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# Optimal Nutrition in Hemodialysis Patients

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## Abstract

Protein energy wasting (PEW) is highly prevalent in patients undergoing maintenance hemodialysis (MHD) patients. Importantly, there is a robust association between the extent of PEW and the risk of hospitalization and death in these patients, regardless of the nutritional marker used. The multiple etiologies of PEW in advanced kidney disease are still being elucidated. Apart from the multiple mechanisms that might lead to PEW, it appears that the common pathway for all the derangements is related to exaggerated protein degradation along with decreased protein synthesis. The hemodialysis procedure per se is an important contributor to this process. Metabolic and hormonal derangements such as acidosis, inflammation and resistance to anabolic properties of insulin resistance and growth hormone are all implicated for the development of PEW in MHD patients. Appropriate management of MHD patients at risk for PEW requires a comprehensive combination of strategies to diminish protein and energy depletion, and to institute therapies that will avoid further losses. The mainstay of nutritional treatment in MHD patients is provision of an adequate amount of protein and energy, using oral supplementation as needed. Intradialytic parenteral nutrition should be attempted in patients who cannot use the gastrointestinal tract efficiently. Other anabolic strategies such as exercise, anabolic hormones, anti-inflammatory therapies and appetite stimulants can be considered as complementary therapies in suitable patients.

Nutritional health is one of the most important considerations in patients with chronic kidney disease especially in those undergoing maintenance hemodialysis (MHD). Advanced kidney disease and renal replacement therapy lead to a number of metabolic and nutritional derangements, which can be termed as *protein-energy wasting (PEW)* of chronic kidney disease (CKD)[1]. PEW is associated with major adverse clinical outcomes and is considered to be a significant co-morbid condition leading to increased rates of hospitalization and death in patients undergoing MHD. This review article is intended to provide a summary of assessment, epidemiology, and etiology of PEW in MHD patients as well as optimal prevention and treatment strategies for this high risk group.

## Assessment of Nutritional Status in MHD patients

Nutritional status refers to the composite quantitative and qualitative assessment of visceral and somatic (muscle) protein stores and energy balance[2,3]. Evaluating nutritional status is a

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critical component of physiologic health and fundamental to identifying PEW[1]. Assessment of protein and energy nutritional status is also a broad and complex topic. A clinically meaningful assessment of nutritional status should be able to identify and risk stratify patients with PEW, distinguishing the causes and consequences of both PEW and the underlying disease states that lead to PEW, and finally determine whether there is a possibility of benefit from nutritional interventions[4]. Therefore, no single parameter is likely to adequately phenotype this co-morbid state and a comprehensive assessment of protein and energy nutritional status requires several different measurements[5].

A summary of nutritional parameters for detecting PEW in MHD patients and their applicability for guiding nutritional therapies is provided in Table 1. Some of these parameters are easy to perform, readily available and inexpensive, while others are sophisticated, not available in many centers, and are either expensive or with an unfavorable cost-benefit ratio. In the research setting, complex and precise methods to assess protein and energy metabolism, i.e. nitrogen balance studies or stable isotope tracer techniques, although not of widespread availability, are the methods of choice to measure acute changes or responses to metabolic interventions, minimizing variability and errors[6].

In ESRD patients undergoing MHD, nutritional screening should include monthly assessments of serum albumin, dry weight, and subjective global assessment (SGA) every 3–6 months. In addition to interpreting absolute values for certain thresholds, trends over time should be considered. Currently, serum albumin is the most commonly used screening tool for detecting patients at risk for PEW. A consistent decrease greater than 0.3 g/dL in serum albumin levels over 2–3 months or more should initiate a more comprehensive assessment of nutritional status. This assessment could include dietary interviews, anthropometry, dual-energy x-ray absorptiometry, and even more sophisticated methods, if available. Direct measures of inflammatory status, such as serum C-reactive protein (CRP), is of significant use in this setting and can be employed to monitor targeted therapies. For all indirect methods, repeated measures and technical standardization are extremely important to reduce variability of results. Regardless of the method, it is important to keep in mind that none is perfect and definitive, and the results should always be analyzed in the clinical context of each individual patient.

## Epidemiology of PEW in MHD patients

Virtually every study evaluating the nutritional status of MHD patients report some degree of abnormality. Unfortunately, many different diagnostic tools were used in the separate studies so the actual prevalence of PEW in MHD patients varies widely, ranging from 20% to 60%[7,8]. Although there is evidence that nutritional parameters improve within 3 to 6 months following initiation of hemodialysis, there also is evidence that PEW is present in up to 40% or more of the MHD population; the prevalence seems to increase with time of MHD treatment[9].

Serum albumin is, by far, the most extensively studied serum protein for assessment of nutritional status in MHD patients. It is a convenient, rather inexpensive and readily available laboratory test. Multiple studies have shown a strong correlation between low levels of serum albumin and increased risk of morbidity and mortality in ESRD patients[10–13]. It is important to note that serum albumin could be a marker of overall health status rather than simply a nutritional marker, an appropriate distinction when one takes into account its complex physiology[14]. Therefore, additional markers, such as SGA have been used to determine the prevalence of PEW in MHD patients. In DOPPS II, 20.5% of US patients were reported to have serum albumin level less than 3.5 g/dL (35 g/L). Based on the serum albumin and the SGA, it was concluded that the prevalence of moderate PEW ranged

from 7.6% (U.S.) to 18% (France) and for severe malnutrition, from 2.3% (Italy) to 11% (U.S.)[15].

An important issue regarding the epidemiology of PEW in MHD is that regardless of the nutritional marker used, i.e. serum albumin, serum prealbumin or SGA, there is a robust association between the extent of PEW and the risk of hospitalization and death[8,16–19]. While there are no randomized clinical trials that tested the efficacy of nutritional interventions on mortality, recent epidemiological data indicate a concomitant improvement in survival when these markers are also improved[20–22].

## Etiology of Protein-Energy Wasting in MHD Patients

The mechanisms leading to PEW in advanced kidney disease are still being elucidated; they cannot be attributed to any single factor in MHD patients (Figure 1). Still, it appears that the common pathway for all the metabolic derangements is related to exaggerated protein degradation and along with decreased protein synthesis.

