Nutrition And Kidney Disease In Humans

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Chronic kidney disease (CKD) is defined as persistent, progressive, and irreversible loss of kidney function. CKD is a worldwide public health problem. In the United States, CKD is estimated to affect 20 million people, and most have mildly decreased glomerular filtration rate with mildly to moderately increased excretion of albumin in the urine.[1] As in humans, CKD is also common in older (15 years of age or older) pets, reaching up to 32%. CKD leads to a number of complications and one syndrome known to affect all individuals with CKD (human, canine and otherwise) is sarcopenia, i.e., loss of lean body mass (LBM). Sarcopenia encompasses both a loss of muscle mass and function. During progression of CKD, the requirements and utilization of different nutrients change significantly, which in combination is believed to lead to increased prevalence of sarcopenia. Given the complex etiology of sarcopenia in CKD, the term protein energy wasting is also used to describe this deranged metabolic state. This particular review is intended to provide a concise overview of mechanism and treatment strategies for protein energy wasting in humans with advanced CKD.

Nutrient Metabolism In Kidney Disease

Protein Metabtolism and Requirements

Amino Acid Metabolism

CKD patients have well-defined abnormalities in their plasma and to a lesser extent in their muscle amino acid profiles.[2] Commonly, essential amino acid concentrations are low and non-essential amino acid concentrations high. The etiology of this abnormal profile is multifactorial. The progressive loss of kidney tissue, where metabolism of several amino acids takes place, is an important factor. Specifically, glycine and phenylalanine concentrations are elevated, and serine, tyrosine, and histidine concentrations are decreased. Plasma and muscle concentrations of branched-chain amino acids (valine, leucine, and isoleucine) are reduced in CKD patients, especially in ones on maintenance dialysis. In contrast, plasma citrulline, cystine, aspartate, methionine, and both 1- and 3-methylhistidine levels are increased. Although inadequate

Several studies have indicated that CKD patients spontaneously restrict their dietary protein in-take, with levels often less than 0.6 g/kg/day among those with CKD stage 5, suggesting that anorexia predisposes CKD patients to malnutrition.[3]

dietary intake is a possible factor in abnormal essential amino acid profiles, certain abnormalities occur even in the presence of adequate dietary nutrient intake, indicating that the uremic milieu has an additional effect. Indeed, it has been suggested that the metabolic acidosis that is commonly seen in uremic patients plays an important role in increased oxidation of branched-chain amino acids.

Chronic Kidney Disease Patients not yet on Maintenance Dialysis

In general, the minimal daily protein requirement is one that maintains a neutral nitrogen balance and prevents protein wasting; this has been estimated to be a daily protein intake of approximately 0.6 g/kg in healthy individuals, with a safe level of protein intake equivalent to the minimal requirement plus 2 standard deviations, or approximately 0.75 g/kg/day. One of the most significant symptoms in advanced CKD is a decrease in appetite. Several studies have indicated that CKD patients spontaneously restrict their dietary protein intake, with levels often less than 0.6 g/kg/day among those with CKD stage 5, suggesting that anorexia predisposes CKD patients

to malnutrition.[3] Accumulation of uremic toxins may not be the sole cause of decreased dietary nutrient intake. **Table 1** depicts factors that can cause decreased nutrient intake as well as other potential mechanisms of protein energy wasting in CKD patients. Individuals with CKD and co-existing diabetes mellitus are more prone to nutritional abnormalities because of additional dietary restrictions; gastrointestinal symptoms common in diabetes such as gastroparesis, nausea, and vomiting; bacterial overgrowth in the gut; and pancreatic insufficiency. Depression, which is common in CKD, is also associated with anorexia. CKD patients often are prescribed a large number of medications, particularly sedatives, phosphate binders, and iron supplements, all of which may have gastrointestinal complications. Finally, socioeconomic status, lack of mobility, and older age all may predispose to decreased dietary protein intake.

