associated with decreased normalized protein catabolic rate and serum albumin levels;[31] this finding could explain paradoxical observations such as the observed increased survival of patients who do not adhere to the strict rules imposed by clinics that prohibit in-center food ingestion during dialysis therapy.[4]

Other nutritional markers of PEW—A serum prealbumin level of <300 mg/l is another indicator of PEW, and a strong predictor of outcome in patients with CKD.[16] Two studies have shown that a change in serum levels of prealbumin over time is associated with corresponding changes in survival of patients on dialysis.[16,17] One of these studies found that although baseline serum prealbumin concentration might not be superior to albumin in predicting mortality in hemodialysis patients, prealbumin concentrations of <200 mg/l are associated with an increased risk of mortality even in patients with normal albumin levels, and a decrease in serum prealbumin levels over 6 months is independently associated with an increased risk of death.[16] Other nutritional indicators that predict survival in patients on dialysis include serum transferrin levels[32,33] and nutritional scoring systems, such as

subjective global assessment[34] and the malnutrition–inflammation score, which also correlate with quality of life (Box 1).[18] Some biomarkers exhibit low levels in the setting of inflammation even without undernutrition.[35] However, among these biomarkers, serum albumin concentration is measured most frequently (at least monthly to quarterly in most countries in patients on dialysis), making it the most readily available biomarker of PEW.

Ameliorating the PEW–death association—Is the association between PEW and death causal or an epiphenomenon? Whereas the debate on causality has continued,[21,36,37] in our opinion a more clinically relevant and timely question is whether a nutritional intervention can increase serum albumin levels or correct PEW in patients with CKD, and by doing so, does survival and quality of life improve? We believe that the answer to both parts of the question is a cautious "yes" based on the experimental data,[38–44] despite the fact that no single well-designed randomized, controlled trial with adequate sample size has yet examined this simple question. Importantly, however, the field of nutritional support (such as nutrition for patients with terminal cancer, for patients who have undergone surgery, or geriatric or disabled populations) is based on the premise that provision of nutritional support improves the patient's immediate or short-term outcomes, independent of the cause of wasting and cachexia, whereas the long-term effects are less clear.[35] Although we do not deny the paucity of randomized, controlled trials and the difficulties surrounding the feasibility of nutritional interventions or testing their effects on hard outcomes,[45] we believe that inadequate nutritional support during hemodialysis treatments, which might have catabolic effects, is not consistent with good practice.

Dialysis meals and oral supplements

The recommended dietary energy intake (DEI) for patients undergoing hemodialysis and peritoneal dialysis is 30–35 kcal/kg per day.[19,46–49] Suggested mean dietary protein intake (DPI) is 1.2 g/kg per day in patients on hemodialysis, and 1.3 g/kg per day in patients on peritoneal dialysis.[19,46–49] Most patients on dialysis, however, have a lower DEI and DPI than the recommended intake. In 1,901 adult patients on the HEMO Study, the mean DEI and DPI were 23.2 ± 9.5 kcal/kg per day and 0.96 ± 0.43 g/kg per day, respectively, on nondialysis days, and 22.2 ± 9.6 kcal/kg per day and 0.90 ± 0.41 g/kg per day, respectively, on dialysis days.[50] Nutritional support for patients on dialysis should make it possible to ensure nutritional intake is in accordance with the current guidelines. 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, which makes it possible to meet the recommended targets of both DEI and DPI. To reach such energy and protein levels, oral supplements should be given two to three times a day, preferably 1 h after main meals. We have identified clinical trials with at least 10 participants in which the effects of enteral nutritional interventions were examined in malnourished patients on dialysis (Tables 1–4).[17,40,43,44,51–80] In most of these studies, enteral therapy was associated with improved nutritional status or other clinical outcomes.

Enteral nutrition for hemodialysis patients—Among hemodialysis patients, who comprise over 90% of all dialysis patients in the USA, PEW is common and associated with poor outcomes.[2] A prospective study by Caglar *et al.*[71] included 55 malnourished patients on hemodialysis who received conventional nutrition counseling for 3 months, followed by 6 months of thrice-weekly intake of a 237 ml oral nutritional supplement specifically designed for patients on dialysis (Nepro®, Abbott Nutrition, Columbus, OH, USA), which was provided during dialysis in the clinic to ensure adherence. Substantial increases in serum albumin and prealbumin concentrations were observed: from 33.3 ± 3.2 g/l and 261 ± 86 mg/l at baseline, to 36.5 ± 2.6 g/l and 307 ± 74 mg/l, respectively at 6 months.[71] In another in-center prospective controlled trial of 40 hemodialysis patients with hypo albuminemia (albumin concentration ≤38 g/l), 20 patients received Nepro® accompanied by

an additional liquid anti- inflammatory and anti-oxidative oral supplement that included borage oil and fish oil (Oxepa®, Abbott Nutrition).[40] After 4 weeks of thrice-weekly nutritional intervention during the hemodialysis treatment, the pre-trial serum albumin level of 34.5 ± 3.1 g/l increased to 36.8 ± 3.4 g/l ($P = 0.02$).[40]

Of the studies listed in Table 1, eight of nine randomized trials using serum albumin concentration as a surrogate outcome measure reported statistically significant improvements in hypoalbuminemia.[17,44,51–55,57] Serum albumin concentration did not considerably increase in the study by Fouque *et al.*,[56] but high serum levels of albumin and prealbumin were observed in those who achieved increased dietary protein intake. In the trial by Cano *et al.*,[17] 186 malnourished patients undergoing hemodialysis were randomly assigned to intradialytic parenteral nutrition versus no intradialytic parenteral nutrition, while both arms received oral supplements. Despite apparently negative results for intradialytic parenteral nutrition, serum levels of albumin and prealbumin increased in both groups treated with oral supple ment therapy, and greater survival was observed in those whose serum prealbumin concentration increased by >30 mg/l at 3 months.[17] These data underline the importance of measuring serum prealbumin levels in the follow-up of patients receiving nutritional support. Leon *et al.*[55] randomly assigned 180 patients on hemodialysis to usual care with targeting of specific nutritional barriers, including poor nutritional knowledge, poor appetite, help needed with shopping or cooking, low fluid intake, inadequate dialysis dose, depression, difficulty chewing or swallowing, gastrointestinal symptoms and acidosis. As part of the intervention, patients with a poor appetite or low fluid intake were given limited amounts of oral nutritional supplements, such as commercially available enteral nutrition drinks and cookies. After 12 months, patients in the intervention group had greater increases in serum albumin levels, energy intake and protein intake than the patients in the control group.[55]

Intradialytic nutrition for hemodialysis patients—Intradialytic and in-center nutrition deserve special comment. Inadequate food intake, especially on hemodialysis treatment days, is common among patients in the USA,[50] whereas meals are routinely served during hemodialysis treatment sessions in many other countries. Until the late 1980s, meals during dialysis were routine practice in the USA and some Veterans Administration hospitals still provide meal trays during dialysis shifts. However, some dialysis clinics in the USA have strict rules against food and drink intake during hemodialysis treatment. When nephrologists and dialysis care providers in the USA were asked as to why meal trays for patients do not exist during dialysis treatments, the most common answers were the following: postprandial hypotension; risk of choking or aspiration; infection control and hygiene issues, including fear of fecal–oral transmission of diseases (such as hepatitis A); increased staff burden and distraction; and diabetes mellitus and phosphorus control (Table 5).[81]

Meals and nutritional supplements are routinely offered, for free in most part, to the majority of out patients on hemodialysis in many European and South-East Asian countries. Dialysis patients in Germany invariably eat during their hemodialysis treatments and have higher serum levels of albumin and greater survival than their US counterparts.[82]

Advantages of in-center meals and supplements—Despite the concerns of nephrologists and dialysis care providers regarding meals during dialysis, over the past few years a number of dialysis clinics have provided and even encouraged oral nutritional supplement. This change in practice has coincided with the emergence of several studies indicating that provision of oral nutritional supplements with a high protein content during hemodialysis is associated with an increase in serum albumin levels.[71,83–85] In addition to improving nutritional status, providing in-center meals and/or oral nutritional supplements

also improves patient adherence and satisfaction. Patients might be more motivated to attend treatments sessions if they know that a meal will be provided. As many patients already ignore the regulations that prohibit eating in some dialysis clinics and still bring their own foods (including those with a high phosphorus content), dialysis clinics could provide a more appropriate food or supplement with a high protein content and low salt content, low phosphorus to protein ratio,[86] and low potassium content,[87] together with administration of a phosphate-binder regimen and multivitamins at the time of meal or ingested supplement. The educational value of the meal provided in the clinic could be an important influence on patient adherence to dietary recommendations.