### Dietary Nutrient Intake, Hemodialysis and Development of PEW in MHD

Decreased dietary nutrient intake is a common aspect of advanced CKD. The prevalence of anorexia has been reported at 35–50% of ESRD patients[23,24]. The factors influencing food intake are complex and involve not only metabolic signals but also anomalies in the organ systems involved in nutrient intake as well as psychological and acquired aspects, including a desire for pleasure, social behavior and customs[25]. Anorexia in many settings is mediated by circulating appetite regulators, such as gastric mediators (such as cholecystokinin, peptide YY, ghrelin or obestatin), adipokines (such as leptin and visfatin) or cytokines (such as TNF, IL-6, IL-1β)[26]. Current understanding of how these factors play a role in the setting of MHD is still in early stages and future studies might provide further insights.

The observation that CKD patients spontaneously decrease their protein and energy intake as they progressively lose kidney function has led some to conclude that uremia per se causes protein catabolism stimulated by decreased nutrient intake. This conclusion has been challenged because even in patients with advanced CKD, balance studies show that there is a concomitant decrease in both protein synthesis and degradation in patients with advanced CKD that is uncomplicated by acidosis or another catabolic illness[27]. The dual change in protein synthesis and degradation results in a net nitrogen balance that is not different from matched healthy controls. On the other hand, in the setting of acute illnesses or stress conditions, accelerated protein degradation is not adequately suppressed and there is inadequate increase in protein synthesis[28]. For example, hospitalized MHD patients can be eating inadequate protein and energy and not be able to adjust rates of protein turnover leading to loss of cellular protein stores[29].

An additional stimulus for protein losses is the dialytic treatment per se. Detailed measurements of protein synthesis and degradation unequivocally demonstrate the catabolic effects of hemodialysis[30]. Both whole-body and skeletal muscle protein homeostasis are disrupted and there is a consistent finding of decreased protein synthesis at the whole-body level and an additional increase in whole-body protein breakdown. There also is evidence for a significant increase in net skeletal muscle protein breakdown. Notably, these undesirable effects persist for at least 2 hours following the completion of hemodialysis.

### Chronic Inflammation as a Catabolic Stimulus in Advanced CKD

Recent epidemiologic studies have pointed out that there is a high prevalence of increased levels of inflammatory markers in patients with advanced CKD. The metabolic and nutritional responses to chronic inflammation are many and closely mimic the PEW that

appears to be common in advanced CKD patients, including exaggerated protein catabolism. This raises the potential that there is a "cause and effect" relationship between inflammation and loss of protein stores.

The etiology of inflammation is multi-factorial in advanced CKD patients (Figure 2)[31]. Although not proven, pro-inflammatory cytokines are thought to play an integral role in the muscle catabolism of ESRD patients. For example, elevated levels of IL-6 are associated with increased muscle proteolysis and the administration of IL-6 receptor antibody can block this catabolism[32]. Anorexia or suppressed nutrient intake is a well-established metabolic response to inflammation[33]; IL-1 and TNFα can cause anorexia through their effects on the satiety center in the central nervous system[34]. One mechanism that could tie together these observations is that impaired insulin/IGF-1 signaling can stimulate muscle protein breakdown. In fact, there is evidence that involvement of pro-inflammatory cytokines with muscle protein catabolism is due to suppression of insulin receptor -1 (IRS-1)-associated phosphatidylinositol 3-kinase (PI3K) activity. This suppression stimulates the activity of the ubiquitin-proteasome proteolytic system (UPS) and activates caspase-3, the two proteolytic pathways that cause degradation of muscle protein[35].

## Insulin Resistance and Deprivation as Catabolic Stimuli in Advanced CKD

Patients with CKD secondary to diabetes mellitus (DM), the leading cause of ESRD in the United States, have a higher incidence of PEW when compared to non-diabetic patients[9]. The degree of insulin resistance and/or insulin deprivation seems to play the most critical role in this process. As with inflammation, decreased insulin or decreased sensitivity to insulin can cause muscle protein losses. Multiple *in vitro* and *in vivo* studies have demonstrated the metabolic effects of insulin extend beyond carbohydrate metabolism[36,37]; specifically, insulin deprivation stimulates protein breakdown and administration of insulin suppresses protein degradation[38]. With adequate amino acid availability, insulin also regulates protein synthesis. These actions are mediated through IRS-1-associated PI3K activity. A deficiency of insulin stimulates the UPS and caspase-3 activity to breakdown muscle protein[39]. It is believed that regulatory abnormalities in these pathways are responsible for the muscle catabolism observed in MHD patients with diabetes or insulin resistance. Several reports demonstrate that among MHD patients, muscle protein breakdown is enhanced in patients with Type II DM when compared to MHD patients without DM[40–42]. This abnormality translates into a greater loss of lean body mass within the first year of MHD in diabetic MHD patients compared to non-diabetic MHD patients. In the absence of severe obesity, insulin resistance is still detectable in MHD patients and strongly associated with increased muscle protein breakdown, even after controlling for inflammation[42].

In addition to the protein catabolism that occurs with insulin resistance, diabetic MHD patients are likely to be more prone to protein depletion because of associated gastrointestinal symptoms (e.g., gastroparesis, nausea and vomiting, bacterial overgrowth in the gut and pancreatic insufficiency).

## Metabolic and Hormonal Derangements Leading to PEW in MHD patients

Metabolic acidosis, a common abnormality in patients with progressive CKD promotes PEW, by increasing protein catabolism, especially in muscle[43]. In addition, acidosis stimulates the oxidation of essential amino acids to raise protein requirements in MHD patients[44]. Even a small correction of a low serum bicarbonate concentration will improve nutritional status by correcting essential amino acid catabolism and down-regulating muscle proteolysis via the ubiquitin-proteasome system. As with the other abnormalities that stimulate muscle protein catabolism, metabolic acidosis acts in large part by suppressing

insulin/IGF-1 signaling in muscle. There are a number of studies indicating improvement in nutritional status with oral bicarbonate supplementation[45]. Therefore, we recommend that the predialysis serum bicarbonate level should be greater than 22 mmol/L in MHD patients although very high levels might be associated with adverse outcomes[46].