Protein Restriction in Chronic Kidney Disease Patients

Dietary protein restriction, with or without supplementation of ketoanalogues of certain amino acids, has long been considered an attractive intervention to slow the progression of kidney disease.[4] This premise is based on earlier studies indicating that excessive dietary protein intake causes hyperfiltration, leading to progression of kidney disease, especially in high risk populations such as individuals with co-existing diabetes mellitus and hypertension. As suggested by a number of meta-analyses, this dietary

TABLE 1

FACTORS LEADING TO NUTRITIONAL AND METABOLIC ABNORMALITIES IN CHRONIC KIDNEY DISEASE PATIENTS

Increased protein and energy requirements	Decreased protein and calorie intake	Increased catabolism/ decreased anabolism
▶ Nephrotic syndrome	▶ Anorexia (Uremic toxins)	▶ Dialysis-induced catabolism *Amino acid losses, Induction of inflammatory cascade*
▶ Losses of nutrients (amino acids and/or proteins) during dialysis	▶ Frequent hospitalizations	
	▶ Inadequate dialysis dose expenditure	▶ Metabolic acidosis
▶ Increased resting energy expenditure *Acute or chronic inflammation, Hyperphosphatemia, Hemodialysis*	▶ Comorbid conditions *Diabetes mellitus, Gastrointestinal diseases, Heart failure, Depression*	▶ Hormonal derangements *Hyperparathyroidism, Insulin resistance, Growth hormone resistance, Testosterone deficiency*
	▶ Multiple medications	

TABLE 2

RECOMMENDED INTAKES OF PROTEIN, ENERGY, AND MINERALS IN KIDNEY DISEASE

		Protein	Energy	Phosphorus	Sodium
Chronic Kidney Disease	**Stages 1-3**	No restriction	No restriction	600-800 mg/day	<2 g/day[a]
	Stages 4-5	0.60-0.75 g/kg/day[b]	30-35 kcal/kg/day[c]	600-800 mg/day[d]	<2 g/day
Dialysis	**Hemodialysis**	>1.2 g/kg/day	30-35 kcal/kg/day[c]	600-800 mg/day[d]	<2 g/day
	Peritoneal Dialysis	>1.3 g/kg/day	30-35 kcal/kg/day[c]	600-800 mg/day[d]	<2 g/day
Acute Kidney Injury	**No dialysis**	1.0-1.2 g/kg IBW/d	30-35 kcal/kg/day	600-800 mg/day[d]	<2 g/day
	Dialysis	1.2-1.4 g/kg IBW/d	30-35 kcal/kg/day	600-800 mg/day[d]	<2 g/day

[a]If hypertensive
[b]With close supervision and frequent dietary counseling.

[c]30 kcal/kg/day for individuals 60 years and older.
[d]Along with phosphate binders, as needed.

IBW/d, ideal body weight per day

protein restriction effect is real, albeit relatively small in the context of progressive kidney disease (0.5 ml/min/year benefit). Several smaller studies suggest that the favorable effects of dietary protein restriction extend beyond slowing the progression of disease. These include amelioration of metabolic acidosis and insulin resistance, antioxidant effects, and decreasing dietary phosphorus load. The optimal range of dietary protein restriction to exert the most beneficial outcome is not established, and the applicability of dietary protein restriction is limited by compliance.