Benefits of intradialytic nutrition—Strong evidence indicates that patients on dialysis are subject to multiple metabolic and nutritional derangements that lead to a chronic and persistent negative nutrient balance.[88] In addition, labor-intensive studies of protein turnover have indicated that the protein catabolic effects of hemodialysis treatment are profound, affecting the homeostasis of both whole-body and skeletal muscle protein.[89] Patients undergoing dialysis experience recurrent infections, acute cardiovascular events, and frequent hospitalizations, in addition to underlying comorbidities. These factors lead to inadequate nutrient supply, altered metabolism, and increased nutrient requirements, mimicking a state of near-starvation.[90] A commonly ignored reason for the observed nutrient deficiency is the inevitable loss of amino acids into the dialyzate during hemodialysis, which is equivalent to 6–8 g per dialysis session, or 6.5 kg per year.[91,92] If the aim of muscle protein catabolism during hemodialysis is to maintain plasma levels of amino acids[93] and to provide amino acid substrate for acute-phase protein synthesis,[94,95] oral supplementation of amino acids could be a simple and appropriate method to deliver amino acids to the splanchnic bed.[96]

The catabolic consequence of dialysis therapy can be mitigated, or even converted to, an anabolic state by provision of intradialytic nutritional supplementation, especially in the form of meals or oral supplements. Studies have been carried out that assess the acute physiological response to dialysis and administration of intradialytic oral supplementation, including stable isotope kinetic studies and those measuring readily available nutritional markers such as serum levels of albumin and prealbumin.[97,98] Veeneman *et al.*[98] examined whole-body protein metabolism by primed, constant infusion of L-[1-^{13}C]valine to ascertain whether consumption of a protein and energy-enriched meal improved protein balance during hemodialysis. Feeding changed the negative whole-body protein balance observed during fasting to a positive protein balance, and strongly improved whole-body protein balance, probably owing to the increased concentrations of amino acids in the blood.[98] In another study of protein turnover, Pupim *et al.*[83] showed that in eight malnourished patients undergoing hemodialysis, highly positive whole-body net protein balance during hemodialysis and improvement of skeletal muscle protein homeostasis was achieved with both intradialytic parenteral nutrition and an intradialytic oral nutritional supplement compared with during the control period. Oral therapy during hemodialysis resulted in persistent anabolic benefits for muscle protein metabolism in the posthemodialysis phase, whereas the anabolic benefits of intradialytic parenteral nutrition dissipated during the same period (Figure 3).[83] These data support both the anabolic and anticatabolic roles of intradialytic enteral nutritional support. Well-designed controlled trials are now needed to examine hard clinical end points such as survival.

Enteral nutrition during peritoneal dialysis—When devising a plan for enteral support for patients undergoing peritoneal dialysis, a few important factors need to be considered. First, peritoneal dialysis is associated with obligatory glucose absorption from the dialyzate, which provides 300–600 kcal per day over that obtained through the diet. These calories obtained through glucose depend on the peritoneal transport rate and dialysis

prescription, and partly compensate for the low oral energy intake of patients on peritoneal dialysis.[99] Second, patients on peritoneal dialysis lose 5–7 g of protein per day in the dialyzate effluent; these losses are substantially increased during episodes of peritonitis.[100,101] The peritoneal protein losses contribute, in part, to the lower serum levels of albumin and higher daily protein requirements observed in patients on peritoneal dialysis than in those treated with hemodialysis.[102] However, the protein losses are not large enough to make a substantial contribution to PEW.[99] Third, intraperitoneal administration of dialyzate has been shown to worsen gastric emptying, including in nondiabetic patients with end-stage renal disease, and could contribute to the inadequate oral intake as well as intolerance of oral supplements frequently seen in these patients.[103]

At least 10 studies of patients on peritoneal dialysis have examined the effect of oral nutritional interventions on measures of nutritional status.[44,53,54,57,74,76–80] Although these studies show mixed results, some generalizations can be made. First, in a single-meal study, administration of oral supplements did not lead to a substantial decrease in dietary intake.[79] This result indicates that oral supplements can increase the total daily energy and protein intake of patients on peritoneal dialysis. Second, a large proportion of patients are either intolerant to, or non adherent with, the supplement prescription;[44,53,76,78,80] in some studies this intolerance or nonadherence affected over 50% of the participants.[44,78] This high drop-out rate has led many studies to be underpowered to detect statistically significant improvements in PEW and also highlights the limitations in using oral supplements. Third, in adherent patients who were able to tolerate supplements, considerable improvements were seen.[53,54,76,80] For example, use of oral nutritional supplements in the randomized controlled trial by Teixidó-Planas *et al.*[80] resulted in substantial increases in triceps skinfold thickness, circumference of the mid-arm muscle, and lean body mass in the as-treated analysis. Fourth, studies that have examined high-biological-value supplements, such as calcium caseinate or egg albumin-based supplements, showed greater benefits than studies using standard oral supplements.[53,54,78,80] This difference could be explained, in part, by increased tolerance and therefore improved adherence to supplements. Taken together, these data indicate that an increase in enteral intake is feasible and could improve PEW in adherent patients on peritoneal dialysis.

Nutrition in CKD patients with diabetes

Although diabetes mellitus is independently associated with poor outcomes and increased mortality, the presence of CKD greatly increases the mortality rate,[104] indicating that CKD itself is a strong independent determinant of poor outcomes. Despite concerns regarding the glycemic burden of nutritional interventions in patients with diabetes mellitus, such considerations might have less relevance in malnourished patients on dialysis. Indeed, in approximately one-third of patients on dialysis with diabetes mellitus, a state of 'burnt-out diabetes' is observed in which frequent episodes of hypoglycemia necessitate a decrease or even total discontinuation of most or all diabetic medications, including insulin injections and oral hypoglycemic agents.[105,106] Many of these patients exhibit normal to low levels of hemoglobin A_{1c}, even without medication for diabetes mellitus and when they originally suffered from diabetic nephropathy as the etiology of their CKD.[107,108] Some studies have found no association between glycemic control and outcomes in patients on dialysis.[109,110] Hemodialysis sessions themselves can lead to moderate to severe intradialytic hypoglycemia.[111,112] Hypoalbuminemia and intradialytic hypotension were found to be the main predictors of intradialytic hypoglycemia in patients with diabetes mellitus undergoing hemodialysis in one study.[111] Therefore, in the USA and many other countries, the dialyzate bath includes high concentrations of glucose (11.1 mmol/l) to avoid hypoglycemia during hemodialysis.[112] In our opinion, a history of diabetes mellitus is not a contraindication for oral nutritional therapy or meals during hemodialysis, and should not be a reason to

withhold nutritional interventions, especially among dialysis patients with hypo albuminemia and normal to low levels of hemoglobin A_{1c}.