The growth hormone (GH) and IGF1 axis is disrupted in advanced CKD leading to decreased anabolism. Pharmacological treatment with recombinant GH (rhGH) leads to improvement in growth in children with CKD, indicating that GH resistance plays an important role in the etiology of PEW in advanced CKD patients[47]. Increased concentrations of parathyroid hormone have been implicated as a protein catabolic factor in uremia, although evidence for this response in humans is sparse. In addition, there are abnormalities in thyroid hormone-stimulated metabolism in MHD patients, specifically, low circulating thyroxine and triiodothyronine concentrations. Since similar changes resemble those found in patients with prolonged malnutrition, it has been suggested that the thyroid hormone responses to malnutrition (and possibly to advanced CKD), is a maladaptive response to a decrease in energy intake. There are no trials of correcting thyroid hormone levels with documentation of improved nutritional status in MHD patients.

## Nutritional Support in MHD patients

Given the significance of the problem, as well as the complexity of the pathophysiological basis of PEW in advanced CKD, it is evident that the prevention and treatment options of PEW in MHD patients are complex. In MHD with PEW or at risk for PEW, there is no single treatment approach that will alleviate the multiple adverse consequences of PEW. An overview of prevention and treatment options for MHD patients are provided in Table 2.

### General Aspects of Nutritional Management

Management of nutritional aspects of MHD patients includes a comprehensive combination of preventive maneuvers to diminish protein and energy depletion. The recommended dietary protein and calorie intake for (sedentary) MHD patients are 1.2 – 1.4 g/kg and 30 – 35 kcal/kg, respectively[48]. Other standard therapies for MHD patients with PEW include provision of adequate dialysis, treatment of metabolic acidosis, adjustments of dietary factors and treatment of infections. Factors that are not so closely linked to the nutritional status include correction of fluid overload and treatment of co-morbid conditions such as diabetes, cardiovascular diseases and infectious diseases. Likewise, a search for signs of chronic inflammation is required and all attempts must be made to eliminate inflammatory responses, especially the use of central venous catheters.

An important consideration regarding strategies to improve dietary protein intake in MHD patients is the potential increase in the intake of several potentially harmful elements, especially phosphorus[49]. While limiting dietary phosphorus intake may indirectly lead to increased risk for PEW, allowing an unrestricted protein intake will undoubtedly increase phosphorus load. A recent observational study showed that a combination of decreased serum phosphorus and increased protein intake had the best outcomes whereas MHD patients whose serum phosphorus and protein intake both decreased over time did the worst[50]. Dietary recommendations to improve protein intake should take into account the phosphorus content of the specific nutrients.

### Nutritional Supplementation

The susceptibility towards PEW from decreased protein and energy intake could be ameliorated by increasing nutrient intake through dietary supplements, especially during hemodialysis. Nutritional supplementation of MHD patients should be delivered by the oral route if at all possible but if not, parenteral nutritional supplements can be provided.

**Oral nutritional supplementation—**Both the short- and long-term benefits of oral nutritional supplements for MHD patients can be accomplished especially when the supplements are provided around the time of hemodialysis, including intradialytic administration. For example, oral feeding can be associated with a robust improvement in whole-body and skeletal muscle protein balance[51]. In terms of beneficial responses to prolonged oral nutritional supplementation in MHD patients, a meta-analysis examined several outcomes including clinical (quality of life, complications, and mortality), biochemical (serum albumin and electrolyte levels), and nutritional (dietary intake and anthropometry) measures[52]. The analysis included 18 studies (5 randomized controlled trials [RCTs], 13 non-RCTs) and the conclusion was that enteral nutritional support can increase total (energy and protein) intake and raise serum albumin concentrations by an average of 0.23 g/dL, with no adverse effects on electrolyte status (serum phosphate and potassium). The practical implication is that oral nutritional supplementation is effective, especially when administered during hemodialysis and is practical, convenient and well-tolerated. It is also important to note that tolerability of oral nutritional supplementation is a challenge[53]. In addition, adverse hemodynamic effects of intradialytic food ingestion should be considered, especially in patients who are predisposed to intradialytic hypotension[54].

In support of oral nutritional supplementation, especially during hemodialysis, a recent study reported significant survival benefit in favor of hypoalbuminemic MHD patients receiving nutritional supplementation versus similarly matched historical controls[21]. Specifically, in a retrospective cohort study of 4,289 matched pairs, Lacson et al reported death rates of 30.9% versus 37.3% in treated versus untreated groups, respectively. While the study had limitations of retrospective design, convenience sampling and residual confounding from unmeasured variables, it highlights the potentially large effect of this strategy in clinical practice.

**Intradialytic Parenteral Nutrition—**While the gastrointestinal route is always preferred for nutritional supplementation, parenteral provision of nutrients, especially during the dialysis procedure (IDPN), is safe, effective and convenient for individuals who cannot tolerate oral or enteral administration of nutrients. While metabolic studies conclusively show a robust anabolic response during IDPN[55], a few reports provide evidence that nutritional status can improve with IDPN in the long-term. Unfortunately, the sample sizes in most reports have been small and did not allow appropriate stratification of MHD patients and were carried out over a short period of time. These shortcomings contribute to the observed inconsistency of results. Notably, there is a high cost of IDPN and these considerations plus regulatory concerns have limited the utilization of this potentially beneficial treatment.

Results from a recent study (FINEs) have provided insights into effects from long-term use of nutritional supplementations in MHD patients with PEW[20]. In this study, 186 MHD patients with PEW were randomly assigned to receive intradialytic parenteral nutrition (for 1 year) plus standard oral supplements compared to those receiving oral supplements only. Two-year mortality was similar in both groups, suggesting that oral nutritional supplementation is equally effective as IDPN when oral intake is possible since both therapies provided adequate amounts of protein and calories.

## Pharmacological Interventions for Treatment of PEW in MHD Patients

**Growth Hormone—**Growth hormone and its major mediator, IGF-1, could have several anabolic properties. Besides the well documented benefits of growth hormone in children with CKD, short-term administration of the hormone to MHD patients can have anabolic responses. Most if not all long-term studies indicate there is a significant increase in lean

body mass in the growth hormone-treated adult maintenance dialysis patients[56–58]. For example, growth hormone was associated with statistically significant gains in lean body mass in a trial consisting of 139 patients[59]. Specifically, MHD receiving GH increased their LBM by 2.5 kg over six months whereas placebo group lost an average of 0.4 kg LBM. In a subsequent multi-center RCT, significant decreases were observed in hsCRP and homocysteine levels along with increases in serum high-density lipoprotein-cholesterol and transferrin levels in hypoalbuminemic MHD patients[60]. Unfortunately, this large RCT was prematurely terminated without an ability to assess the effects of GH on hospitalization or death.

**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. For example, megestrol acetate, a steroid-like progestagen led to increased appetite and weight gain in breast cancer patients[61]. 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 TNF-α[61]. The increase in appetite was associated with an increase in weight, mainly due to increased fat and not lean body mass. Moreover, megestrol acetate has been associated with side effects including hypogonadism, impotence, and increased risk of thromboembolism (per package insert). In MHD patients, megestrol acetate can stimulate appetite and induce small increases in serum albumin but large-scale prospective studies are needed to assess whether these drugs provide adjunctive nutritional therapy for MHD or CKD patients. There are no systematic evaluation of other appetite-stimulating and weight gain responses to dronabinol, cyproheptadine, melatonin, and thalidomide in MHD patients.

**Anabolic Steroids—**There are reports of significant improvements in body composition and physical function of MHD patients who are given nandrolone decanoate[62]. In addition, there was an increase in quadriceps muscle cross-sectional area (MRI measurements) and an increase in lean body mass by DEXA. Curiously, the combination of resistance exercise with nandrolone decanoate did not improve the beneficial effects of the drug.

## Exercise as an Anabolic Intervention in MHD Patients

Exercise training can maintain and/or improve exercise capacity and endurance in the general population. In addition, resistance exercise can increase muscle mass, strength and appetite as well as lessen muscle weakness and frailty in elderly patients. Resistance exercise can increase oxygen consumption but whether this response only occurs when there is a positive muscle protein balance is unknown. The rates of both muscle synthesis and breakdown increase during a resistance exercise session in normal adults and if resistance exercise is combined with nutrient supplementation, anabolism is maximized while muscle breakdown declines somewhat. Short-term (i.e., a single HD session) metabolic studies indicate that exercise when combined with intradialytic oral or parenteral nutrition will improve net protein balance in MHD patients[63] but longer term evaluations of resistance exercise performed during hemodialysis in MHD patients have not shown substantial nutritional benefits[62,64,65]. Nonetheless, the beneficial effects of exercise on quality of life and physical functioning must be taken into account when considering an exercise regimen for a MHD patient. We recommend an adequate nutritional supplement during exercise unless the patient is considered for supervised weight loss.

Another important nutritional issue in terms of MHD patients is obesity. The recent USRDS data showed that the average BMI of HMD patients is greater than 29 kg/m$^{2.}$[66] This issue is important because there is a plethora of epidemiological studies indicating that higher body

mass index, regardless of its etiology (i.e. increased adiposity and/or lean body mass) is associated with an improved survival of ESRD patients[67]. While the exact mechanism(s) underlying this association has not been elucidated, there is a potentially beneficial effect of increasing protein and energy intakes because weight gain might be a potentially beneficial outcome.

### Anti-inflammatory Interventions

Anti-inflammatory interventions aimed at ameliorating the changes in nutritional status in ESRD patients are summarized in Table 2. Pentoxifylline, a drug that blocks TNF-α release, was administered intravenously to patients with Stage 4–5 CKD[68]. The intervention alone led to an improvement in protein breakdown along with an additional improvement in the anabolic effects of a balanced amino acid mixture given concurrently. Besides pentoxifylline and resistance exercise, thalidomide, IL-1 receptor antagonists, TNFα receptor blockers, fish oil, statins, ACE inhibitors, PPAR-gamma agonists plus certain antioxidants have been proposed as anti-inflammatory strategies in MHD patients. Combined administration of γ-tocopherol and docosahexaenoic acid over 3 months was associated with a significant decrease in IL-6 and the white blood cell count in MHD patients[69]. More recently, Hung et al reported significant improvements in hsCRP and IL-6 levels in MHD patients receiving 4 weeks of IL-1ra[70]. The same patients displayed numerical improvements in serum albumin, serum prealbumin and lean body mass. These results indicate the need for further, larger scale studies examining the role of anti-cytokine therapies as nutritional interventions in MHD patients.

### Summary

In summary, the available evidence suggests that PEW is highly prevalent in MHD patients and is associated with poor outcomes. The etiology of PEW in MHD patients is multifactorial and include decreased dietary nutrient intake, the hormonal and metabolic derangements associated with advanced kidney disease and the adverse effects of RRT and other concurrent morbid conditions. Nevertheless, the imbalance between protein synthesis and degradation seems to be the major driver for this disturbance, which can be compensated by various anabolic strategies. Nutritional supplementation administered orally or parenterally, is effective in the treatment of PEW. Resistance or endurance exercise, while although effective in the short term, seems to lack consistent evidence in improving LBM over long-term. Various anabolic agents are shown to increase visceral protein concentrations and muscle mass and strength simultaneously. Further larger scale randomized controlled trials of anabolic interventions, individually or combined should be performed in MHD patients to assess their efficacy regarding quality of life, morbidity and mortality.

## REFERENCES

1. 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. [PubMed: 18094682]
2. Sardesai, VM. Fundamentals of Nutrition. In: Dekker, M., editor. Introduction to Clinical Nutrition. New York: Sardesai, V.M.; 1998. p. 1-13.
3. Ikizler TA, Hakim RM. Nutrition in end-stage renal disease. Kidney Int. 1996; 50:343–357. [PubMed: 8840260]
4. Jeejeebhoy KN. Nutritional assessment. Nutrition. 2000; 16:585–590. [PubMed: 10906564]
5. Association AD. Identifying patients at risk: ADA's definitions for nutrition screening and nutrition assessment. Council on Practice (COP) Quality Management Committee. J Am Diet Assoc. 1994; 94:838–839. [PubMed: 8046173]