Nutritional therapy and ketoanalogues

PEW is also common in patients with nondialysis-dependent CKD,[3] in whom a decline in protein and calorie intake usually develops when glomerular filtration rate (GFR) falls to <25–35 ml/min/1.73 m^2,[113] although such changes may start when the GFR is as high as 55 ml/min/1.73 m^2.[114] Although the influence of actual protein and energy intake on outcomes is not well-studied in patients with nondialysis-dependent CKD, various biochemical markers of nutrition and inflammation correlate with increased mortality and rates of cardiovascular events (Figure 4).[20,115–117] Enteral protein intake has, however, not been well-examined as a therapeutic strategy in this patient population, largely because of the belief that a low intake of protein is necessary to slow the progression of CKD and improve outcomes.[118,119] A high intake of protein could affect GFR through various mechanisms, including alterations of glomerular hemodynamics.[120] Restricted protein intake (for instance <0.8 g/kg per day or even <0.6 g/kg per day[121–124] as compared with the 1.2 g/kg per day that is recommended for patients on dialysis), in particular in combination with keto analogues of amino acids, has been used successfully to delay the progression of CKD in some,[125,126] but not all,[127,128] studies. The benefit of a low protein diet might, at least in part, be related to its low phosphorus content,[121,122] as a decreased phosphorus burden can slow the progression of renal failure and improve other outcomes in indivi duals with nondialysis-dependent CKD.[129–131]

Whereas a low protein diet can be implemented by adhering to dietary restriction, manufactured disease-specific and hypercaloric oral supplements can improve management of CKD without causing malnutrition. However, very few studies have examined the use of oral nutritional supplements in patients with nondialysis-dependent CKD. In a Spanish study of 22 patients with non dialysis-dependent CKD on a low protein diet (0.6 g/kg per day), half the patients also received a portion of their prescribed dietary proteins and calories via a low protein and hypercaloric supplement for 6 months.[132] In the group receiving the oral supplement, the nutritional measures were better and their protein intake seemed to be closer to the target low protein diet objective than that of the control group. Patients receiving the supplement also had better adherence and a smaller decrease in renal function than the control group.[132]

The Modification of Diet in Renal Disease study examined the effect of a low protein diet versus a very low protein diet supplemented with keto acids and amino acids on GFR and on the incidence of end-stage renal disease and death.[133] Intention to treat analyses did not indicate any benefit with the very low protein diet.[133] In a series of *post hoc* analyses of the Modification of Diet in Renal Disease study, a lower achieved protein intake (0.5–1 g/kg per day) was associated with slowing of the progression of CKD,[134] but the very low protein diet supplemented with a mixture of essential keto acids and amino acids (0.28 g/kg per day) compared with a low protein diet (0.58 g/kg per day) was associated with increased mortality and accelerated progression of renal failure.[135] As it is unclear why some patients achieved low protein intake but others did not,[134,135] these results might not be construed as conclusive evidence towards the benefit or harm of a low protein diet with or without ketoanalogues. Nevertheless, enthusiasm about the use of ketoanalogues seems to be increasing,[136–140] as reflected in a consensus statement that mentions bene ficial effects that include: a decrease in uremic toxins; reduced protein uria; salutary effects on mineral and bone disorders and on lipid profile; as well as a potential delay in the progression of kidney disease and dialysis initiation with reduced likelihood of engendering malnutrition.[141] We believe that ketoanalogues could have a role in the treatment of patients with nondialysis-

dependent CKD, especially if combined with a tailored low protein diet with high-biological-value supplements or oral nutritional supplements specifically designed for this patient population.[132] Emerging data indicate that in patients on peritoneal dialysis, ketoanalogues could contribute to preserving residual renal function,[136] although their role in the treatment of patients on maintenance hemodialysis with minimal residual renal function is questionable. Caution with regard to the use of ketoanalogues should be exercised even in patients on peritoneal dialysis as long-term safety of these dietary regimens in the clinical setting has not yet been established.

Nutritional therapy in transplant recipients

After a successful renal transplantation with a functioning allograft, patients normally experience a dramatic increase in appetite and weight gain.[142,143] However, in many transplant recipients, especially in those with chronic allograft nephropathy, a worsening nutritional status is observed similar to that seen in patients with nondialysis-dependent CKD. Several specific factors relating to transplantation can potentially induce PEW in kidney transplant recipients in addition to conditions related to uremia. The immune response to the graft, the frequency and severity of rejection events, the degree of impaired renal function, and the use of immunosuppressive regimens might all contribute to the pathways that cause PEW.[144] The deleterious effects of PEW on clinical outcomes might be mediated by the inflammatory response, leading to worsening anemia,[145] erythropoietin hyporesponsiveness[146] and *de novo* diabetes mellitus.[147] Examining the nutritional status of transplant recipients and the influence of a transplant on clinical outcomes has been hampered by a lack of clinically applicable and standardized methods to assess the presence of PEW in these patients.

Investigators of a cohort study of 993 prevalent renal transplant recipients examined the relationship between nutritional status by means of assessing the malnutrition–inflammation score and relevant clinical indicators.[144] The malnutrition–inflammation score negatively correlated with abdominal circumference and positively correlated with markers of inflammation, including serum levels of C-reactive protein, interleukin 6, and tumor necrosis factor; the malnutrition–inflammation score reflected both PEW and inflammation in kidney transplant recipients.[144] Emerging data indicate that a poor nutritional status before or after renal transplantation is associated with poor outcomes, including increased mortality and reduced graft survival.[148–151] We recommend, therefore, that the same enteral nutritional support should be given to transplant recipients as for patients with nondialysis-dependent CKD.

Enteral nutrition in children with CKD

PEW often presents as growth retardation in children with CKD. One of the major goals in the treatment of infants and children with CKD is to achieve normal growth and development. Even fairly mild CKD can cause substantial anorexia in children.[152] Poor growth owing to inadequate food intake has been observed in infants with a GFR as high as 70 ml/min/1.73 m^2.[153] Meeting normal nutritional requirements in infants with CKD can be difficult: the nutrition care plan requires frequent monitoring and adjustments in response to changes in the child's nutritional status, age, development, anthropometrics, food preferences, residual renal function, renal replacement therapy, medications, and psychosocial status.[154] In the majority of cases, infants with severe CKD will require tube feeding.[155] Certain formulas, such as Good Start® (Nestlé, Vevey, Switzerland) and Similac® PM 60/40 (Abbott Nutrition), contain low amounts of phosphorus and potassium and are preferred for some infants with CKD. To meet requirements, commercial carbohydrate and/or fat products can be added to feedings to increase their standard energy density from 20 kcal/oz or 0.67 kcal/ml to as high as 60 kcal/oz or 2 kcal/ml without

substantially increasing electrolyte and mineral content. A gradual increase in energy density often improves tolerance.

Infants and children with CKD who experience anuria and polyuria have very different food and fluid requirements from those who do not have these conditions. Both these subsets of children require adequate nutrition to maximize growth. Children with polyuria may be given and maintained on a diluted formula and undergo pre-emptive kidney transplantation, thus never requiring dialysis. However, it is important to monitor the amount of nutrients being delivered to infants with polyuria. Those who are oliguric or anuric often require frequent (sometimes daily) dialysis to offset the large-volume feeds that occur with standard formulas. In the absence of pediatric renal feeding supplements, adult renal products that are available with normal and reduced protein content, and designed to be calorie dense and low in minerals and electrolytes, can be recommended for children who are aged >4 years; these adult supplements have also been successfully used at diluted strength in children aged <1 year.[156] A study showed that children with CKD and hyperkalemia demonstrated improved growth rates while receiving adult renal formulas, which were well-tolerated and effective in lowering potassium exposure.[157]

The early anticipation and correction of PEW, especially in infants, is important to avoid loss of growth potential. Initial studies demonstrated that growth of infants with CKD is compromised when energy intake falls below 80% of the recommended daily allowance.[158] Increasing energy intake to the recommended daily allowance can increase weight gain and stabilize growth rates in children of all ages and achieve catch-up growth in infants who are treated before they reach 2 years of age.[159] According to some studies, however, the energy requirements of children with CKD have not been shown to differ from healthy children,[160] nor is there evidence that children with CKD will show improved growth if their intake exceeds recommended amounts for healthy children.[154] Growth hormone therapy is indicated and widely accepted for treatment of growth retardation in children with CKD, but its use is only justified after ensuring adequate nutritional management.[161,162] Given the importance of growth and development in children, we encourage monitored in-center enteral nutrition therapy for all infants and children who require maintenance dialysis treatment.