6. Pupim, L.; Martin, CJ.; Ikizler, TA. Assessment of Protein-Energy Nutritional Status. In: Kopple, JD.; Massry, SG., editors. Nutritional Management of Renal Disease. 2nd ed.. Philadelphia: LIPPINCOTT WILLIAMS & WILKINS; 2004. p. 223-240.
7. Pifer TB, McCullough KP, Port FK, et al. Mortality risk in hemodialysis patients and changes in nutritional indicators: DOPPS. Kidney Int. 2002; 62:2238–2245. [PubMed: 12427151]
8. Lopes AA, Bragg-Gresham JL, Elder SJ, et al. Independent and Joint Associations of Nutritional Status Indicators With Mortality Risk Among Chronic Hemodialysis Patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Journal of Renal Nutrition. 2010; 20:224–234. [PubMed: 20060319]
9. Cano NJ, Roth H, Aparicio M, et al. Malnutrition in hemodialysis diabetic patients: evaluation and prognostic influence. Kidney Int. 2002; 62:593–601. [PubMed: 12110023]
10. Anderson CF, Wochos DN. The utility of serum albumin values in the nutritional assessment of hospitalized patients. Mayo Clin Proc. 1982; 57:181–184. [PubMed: 6801397]
11. Reinhardt GF, Myscofski JW, Wilkens DB, Dobrin PB, Mangan JE Jr, Stannard RT. Incidence and mortality of hypoalbuminemic patients in hospitalized veterans. JPEN J Parenter Enteral Nutr. 1980; 4:357–359. [PubMed: 6774116]
12. Apelgren KN, Rombeau JL, Twomey PL, Miller RA. Comparison of nutritional indices and outcome in critically ill patients. Crit Care Med. 1982; 10:305–307. [PubMed: 7075221]
13. Kaw M, Sekas G. Long-term follow-up of consequences of percutaneous endoscopic gastrostomy (PEG) tubes in nursing home patients. Dig Dis Sci. 1994; 39:738–743. [PubMed: 8149838]
14. Ikizler TA. The Use and Misuse of Serum Albumin as a Nutritional Marker in Kidney Disease. Clin J Am Soc Nephrol. 2012
15. Combe C, McCullough KP, Asano Y, Ginsberg N, Maroni BJ, Pifer TB. Kidney Disease Outcomes Quality Initiative (K/DOQI) and the Dialysis Outcomes and Practice Patterns Study (DOPPS): Nutrition guidelines, indicators, and practices. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2004; 44:39–46. [PubMed: 15486873]
16. Kalantar-Zadeh K, Cano NJ, Budde K, et al. Diets and enteral supplements for improving outcomes in chronic kidney disease. Nat Rev Nephrol. 2011; 7:369–384. [PubMed: 21629229]
17. Kalantar-Zadeh K, Kuwae N, Wu DY, et al. Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. Am J Clin Nutr. 2006; 83:202–210. [PubMed: 16469976]
18. Mehrotra R, Duong U, Jiwakanon S, et al. Serum albumin as a predictor of mortality in peritoneal dialysis: comparisons with hemodialysis. Am J Kidney Dis. 2011; 58:418–428. [PubMed: 21601335]
19. Noori N, Kovesdy CP, Dukkipati R, et al. Survival predictability of lean and fat mass in men and women undergoing maintenance hemodialysis. Am J Clin Nutr. 2010; 92:1060–1070. [PubMed: 20844076]
20. 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. [PubMed: 17656473]
21. Lacson E Jr, Wang W, Zebrowski B, Wingard R, Hakim RM. Outcomes Associated With Intradialytic Oral Nutritional Supplements in Patients Undergoing Maintenance Hemodialysis: A Quality Improvement Report. Am J Kidney Dis. 2012
22. Cheu C, Pearson J, Dahlerus C, et al. Association between Oral Nutritional Supplementation and Clinical Outcomes among Patients with ESRD. Clinical Journal of the American Society of Nephrology. 2012
23. Bossola M, Tazza L, Giungi S, Luciani G. Anorexia in hemodialysis patients: an update. Kidney Int. 2006; 70:417–422. [PubMed: 16775598]
24. Carrero JJ. Identification of patients with eating disorders: clinical and biochemical signs of appetite loss in dialysis patients. J Ren Nutr. 2009; 19:10–15. [PubMed: 19121763]
25. Carrero JJ. Mechanisms of altered regulation of food intake in chronic kidney disease. J Ren Nutr. 21:7–11. [PubMed: 21195909]
26. Chung SH, Carrero JJ, Lindholm B. Causes of Poor Appetite in Patients on Peritoneal Dialysis. Journal of Renal Nutrition. 2011; 21:12–15. [PubMed: 21195910]