Beyond protein and calorie control

Enteral nutritional support can provide a variety of macronutrients and micronutrients in addition to calories and protein. Earlier studies examined the effect of essential amino acid supplementation on the nutritional status of patients with CKD.[43,44,51,58–60,69,70] Supplemental fish oil and other sources of omega 3 fatty acid have been tested. In a randomized trial by Tietze *et al.*,[62] fish protein (8 g daily) and fish-based ingredients were tested for up to 6 months with some success. Kalantar-Zadeh *et al.*[40] supplemented a thrice-weekly CKD-specific supplement with an additional 237 ml can of fish oil, borage oil, and other antioxidative and anti-inflammatory ingredients (originally designed for patients with acute pulmonary failure[163]). Fanti *et al.*[73] showed that an oral soy isoflavone supplement taken for 8 weeks lowered serum levels of C-reactive protein in patients undergoing hemodialysis. In a randomized trial, Ewers *et al.*[164] examined the effects of oral unsaturated fat for 6 weeks in 14 patients undergoing hemodialysis and found that levels of C-reactive protein were decreased. Native (nutritional or inactive) vitamin D compounds, such as cholecalciferol, and other antioxidative vitamins can also be used in the form of multivitamins or as added ingredients to oral nutritional supplements.[40] Other under-utilized and as yet undiscovered dietary and pharmacological ingredients are likely to be used as adjunct to conventional calorie and protein in the future.

Nonenteral nutritional interventions

In addition to meals and nutritional supplements during hemodialysis, there are other potential interventions to improve the nutritional status of patients, including appetite stimulants with or without antidepressant properties (megesterol,[165] ghrelin,[166] and mirtazapine[167]), anabolic hormones (testosterone) and growth factors,[168] and anti-oxidative and anti-inflammatory agents (pentoxifylline and cytokine modulatory agents) (Box 2).[169,170] In patients undergoing hemodialysis with severe hypoalbuminemia (albumin concentration <30 g/l) who do not improve with oral interventions, even with adjunctive pharmacological therapy, or those in whom enteral interventions are not possible, parenteral interventions such as intradialytic parenteral nutrition should be considered.[97,171] Intradialytic parenteral nutrition is especially effective in patients with such low serum albumin values.[39] Finally, non-nutritional interventions, such as dialysis treatment modalities and techniques that lead to decreased inflammation or protein loss, should also be considered.[172,173]

Conclusions

In patients with CKD, PEW is a condition that is distinct from undernutrition and is associated with inflammation, increased resting energy expenditure, low levels of albumin and prealbumin, sarcopenia, weight loss and poor clinical outcomes. Although the debate on the relative contribution of inflammation versus malnutrition to the development of PEW continues, dietary interventions and nutritional support seem effective in mitigating or correcting PEW and improving outcomes in patients with CKD. Another ongoing debate is that regarding the recommendation of low protein intake with or without amino acid supplementation or ketoanalogues for patients with nondialysis-dependent CKD.[174] Based on the data discussed in this Review, we suggest provision of maintenance meals and dietary supplements during each hemodialysis session and visit to the dialysis clinic. A maintenance regimen can ensure adequate protein intake and reinforce similar dietary habits at home. If serum levels of albumin remain <40 g/l despite maintenance meals or oral supplements, then the intensity of the dietary protein intake should be increased and other potential causes of hypoalbuminemia, such as persistent inflammation and urinary albumin losses, should be examined. Alternatively, tube feeding can be considered in those not capable of swallowing or at high risk of aspiration. Several ongoing randomized, controlled trials are examining the role of CKD-specific oral nutritional support[175] or in-center meals during hemodialysis, with a focus on phosphorus control.[176] We recommend that all patients with CKD are assessed periodically (monthly or quarterly) for the presence of PEW and be offered oral nutritional support following the algorithm shown in Figure 5. We also recommend the frequent intake of small amounts of protein-rich liquid oral supplement with prescribed pills to replace water, which has been shown to improve outcomes in elderly individuals and those in nursing homes.[177]

As we move towards longer hemodialysis sessions,[178] and in anticipation of drastic changes in practice patterns as a result of implementation of the expanded bundle payment system in the USA, we need to rethink meals and oral supplements provided during dialysis therapy. Although meals during dialysis are routine practice in Europe and most other countries, the majority of patients on dialysis in the USA are deprived of nutritional intervention during dialysis. The consistent strong association of nutritional status, and in particular serum albumin levels, with survival in patients with CKD has been clearly shown. Given the fact that the provision of meals and oral supplements would require only a small fraction of the funds currently used for the expensive medications given to patients on dialysis with no proven outcome modification,[179] providing meals or oral nutritional supplements and other nutritional interventions to patients with CKD is the most promising way to increase serum albumin concentration and improve longevity and quality of life in this patient population.

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Key points

■ Protein-energy wasting (PEW) is common in patients with chronic kidney disease (CKD) and is manifested by low serum levels of albumin or prealbumin, sarcopenia, and weight loss

■ PEW is one of the strongest predictors of mortality in patients with CKD

■ Although PEW might be the result of non-nutritional conditions, dietary interventions such as enteral feeding with high-protein meals or supplements might improve nutritional status and outcomes

■ In-center meals and oral supplements during dialysis therapy and at home are inexpensive interventions that might improve survival and quality of life in patients with CKD

■ Adjunctive pharmacological therapies, such as appetite stimulants, anabolic hormones, and antioxidative or anti-inflammatory agents, might augment dietary interventions

■ Intraperitoneal or intradialytic parenteral nutrition should be considered for patients with PEW whenever enteral interventions are not possible or ineffective

Box 1 Diagnostic criteria for PEW and enteral nutrition in patients with CKD

Biochemical markers

- Serum albumin concentration <40 g/l for hemodialysis patients, or <38 g/l for peritoneal dialysis patients and patients with nondialysis-dependent CKD*
- Serum prealbumin concentration <300 mg/l (for maintenance dialysis patients)‡
- Serum transferrin concentration <1.85 μmol/l (or total iron-binding capacity <2.46 μmol/l)
- Serum levels of total cholesterol <2.59 mmol/l

Body mass

- BMI <23 kg/m^2§
- Unintentional loss of dry weight over time: 5% over 3 months or 10% over 6 months
- Total body fat percentage <10%‖

Muscle mass

- Sarcopenia: reduced lean body mass >5% over 3 months or >10% over 6 months
- Reduced mid-arm muscle circumference (<10th percentile)¶
- Low serum creatinine concentration (adjusted for renal status), or low calculated creatinine appearance#

Dietary intake (unintentionally low)**

- Dietary protein intake <1.0 g/kg per day for dialysis patients, or <0.5 g/kg per day for patients with nondialysis-dependent CKD
- Dietary energy intake <25 kcal/kg per day for at least 2 months
- Relative anorexia: Subjectively reported poor appetite

Nutritional scoring systems

- Malnutrition–inflammation score ≥5[180]
- Subjective global assessment and its modifications (Dialysis Malnutrition Score[181] and Canada–USA Study[182]) in the malnourished range
- Other scoring tools in the malnourished range[183–185]

*Serum albumin levels are based on bromocresol green. Use of bromocresol purple can result in low values. ‡These values may be considered within the normal range in patients with nondialysis-dependent CKD or in other patient populations. §Racial and ethnic variations should be considered; e.g. low BMI ranges might be considered within the acceptable range in Asian patients with CKD. Weight must be edema-free body mass (e.g. postdialysis dry weight). ‖Distinction between subcutaneous and visceral fat should be considered. ¶In relation to the 50th percentile of a reference population. #In patients undergoing thrice-weekly hemodialysis who have minimal residual renal function a low predialysis serum creatinine concentration of <442 μmol/l could be a sign of sarcopenia. Creatinine appearance is influenced by both muscle mass and meat intake. **Assessed by dietary diaries and interviews; protein intake in patients on dialysis can be estimated by calculation of normalized protein equivalent of total nitrogen appearance as determined

by urea kinetic measurements. Abbreviations: CKD, chronic kidney disease; PEW, protein-energy wasting.