27. Lim VS, Kopple JD. Protein metabolism in patients with chronic renal failure: role of uremia and dialysis. Kidney International. 2000; 58:1–10. [PubMed: 10886544]
28. Raj DS, Adeniyi O, Dominic EA, et al. Amino acid repletion does not decrease muscle protein catabolism during hemodialysis. Am J Physiol Endocrinol Metab. 2007; 292:E1534–E1542. [PubMed: 17264222]
29. Ikizler TA, Greene JH, Wingard RL, Hakim RM. Nitrogen balance in hospitalized chronic hemodialysis patients. Kidney Int Suppl 57. 1996; 50:S53–S56.
30. Ikizler TA, Pupim RB, Brouillette JR, et al. Hemodialysis stimulates muscle and whole-body protein loss and alters substrate oxidation. Am J Physiol Endocrinol Metab. 2002; 282:E107–E116. [PubMed: 11739090]
31. Ikizler TA. Nutrition, inflammation and chronic kidney disease. Curr Opin Nephrol Hypertens. 2008; 17:162–167. [PubMed: 18277149]
32. Nishimoto N, Kishimoto T. Interleukin 6: from bench to bedside. Nat Clin Pract Rheumatol. 2006; 2:619–626. [PubMed: 17075601]
33. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. Am J Clin Nutr. 2004; 80:299–307. [PubMed: 15277149]
34. DeBoer MD, Scarlett JM, Levasseur PR, Grant WF, Marks DL. Administration of IL-1β to the 4th ventricle causes anorexia that is blocked by agouti-related peptide and that coincides with activation of tyrosine-hydroxylase neurons in the nucleus of the solitary tract. Peptides. 2009; 30:210–218. [PubMed: 19028534]
35. Lecker SH, Goldberg AL, Mitch WE. Protein degradation by the ubiquitin-proteasome pathway in normal and disease States. J Am Soc Nephrol. 2006; 17:1807–1819. [PubMed: 16738015]
36. Deger SM, Sundell MB, Siew ED, et al. Insulin Resistance and Protein Metabolism in Chronic Hemodialysis Patients. J Ren Nutr. 2012
37. 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. [PubMed: 18451670]
38. Flakoll, PJ.; Carlson, M.; Cherrington, AC. Physiological action of insulin. In: Leroith, DTS.; Olefsky, J., editors. Diabetes Mellitus: A fundamental and Clinical Text. 2nd ed.. Philadelpia, PA: Williams & Wilkins; 2000. p. 148-161.
39. Wang X, Hu Z, Hu J, Du J, Mitch WE. Insulin resistance accelerates muscle protein degradation: activation of the ubiquitin-proteasome pathway by defects in muscle cell signaling. Endocrinology. 2006
40. Pupim LB, Flakoll PJ, Majchrzak KM, Aftab Guy DL, Stenvinkel P, Ikizler TA. Increased muscle protein breakdown in chronic hemodialysis patients with type 2 diabetes mellitus. Kidney Int. 2005; 68:1857–1865. [PubMed: 16164664]
41. Pupim LB, Heimburger O, Qureshi AR, Ikizler TA, Stenvinkel P. Accelerated lean body mass loss in incident chronic dialysis patients with diabetes mellitus. Kidney Int. 2005; 68:2368–2374. [PubMed: 16221242]
42. Siew ED, Pupim LB, Majchrzak KM, Shintani A, Flakoll PJ, Ikizler TA. Insulin resistance is associated with skeletal muscle protein breakdown in non-diabetic chronic hemodialysis patients. Kidney Int. 2007; 71:146–152. [PubMed: 17063174]
43. Bailey JL, Wang X, England BK, Price SR, Ding X, Mitch WE. 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. 1996; 97:1447–1453. [PubMed: 8617877]
44. Graham KA, Reaich D, Channon SM, Downie S, Goodship THJ. Correction of acidosis in hemodialysis decreases whole body protein degradation. J Am Soc Nephrol. 1997; 8:632–637. [PubMed: 10495793]
45. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate Supplementation Slows Progression of CKD and Improves Nutritional Status. J Am Soc Nephrol. 2009

46. Wu DY, Shinaberger CS, Regidor DL, McAllister CJ, Kopple JD, Kalantar-Zadeh K. Association between serum bicarbonate and death in hemodialysis patients: is it better to be acidotic or alkalotic? Clin J Am Soc Nephrol. 2006; 1:70–78. [PubMed: 17699193]
47. Tonshoff B, Schaefer F, Mehls O. Disturbance of growth hormone-insulin-like growth factor axis in uraemia. Implications for recombinant human growth hormone treatment. Pediatr Nephrol. 1990; 4:654–662. [PubMed: 2088470]
48. Kopple JD. National kidney foundation K/DOQI clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2001; 37:S66–S70. [PubMed: 11158865]
49. Kovesdy CP, Shinaberger CS, Kalantar-Zadeh K. Epidemiology of dietary nutrient intake in ESRD. Semin Dial. 2010; 23:353–358. [PubMed: 20557492]
50. Shinaberger CS, Greenland S, Kopple JD, et al. Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease? Am J Clin Nutr. 2008; 88:1511–1518. [PubMed: 19064510]
51. Pupim LB, Majchrzak KM, Flakoll PJ, Ikizler TA. Intradialytic oral nutrition improves protein homeostasis in chronic hemodialysis patients with deranged nutritional status. J Am Soc Nephrol. 2006; 17:3149–3157. [PubMed: 17021267]
52. 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. [PubMed: 16129200]
53. Caglar K, Fedje L, Dimmitt R, Hakim RM, Shyr Y, Ikizler TA. Therapeutic effects of oral nutritional supplementation during hemodialysis. Kidney Int. 2002; 62:1054–1059. [PubMed: 12164890]
54. Barakat MM, Nawab ZM, Yu AW, Lau AH, Ing TS, Daugirdas JT. Hemodynamic effects of intradialytic food ingestion and the effects of caffeine. J Am Soc Nephrol. 1993; 3:1813–1818. [PubMed: 8329676]
55. Pupim LB, Flakoll PJ, Brouillette JR, Levenhagen DK, Hakim RM, Ikizler TA. Intradialytic parenteral nutrition improves protein and energy homeostasis in chronic hemodialysis patients. J Clin Invest. 2002; 110:483–492. [PubMed: 12189242]
56. Ericsson F, Filho JC, Lindgren BF. Growth hormone treatment in hemodialysis patients--a randomized, double-blind, placebo-controlled study. Scand J Urol Nephrol. 2004; 38:340–347. [PubMed: 15669595]
57. Ikizler TA, Wingard RL, Breyer JA, Schulman G, Parker RA, Hakim RM. Short-term effects of recombinant human growth hormone in CAPD patients. Kidney Int. 1994; 46:1178–1183. [PubMed: 7861714]
58. Johannsson G, Bengtsson BA, Ahlmen J. Double-blind, placebo-controlled study of growth hormone treatment in elderly patients undergoing chronic hemodialysis: anabolic effect and functional improvement. American Journal of Kidney Diseases. 1999; 33:709–717. [PubMed: 10196013]
59. Feldt-Rasmussen B, Lange M, Sulowicz 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. [PubMed: 17554147]
60. Kopple JD, Cheung AK, Christiansen JS, et al. OPPORTUNITY™: a large-scale randomized clinical trial of growth hormone in hemodialysis patients. Nephrol Dial Transplant. 2011; 26:4095–4103. [PubMed: 21750157]
61. Yeh S, Wu SY, Levine DM, et al. Quality of life and stimulation of weight gain after treatment with megestrol acetate: correlation between cytokine levels and nutritional status, appetite in geriatric patients with wasting syndrome. J Nutr Health Aging. 2000; 4:246–251. [PubMed: 11115810]
62. Johansen KL, Painter PL, Sakkas GK, Gordon P, Doyle J, Shubert T. 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. [PubMed: 16825332]

63. Pupim LB, Flakoll PJ, Levenhagen DK, Ikizler TA. Exercise Augments the Acute Anabolic Effects of Intradialytic Parenteral Nutrition in Chronic Hemodialysis Patients. Am J Physiol Endocrinol Metab. 2004; 286:E589–E597. [PubMed: 14678952]

64. Dong J, Sundell MB, Pupim LB, Wu P, Shintani A, Ikizler TA. The effect of resistance exercise to augment long-term benefits of intradialytic oral nutritional supplementation in chronic hemodialysis patients. J Ren Nutr. 2011; 21:149–159. [PubMed: 20580251]

65. Kopple JD, Wang H, Casaburi R, et al. Exercise in maintenance hemodialysis patients induces transcriptional changes in genes favoring anabolic muscle. J Am Soc Nephrol. 2007; 18:2975–2986. [PubMed: 17942969]

66. Collins AJ, Foley RN, Chavers B, et al. 'United States Renal Data System 2011 Annual Data Report: Atlas of chronic kidney disease & end-stage renal disease in the United States. Am J Kidney Dis. 2012; 59(A7):e1–e420.

67. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB. Survival advantages of obesity in dialysis patients. Am J Clin Nutr. 2005; 81:543–554. [PubMed: 15755821]

68. Biolo G, Ciocchi B, Bosutti A, Situlin R, Toigo G, Guarnieri G. Pentoxifylline acutely reduces protein catabolism in chronically uremic patients. Am J Kidney Dis. 2002; 40:1162–1172. [PubMed: 12460034]

69. Himmelfarb J, Phinney S, Ikizler TA, Kane J, McMonagle E, Miller G. Gamma-tocopherol and docosahexaenoic acid decrease inflammation in dialysis patients. J Ren Nutr. 2007; 17:296–304. [PubMed: 17720098]

70. Hung AM, Ellis CD, Shintani A, Booker C, Ikizler TA. IL-1beta receptor antagonist reduces inflammation in hemodialysis patients. J Am Soc Nephrol. 2011; 22:437–442. [PubMed: 21310819]

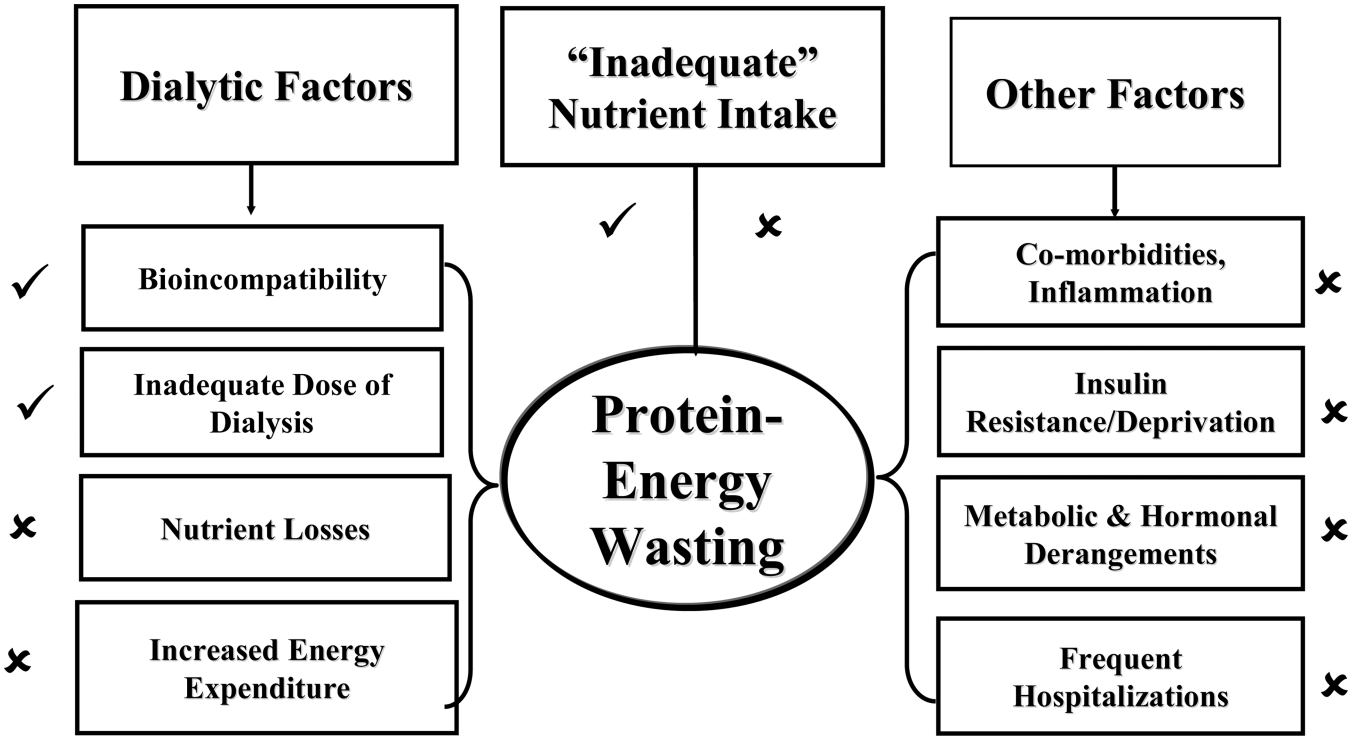


**Figure 1. Causes of protein-energy wasting in advanced kidney disease**

The factors that are adequately managed are marked with a check sign and factors that need further attention are marked with an X sign. While a significant number of chronic dialysis patients report adequate intake, the optimal protein and calorie intake is still debated and marked with both a check and an X sign.