Box 2 Improving nutritional status in dialysis patients

Oral nutritional interventions

- Meals during dialysis treatment
- Oral nutritional supplements
- Tube feeding (via temporary nasogastric tubing or percutaneous endoscopic gastrostomy)

Parenteral or peritoneal nutrition

- Intradialytic parenteral nutrition
- Intraperitoneal nutrition
- Total parenteral nutrition

Pharmacological

- Appetite stimulants
- Promotility agents in patients with gastroparesis
- Antidepressants
- Anti-inflammatory and/or antioxidative agents
- Anabolic and/or muscle-enhancing agents

Other interventions

- Dialysis technique
- Dialysis treatment factors
- Improving dental health, including use of dentures

Review criteria

We reviewed the literature to identify all clinical trials with at least 10 participants in which the effects of enteral (oral or tube-feeding) nutritional interventions were examined in malnourished patients with chronic kidney disease. Both the PubMed and Google Scholar databases were searched for all studies published or reported in English or with an English abstract since 1970. One paper in Spanish was considered relevant and translated into English. Full-text articles deemed pertinent were selected and the reference lists of the identified reports and articles were searched for further material.

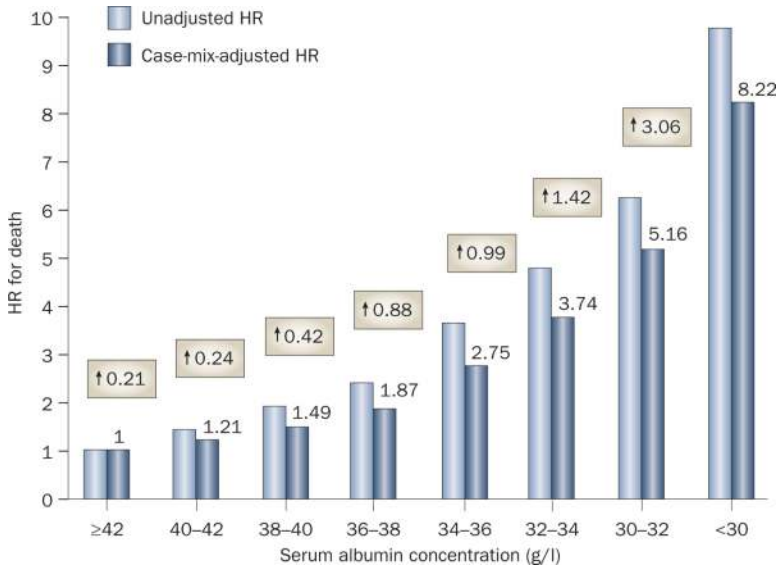

Figure 1.

Baseline serum albumin concentration and survival in patients on hemodialysis. Mortality predictability of 3-month averaged serum albumin levels in 58,058 patients on hemodialysis from 524 DaVita dialysis facilities in the USA. Case-mix-adjusted covariates included age, sex, diabetes mellitus, African-American race, Hispanic ethnicity, and dialysis vintage. The arrows and numbers indicate the incremental increase in mortality risk compared with the previous group. Abbreviation: HR, hazard ratio. Data obtained from Kalantar-Zadeh, K. *et al. Nephrol. Dial. Transplant.* **20**, 1880–1888 (2005).

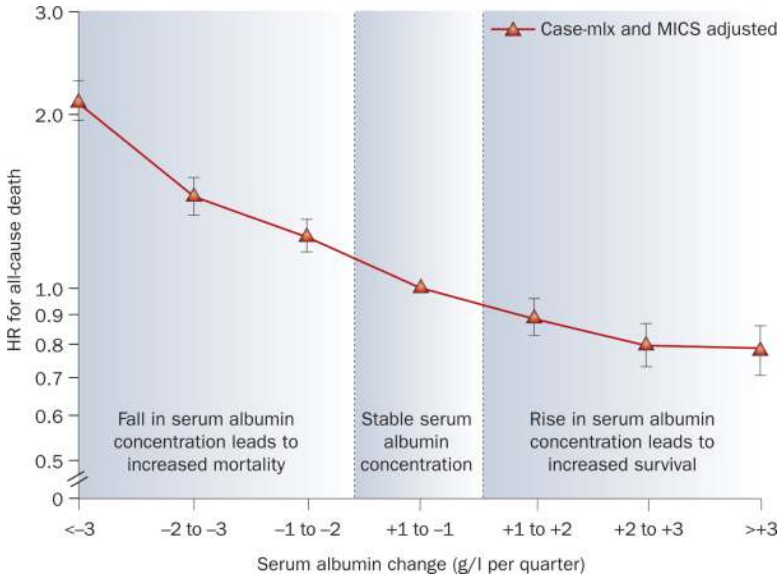

Figure 2.

Change in serum albumin levels and survival in hemodialysis patients. Association of the change in serum albumin concentration over two consecutive calendar quarters with subsequent mortality over 2 years in 30,827 patients on maintenance hemodialysis. Abbreviations: HR, hazard ratio; MICS, malnutrition– inflammation complex syndrome. Kalantar-Zadeh, K. *et al.* Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction. *Nephrol. Dial. Transplant.* (2005) **20** (9), 1880–1888 © by permission of Oxford University Press.

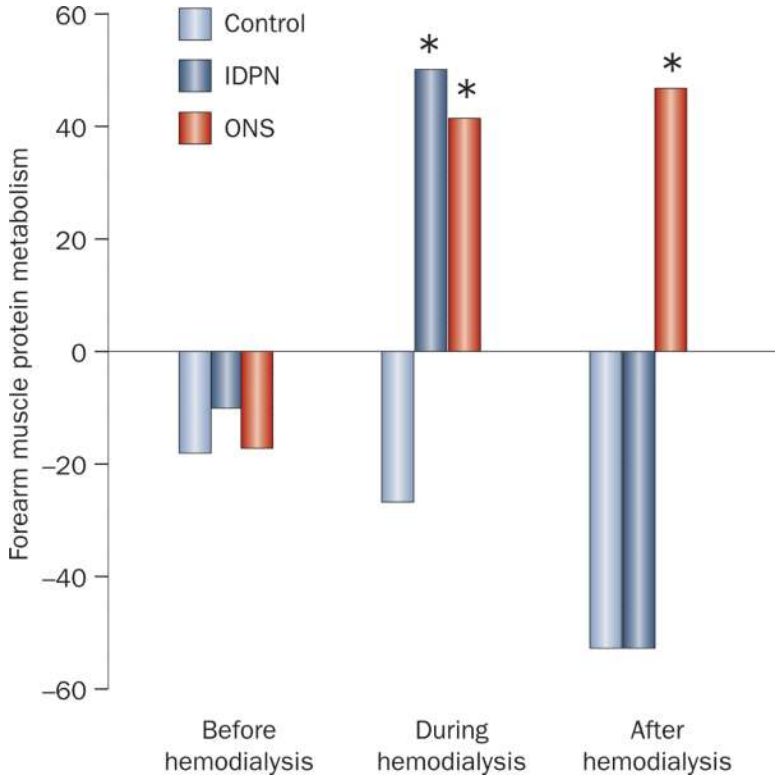

Figure 3.

Effect of nutritional therapy modality on forearm muscle homeostasis. Metabolism of forearm muscle protein before, during and after hemodialysis, comparing controls, IDPN, and ONS in eight patients with deranged nutritional status. Skeletal muscle protein homeostasis during hemodialysis improved with both IDPN and ONS versus control (P = 0.005 and P = 0.009, respectively). ONS resulted in persistent anabolic benefits in the posthemodialysis phase when anabolic benefits of IDPN had dissipated. *P <0.05 versus control. Abbreviations: IDPN, intradialytic parenteral nutrition; ONS, oral nutritional support. Data obtained from Pupim, L. B., Majchrzak, K. M., Flakoll, P. J. & Ikizler, T. A. *J. Am. Soc. Nephrol.* **17**, 3149–3157 (2006).