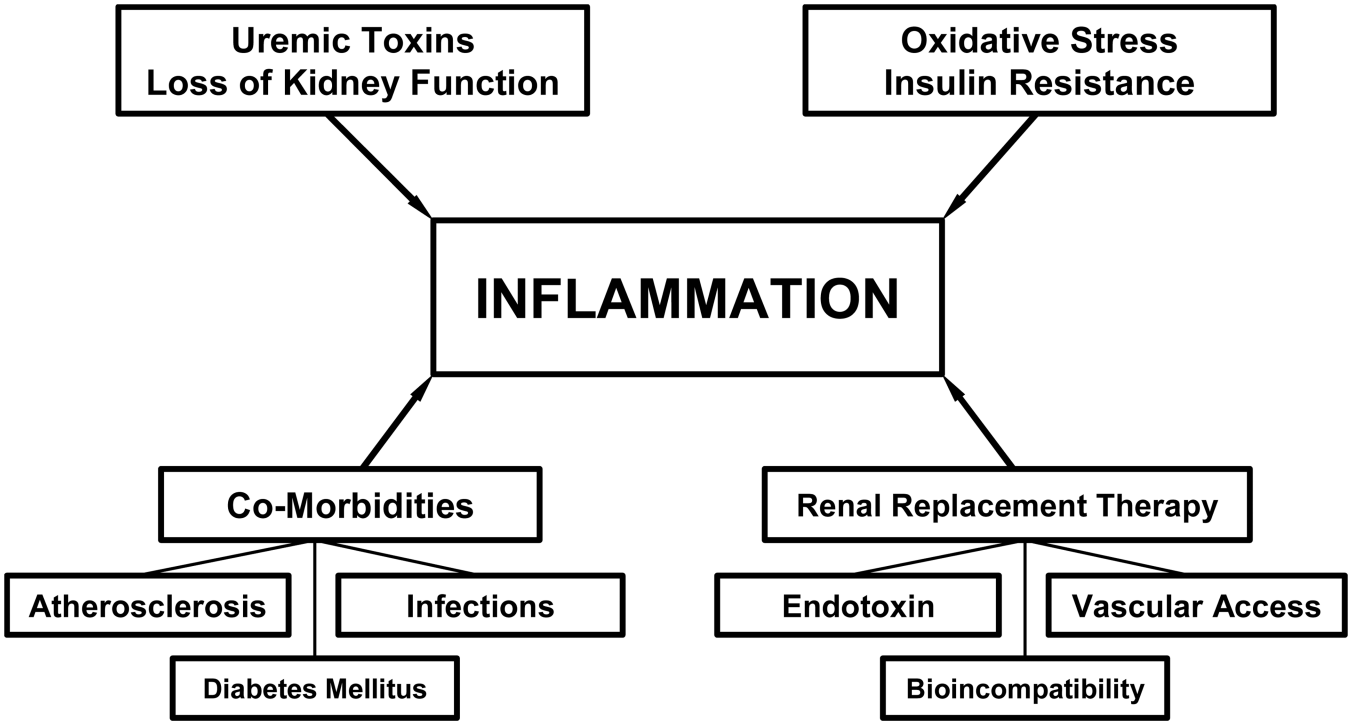


**Figure 2. A number of modifiable and non-modifiable factors lead to the chronic inflammatory state of advanced kidney disease**

## Table 1
### Suggested strategies to monitor nutritional status and guide therapy in advanced CKD

| **Simple (monthly) Assessment** | **Findings** | **Possible Interventions** |
|---|---|---|
| BW | Continuous decline or < 85% IBW | Suspect of PEW and perform more detailed nutritional assessment; |
| Serum albumin | < 4.0 g/dl | Consider preventive measures |
| Serum creatinine | Relatively low pre-dialysis values | |
| **Detailed Assessment** | **Findings** | **Possible Interventions (simple)** |
| Serum prealbumin | < 30 mg/dl, and/or | Dietary counseling: DPI ≥ 1.2 g/kg/d, energy intake 30–35 kcal/d |
| Serum transferrin | < 200 mg/dl, and/or | |
| LBM and/or Fat mass | Unexpected decrease | Increase dialysis dose to Kt/V > 1.4 |
| SGA | Worsening | Use biocompatible membranes |
| | | Upper GI motility enhancer |
| **Repeat Detailed Assessment (2 to 3 months from previous)** | **Findings** | **Possible Interventions (moderate to complex)** |
| Serum prealbumin | < 30 mg/dl, | *Nutritional supplements:* |
| Serum transferrin | < 200 mg/dl | Oral, enteric tube feeding, IDPN (if indicated) |
| LBM and/or Fat mass | Unexpected decrease | *Anabolic Factors:* |
| C-reactive protein | > 10 mg/l | Anabolic steroids |
| | | rhGH (experimental) |
| | | *Appetite Stimulants* |
| | | Megase; Ghrelin(experimental) |
| | | *Anti-inflammatory(experimental)* |
| | | IL-1receptor antagonist, pentoxifylline |

Adapted from Pupim LB, Cuppari L, Ikizler TA. Nutrition and metabolism in kidney disease. *Semin Nephrol* 2006; **26:** 134–157 with permission.
IBW: Ideal body weight; DPI: Dietary Protein Intake; LBM: Lean body Mass; SGA: Subjective Global Assessment; GI: Gastrointestinal; IDPN: Intradialytic parenteral nutrition; rhGH: recombinant human Growth Hormone

## Table.2
## Proposed nutritional and anti-inflammatory interventions in chronic disease states

Nutritional interventions:

*Chronic Dialysis Patients*

- Continuous dietary counseling
- Appropriate amount of dietary protein and calorie intake (dietary protein and energy intake > 1.2 g/kg/d and > 30 kcal/kg/d, respectively)
- Optimal dose of dialysis
- Use of biocompatible hemodialysis membranes
- Nutritional support in chronic dialysis patients who are unable to meet their dietary needs
    - Oral supplements
    - Tube feeds (if medically appropriate)
    - Intradialytic parenteral nutritional supplements for hemodialysis patients
    - Amino acid dialysate for peritoneal dialysis patients
    - Resistance exercise combined with nutritional supplementation
- Anabolic steroids
- Appetite stimulants (Not proven or Experimental)
    - Megestrol acetate, dronabinol,, melatonin, thalidomide and ghrelin)
- Growth Factors (Experimental):
    - Recombinant human growth hormone
    - Recombinant Human Insulin-like Growth Factor – 1
- Anti-inflammatory Interventions:
    - Pentoxifylline
    - Targeted anticytokine therapy (IL-1 receptor antagonist, TNFα blocker)
    - Statins
    - Thiazolidinediones
    - ACE-inhibitors
    - Resistance exercise
    - Thalidomide
    - Fish oil and Vitamin E