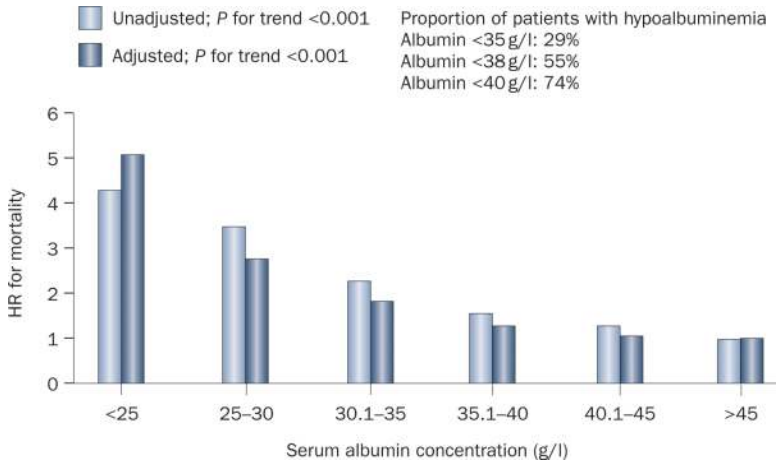

Figure 4.

Serum albumin concentration and survival in patients with nondialysis-dependent CKD. Unadjusted and multivariable-adjusted all-cause mortality associated with various categories of serum albumin level in 1,220 US veterans with nondialysis-dependent CKD. Most patients had CKD stage 3 (56%) and stage 4 (30%), with fewer patients having CKD stage 1 (1%), stage 2 (7%), and stage 5 (5%). Adjustments were made for age, race, Charlson comorbidity index, etiology of CKD, diabetes mellitus, cardiovascular disease, smoking, systolic and diastolic blood pressure, BMI, estimated glomerular filtration rate, serum levels of calcium, phosphorus, hemoglobin, bicarbonate, cholesterol, and 24 h urine protein. Abbreviations: CKD, chronic kidney disease; HR, hazard ratio. Permission obtained from Kovesdy, C. P., George, S. M., Anderson, J. E. & Kalantar-Zadeh, K. *Am. J. Clin. Nutr.* **90**, 407–414 (2009).

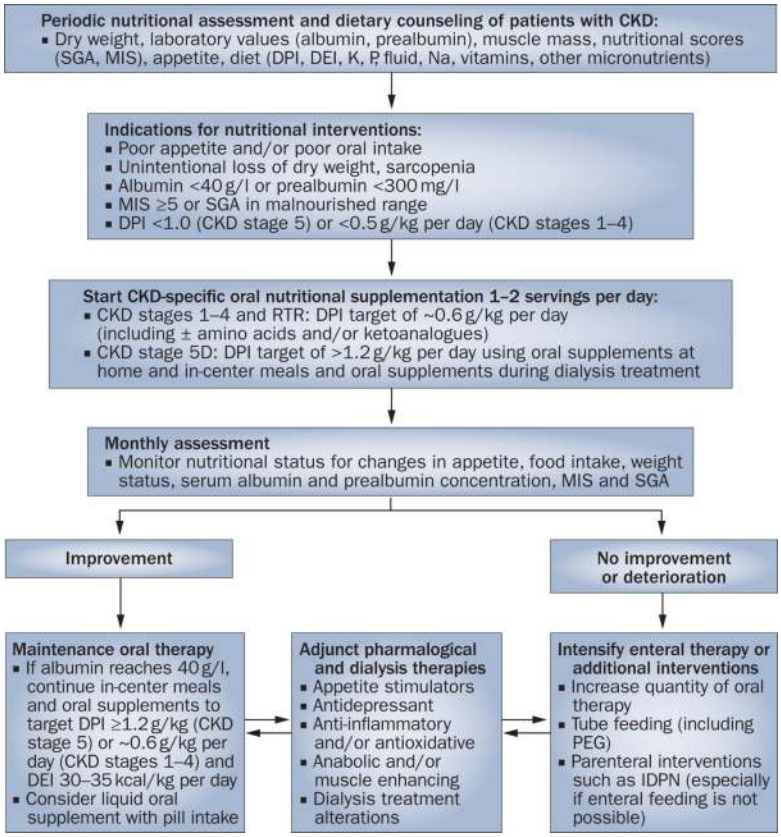

Figure 5.

Proposed algorithm for enteral nutritional support in patients with CKD. The target of total protein intake should be a DPI of ≥1.2 g/kg per day for patients on dialysis, and 0.6 g/kg per day for patients with nondialysis-dependent CKD, including renal transplant recipients. Abbreviations: CKD, chronic kidney disease; DEI, dietary energy intake; DPI, dietary protein intake; IDPN, intradialytic parenteral nutrition; K, potassium; MIS, malnutrition–inflammation score; Na, sodium; P, phosphorus; PEG, percutaneous endoscopic gastrostomy; RTR, renal transplant recipient; SGA, subjective global assessment.

Table 1

Randomized trials of nutritional support in patients undergoing hemodialysis or peritoneal dialysis*

Study	Intervention modality, study design and duration	Patients and condition (*n*)	Results and conclusions
Laorpatanaskul *et al.* (1991)[51]	EAA (6.3 g per day vs none) over 12.3 months	HD (15)	Increased BMI, triceps skinfold thickness, mid-upper-arm circumference, serum albumin level, plasma EAA levels, appetite, well-being Decreased serum triglyceride levels Well-tolerated without adverse effects
Eustace *et al.* (2000)[44]	EAA (3.6 g with meals three-times daily) vs placebo for 3 months	HD/PD (47) Albumin concentration ≤38 g/l	Serum albumin concentration in HD patients (EAA vs placebo) increased by 2.2 g/l (P=0.02) Improvement in grip strength and SF-12® mental health Correlation between baseline CRP levels and improvement in albumin levels (r = 0.83)
Sharma *et al.* (2002)[52]	CKD-specific ONS (Reno care II, Criticare, Mumbai, India) 500 kcal and 15 g protein vs standard home-prepared ONS (500 kcal and 15 g protein) vs routine care for 1 month	HD (40) Case (10 and 16) Control (14) Baseline albumin concentration 34 g/l	Improved functional status Signifcant increase in albumin concentration in the groups receiving CKD-specifc ONS and home-prepared ONS vs routine care (39 g/l and 40 g/l vs 35 g/l, respectively) Mild hyperphosphatemia observed, but no intolerance
Aguirre Galindo *et al.* (2003)[53]	Malnourished patients received 1.4 g/kg protein and 35 kcal/kg per day for 4 months Group A: 100% natural protein Group B: 50% calcium caseinate + 50% natural protein	PD (100) Group A (50) Group B (50)	Albumin changes: Group A: 28.7 ± 4.3 g/l to 30.4 ± 3.9 g/l Group B: 26.6 ± 5.6 g/l to 31.2 ± 4.1 g/l (P<0.05) In group B, a constant increase in serum albumin levels of 0.0019 g/l in every month of treatment with calcium caseinate was observed (P<0.01)
González-Espinoza *et al.* (2005)[54]	Egg albumin-based ONS; open-label controlled trial with 6-month follow-up	PD (28) Case (13) Control (15)	Serum albumin levels increased from 26.4 g/l to 30.5 g/l in the study group vs 26.6 to 28.0 g/l in the control group DPI, DEI and nPNA increased significantly more in the study group than in the control group Malnutrition decreased 6% in the control group vs 28% in the study group Most important predictors of serum albumin concentration: egg albumin-based ONS and DPI (P<0.05)
Leon *et al.* (2006)[55]	Targeting several nutritional barriers (ONS was a small component of intervention) for 12 months	HD (180) Albumin concentration <37 g/l	Albumin levels: +2.1 g/l in intervention group vs +0.6 g/l in control group (P<0.01) DEI: +4.1 kcal/kg per day in intervention group vs -0.6 kcal/kg per day in control group (P<0.001) DPI: +0.13 g/kg per day in intervention group vs -0.06 g/kg per day in control group (P<0.001) No relationship between change in albumin levels and inflammatory markers
Cano *et al.* (2007)[17]	ONS vs ONS + IDPN for 1 year ONS: 5.9 kcal and 0.39 g protein per day IDPN: 6.6 kcal and 0.26 g protein per day	HD (186) ONS (93) ONS + IDPN (93)	After 3 months: increased BMI, serum albumin levels, and prealbumin levels in both groups (P<0.01), independent from CRP No between-group difference An increase in serum prealbumin levels of >30 mg/l within 3 months predicted improved 2-year survival, hospitalization rate and Karnofsky score in all patients
Fouque *et al.* (2008)[56]	CKD-specific ONS (Renilon®, Nutricia, Schiphol, The Netherlands) vs standard care for 3 months	HD (86) Case (46) Control (40) Baseline albumin concentration 35.2 g/l in both groups	Increased DPI (P<0.01) and DEI (P<0.01), and improved subjective global assessment and quality of life (P<0.05) in the group receiving ONS No difference in albumin or prealbumin levels between groups, but any change in albumin and prealbumin levels correlated with protein intake Phosphatemia was unaffected and use of phosphate binders remained stable or decreased
Moretti *et al.* (2009)[57]	Standard ONS (Proteinex®, Llorens, Miami, FL, USA)	HD/PD (49)	Serum albumin levels increased from 34.9 g/l to 35.2 g/l (P=0.03) at 3 months in the group receiving ONS

Study	Intervention modality, study design and duration	Patients and condition (*n*)	Results and conclusions
	for 1 year; crossover controlled trial		The control group experienced a significant decrease in albumin levels, from 33.5 g/l to 31.9 g/l (P= 0.01) nPCR increased by month 4 of treatment from 1.05 to 1.16 in the ONS group (decreased from 1.11 to 0.98 during the first 6 months in the control group)

*Crossover studies were excluded unless stated otherwise. Abbreviations: CKD, chronic kidney disease; CRP C-reactive protein; DEI, dietary energy intake; DPI, dietary protein intake; EAA, essential amino acid; HD, hemodialysis; IPDN, intradialytic parenteral nutrition; nPCR, normalized protein catabolic rate; nPNA, nonprotein nitrogen appearance; ONS, oral nutritional supplement; PD, peritoneal dialysis; r, coefficient of correlation.

Table 2

Nonrandomized trials in patients undergoing hemodialysis (before 2000)*

Study	Intervention modality, duration and study design	Patients and condition (*n*)	Results and conclusions
Hecking *et al.* (1978)[58]	EAA (15.7 g per day) for 3 months; double-blind crossover	HD (13) 1 g protein per kg body weight per day	Increased urea, uric acid, lysine, complement component 3 Decreased phenylalanine A liberal diet of 1 g protein per kg body weight is sufficient in HD patients EAA offers no advantage
Phillips *et al.* (1978)[59]	EAA for 1 month, follow-up for 3 months	HD (16) Usual diet 60-100 g protein per day	Increased levels of EAA and serum albumin Decreased plasma levels of EAA in HD patients can be corrected successfully with oral EAA supplements
Acchiardo *et al.* (1982)[60]	EAA (6.6 g per day + 660 kcal per day) vs calories alone (660 kcal per day) over 105 days	HD (15) EAA + calories (7) Calories alone (8)	Increased hematocrit, total protein, levels of albumin and transferrin, T-lymphocyte count and bone density in the EAA group Non-EAA did not show any benefit
Allman *et al.* (1990)[61]	Polycose® (Abbott Nutrition, Columbus, OH, USA) glucose polymer (400-600 kcal) for 6 months; controlled	HD (21) Case (9) Control (12)	Increased energy intake of 1,630 kJ (P<0.05), weight gain of 3.1 kg (P<0.005), increase in body fat of 1.8 kg and lean body mass of 1.3 kg Weight gain was maintained after 6 months
Tietze *et al.* (1991)[62]	Fish protein (8 g per day); randomized, double-blind, placebo-controlled crossover lasting 6 months	HD (43) Case (19) Control (24)	Increased levels of EAA and non-EAA EAA/non-EAA and alanine:branched-chain amino acids ratios normalized Body weight, weight index, and arm-muscle circumference increased
Cuppari *et al.* (1994)[63]	Protein (16.9 g per day), calories (800 kcal per day) for 120 days; follow-up study	HD (14)	Increased BMI, triceps skinfold thickness, mid-arm-muscle circumference
Beutler *et al.* (1997)[64]	CKD-specific ONS (ReNeph, Nutra/Balance, Indianapolis, IN, USA) vs usual diet for 4 months	HD (11) Case (6) Control (5)	Albumin levels increased with ONS from 32.0 g/l to 33.2 g/l DPI and DEI improved, and PCR increased slightly in those taking ONS Albumin levels did not significantly increase in the control group (32.0 to 31.6 g/l)
Cockram *et al.* (1998)[65]	Standard ONS (Magnacal® , Novartis Nutrition, Minneapolis, MN, USA) vs CKD-specifc ONS (Nepro®, Abbott Nutrition) for 2 weeks	HD (79) Stable, anuric patients	Nutritional supplement was the sole source of nutrition CKD-specii c ONS was well-tolerated, with no gastrointestinal symptoms Improved phosphorus and calcium levels
Milano *et al.* (1998)[66]	Glucose polymer (100 g per day, 380 kcal) for 6 months	HD (22) Moderate to severe PEW	Increased weight, BMI and triceps skinfold thickness at 3 months and 6 months Increased nutritional score in four patients Few gastrointestinal adverse effects Increased triglyceride level (1.54 to 2.66 mmol/l) Fat mass was maintained for 6 months after supplementation was discontinued
Kuhlmann *et al.* (1999)[67]	CKD-specifc ONS (Renamil®, KoRa Healthcare, Dublin, Ireland) and Renapro®;, KoRa Healthcare) vs routine diet for 3 months	HD (18) Malnourished (based on SGA and biochemical parameters)	CKD-specific ONS showed increased weight (1.2 kg) and albumin levels (1.0 ± 0.5 g/l); weight change correlated with DEI Unchanged prealbumin and cholesterol levels Good compliance and tolerance

*Some randomized crossover studies were included. Abbreviations: CKD, chronic kidney disease; DEI, dietary energy intake; DPI, dietary protein intake; EAA, essential amino acid; HD, hemodialysis; ONS, oral nutritional supplement; PCR, protein catabolic rate; PEW, protein-energy wasting; SGA, subjective global assessment.

Table 3

Nonrandomized trials in patients undergoing hemodialysis (from 2000)*

Study	Intervention modality, duration and study design	Patients and condition (*n*)	Results and conclusions
Patel *et al.* (2000)[68]	Standard ONS (Ensure®, Abbott Nutrition and Protein-Forte, Fresenius Kabi, Bad Homburg, Germany) for 2 months	HD (17) Low nPCR and DPI <1.2 g/kg body weight per day	Baseline albumin 42 g/l A baseline nPCR of 0.95 increased to 1.21 DPI increased from 0.75 g/kg per day to 1.10 g/kg per day at 2 months and 0.78 g/kg per day at 8 months (P<0.0001)
Bronich *et al.* (2001)[43]	EAA tablets (Aminess® N, Recip, Årsta, Sweden) three-times daily with meals (6.8 g per day) for 4 months; open-label, pilot trial	HD (18) Albumin concentration <38 g/l Kt/V >1.0	Albumin levels increased by 2 g/l (P=0.001) Lowest weight group increased from 74.5 kg to 77.1 kg (P=0.05) Grip strength increased CRP levels decreased in 56% of patients No significant change in food intake, and good compliance
Hiroshige *et al.* (2001)[69]	Oral branched-chain amino acids (12 g per day) for 12 months; placebo-controlled, double-blind, randomized crossover	HD (28) Elderly (>70 years) Albumin concentration <35 g/l	Increased appetite and food intake, branched-chain amino acids, albumin levels (from 33 g/l to 39 g/l), and anthropometrics In 14 placebo patients in the second 6 months (intervention crossover): albumin levels increased from 33 g/l to 38 g/l
Oguz *et al.* (2001)[70]	Oral EAA (n=6) vs IDPN (n = 14) for 4 months	HD (20) Malnourished	Increased levels of albumin, creatinine and T-lymphocyte counts in IDPN group Increased serum calcium levels and T-lymphocyte counts in oral EAA group No change in anthropometrics
Caglar *et al.* (2002)[71]	In-center CKD-specific ONS (Nepro®, Abbott Nutrition) thrice-weekly on hemodialysis (415 kcal and 16.6 g protein per session) for 6 months; observation and intervention	HD (85) Albumin concentration ≤37 g/l	No change during 3-month baseline period During intervention period, albumin levels increased from 33.3 g/l to 36.5 g/l, P <0.0001 Prealbumin levels increased from 261 mg/l to 307 mg/l, P= 0.002 SGA increased by 14% (P=0.023) Increase in BMI and dry weight (NS)
Holley & Kirk (2002)[72]	Tube feeding with CKD-specific ONS vs standard ONS for 11 months	HD (10) Case (9) Control (1)	Albumin levels increased from 28 g/l to 34 g/l, P=0.04 Hypophosphatemia occurred in 8 of 10 patients, 1 patient died as a result of an infected PEG tube
Kalantar-Zadeh *et al.* (2005)[40]	In-center (dialysis clinic) with low albumin concentration ≤38 g/l: Nepro®/Oxepa® (Abbott Nutrition) thrice-weekly on HD for 4 weeks	HD (40) Case (20) Control (20)	Pre-trial serum albumin levels (34.5 ± 3.1 g/l) increased to 36.8 ± 3.4 g/l (P=0.02) between 18 and 26 days after the start of the intervention No major adverse effects observed Well tolerated including oral Oxepa®
Fanti *et al.* (2006)[73]	2:1 isoflavone-containing soy-based ONS vs isoflavone-free milk protein for 8 weeks; double-blind	HD (25) Case (15) Control (10) CRP levels >95.24 nmol/l	Increased blood isoflavone levels and decreased CRP levels in patients receiving soy ONS (P<0.02) Delta-isoflavone correlated with albumin variation (r= 0.52, P=0.05) and insulin-like growth factor 1 (r=0.52, P<0.05)
Poole & Hamad (2008)[74]	Follow-up study in malnourished patients with ESRD	HD (157) PD (33)	Serum albumin was higher in HD patients than in PD patients before, during, and after supplement (P<0.05) Serum albumin improved in HD patients but not in PD patients In the 121 patients with diabetes, albumin levels increased (P ≤0.05) and the improvement persisted after the supplement was stopped
Scott *et al.* (2009)[75]	One can of enteral nutrition (Nepro®) thrice-weekly during hemodialysis vs standard care for 3 months; open-label prospective trial	HD (88)	Serum albumin concentration did not differ between baseline and month 3 in the nutrition group (36.8 g/l vs 37.5 g/l), but decreased in controls (39.3 g/l vs 38.1 g/l; P=0.04) Kidney Disease Quality of Life-Short Form score improved in the treated group (P<0.02) Good tolerance of ONS Compliance 80%

*Some randomized crossover studies were included. Abbreviations: CKD, chronic kidney disease; CRP C-reactive protein; DPI, dietary protein intake; EAA, essential amino acid; ESRD, end-stage renal disease; HD, hemodialysis; IDPN, intradialytic parenteral nutrition; nPCR, normalized

protein catabolic rate; NS, not significant; ONS, oral nutritional supplement; PD, peritoneal dialysis; PEG, percutaneous endoscopic gastrostomy; *r*, coefficient of correlation; SGA, subjective global assessment.

Table 4

Nonrandomized trials in patients undergoing peritoneal dialysis

Study	Intervention modality, duration and study design	Patients and condition (*n*)	Results and conclusions
Shimomura *et al.* (1993)[76]	Protein dessert with high biological value (0.1-0.3 g/kg daily) for >6 months	CAPD (18) No control arm	Increased serum levels of total protein, albumin, prealbumin, transferrin, total amino acids, EAA/non-EAA ratio, Kt/V urea, PCR Albumin levels rose from 32.5 g/l to 33.1 g/l in patients given the dessert, whereas patients in the control group had an albumin level of 38.8 g/l and 37.7 g/l before and after the study period, respectively
Patel & Raftery (1997)[77]	Standard ONS (Protein Forte [Fresenius Kabi, Bad Homburg, Germany] and Ensure® Plus [Abbott Nutrition, Columbus, OH, USA]) vs routine care for 8 weeks	PD (22) Case (10) Control (12)	Increased serum albumin levels, nPCR, DPI and DEI in the group taking supplements Significant difference in BMI and protein intake between the groups
Heaf *et al.* (1999)[78]	Standard ONS (Fortimel [Nutricia, Schiphol, The Netherlands]) vs usual diet for 10 weeks	PD (42) Case (12) Control (30) Albumin concentration <36 g/l	No improvement in nutritional status; albumin levels decreased in both groups Condition worsened in half of patients because of nausea
Boudville *et al.* (2003)[79]	CKD-specific ONS (Nepro®, Abbott Nutrition) vs calorie-free placebo; crossover design	PD (13) Baseline albumin concentration 34.8 g/l	Drinking the supplement 2h before lunch resulted in a significant increase in total caloric intake as compared with during the placebo visit (843 kcal vs 430 kcal, respectively; $P<0.001$) and protein intake (41.3 g vs 27.6 g, respectively; $P= 0.006$)
Teixidó-Planas *et al.* (2005)[80]	Non-CKD-specific ONS (Protenplus®, Fresenius); multicenter, randomized study for 6-12 months	PD (70) Case (35) Control (35)	Increased total lymphocyte count in the 'intention to treat' analysis In the 'as treated' analysis (9 cases, 20 controls): increased body weight ($P<0.03$), triceps skinfold thickness ($P<0.01$), mid-arm-muscle circumference ($P<0.03$), lean body mass ($P<0.002$), creatinine generation rate ($P<0.002$) in the group taking the supplement High noncompliance rate: 15 patients stopped ONS

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; CKD, chronic kidney disease; DEI, dietary energy intake; DPI, dietary protein intake; EAA, essential amino acid; nPCR, normalized protein catabolic rate; ONS, oral nutritional supplement; PD, peritoneal dialysis.

Table 5

Meals and oral supplements for hemodialysis patients with CKD and low serum albumin concentration

Effects of meals and oral supplements	Supportive comments	Rebuttals
Advantages		
Improved nutritional status, hypoalbuminemia and clinical outcomes	The majority of studies have shown improved nutritional status and hypoalbuminemia in patients with PEW who receive intradialytic feeding	Most of these studies have small sample sizes or are not randomized or controlled; some studies show no benefit
Prevents sarcopenia and mitigates postdialysis catabolism	Intradialytic enteral feeding, but not intradialytic parenteral nutrition, opposes posthemodialysis muscle wasting and catabolism	Limited *in vivo* studies to support anticatabolic data
Better control of phosphorus, potassium, salt and fluid levels	In-center meals and supplements are specifically designed for patients with CKD and contain appropriate nutrients	Feeding during dialysis could reinforce the bad habit of overeating
Increased adherence with hemodialysis treatment	Patients look forward to their meals and supplements during dialysis treatment	The contribution of intradialytic nutrition or in-center meals to adherence is questionable
Improved patient satisfaction and quality of life	Patients who receive food during dialysis are happier than those who do not receive a meal	Evidence is inadequate
Disadvantages		
Low blood pressure and labile circulation during food ingestion	Feeding during hemodialysis leads to low blood pressure and dificulties in achieving effective ultrailtration	No clear evidence of harmful hypotension upon feeding
Risk of aspiration	Risk of choking during feeding is high, especially in patients with a history of intradialytic hypotension	Highly unlikely in sitting position and in patients who can eat at home without aspiration
Infectious control and hygiene	Fecal-oral transmission of infection including hepatitis A; food crumbs and insects in the dialysis clinic	The same concerns could apply to providing hospital meals for inpatients
Burden on dialysis staff and financial constraints	Distraction to dialysis staff who need to focus on dialysis treatment and patient care	Providing nutrition should be regarded as an integrated part of patient care
Only a small number of required meals are provided	Thrice-weekly meals account for only 15% of the meal frequencies	Evidence indicates that catabolic effects of hemodialysis can be mitigated or even reversed by intradialytic nutrition

Abbreviations: CKD, chronic kidney disease; PEW, protein-energy wasting.