In addition to protein restriction alone, a number of studies have also examined the effects of keto- or amino acid–supplemented low-protein diets (LPDs) or very low protein diets (VLPDs) on certain metabolic and renal outcome parameters. Several studies indicate that protein-restricted diets supplemented with keto/amino acids result in a significant decrease in urea production and a beneficial effect on insulin resistance and oxidative stress in humans.[5]
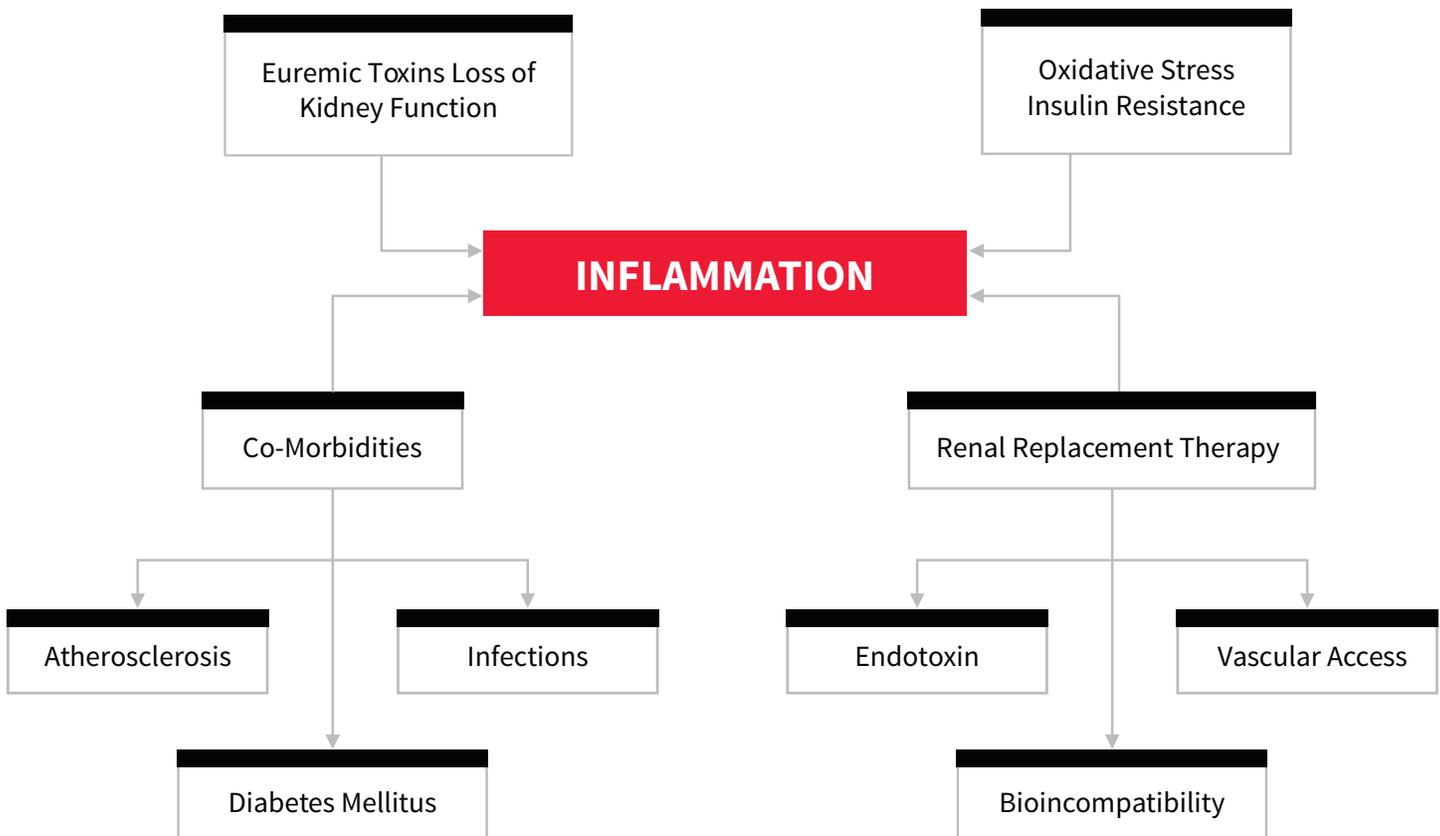
An important consideration regarding dietary protein restriction in CKD is the potential to adversely affect nutritional status. These concerns have been mostly ameliorated by a number of studies showing that well-designed diets planned by skilled dietitians and followed by motivated and compliant patients are effective and do not have harmful effects on the nutritional condition. Long-term follow-up of several relatively large cohorts of CKD patients who received 0.47 g/kg/day protein with ketoacid supplementation showed no detrimental effect on clinical outcomes. Accordingly, one can conclude that prescribing LPD or VLPD with or without keto- or amino acid supplementation with adequate caloric intake and close supervision does not seem to lead to protein energy wasting.

There are very limited data regarding the optimal level of dietary protein intake in patients with a kidney transplant. In general, these patients

Multiple factors can lead to systemic inflammation in patients with chronic kidney disease. Most of these factors are persistent, leading to a persistent inflamed state with short and long term adverse consequences.

Euremic Toxins Loss of Kidney Function		Oxidative Stress Insulin Resistance

INFLAMMATION

Co-Morbidities		Renal Replacement Therapy

Atherosclerosis	Infections	Endotoxin	Vascular Access

Diabetes Mellitus	Bioincompatibility

should also be considered as having CKD, and the same strategies for dietary protein intake and prescription should be applied. **Table 2** depicts the most current recommendations for dietary protein and energy intake for patients with different stages of CKD.

Maintenance Dialysis Patients
Once CKD patients are initiated on maintenance dialysis, dietary restrictions are used to prevent hyperphosphatemia, hyperkalemia, or metabolic acidosis; however, these restrictions could predispose dialysis patients to an increased risk of protein energy wasting, primarily due to the increased metabolic stress associated with dialysis therapies. Nutrient losses through hemodialysis (HD) or peritoneal membranes, loss of residual kidney function due to long-term dialysis treatment, and increased inflammation due to indwelling catheters, bioincompatible hemodialysis membranes, and peritoneal dialysis (PD) solutions all may lead to an overly catabolic milieu and increase the minimal amount of nutrient intake needed to maintain a neutral nitrogen balance (**Table 2**). 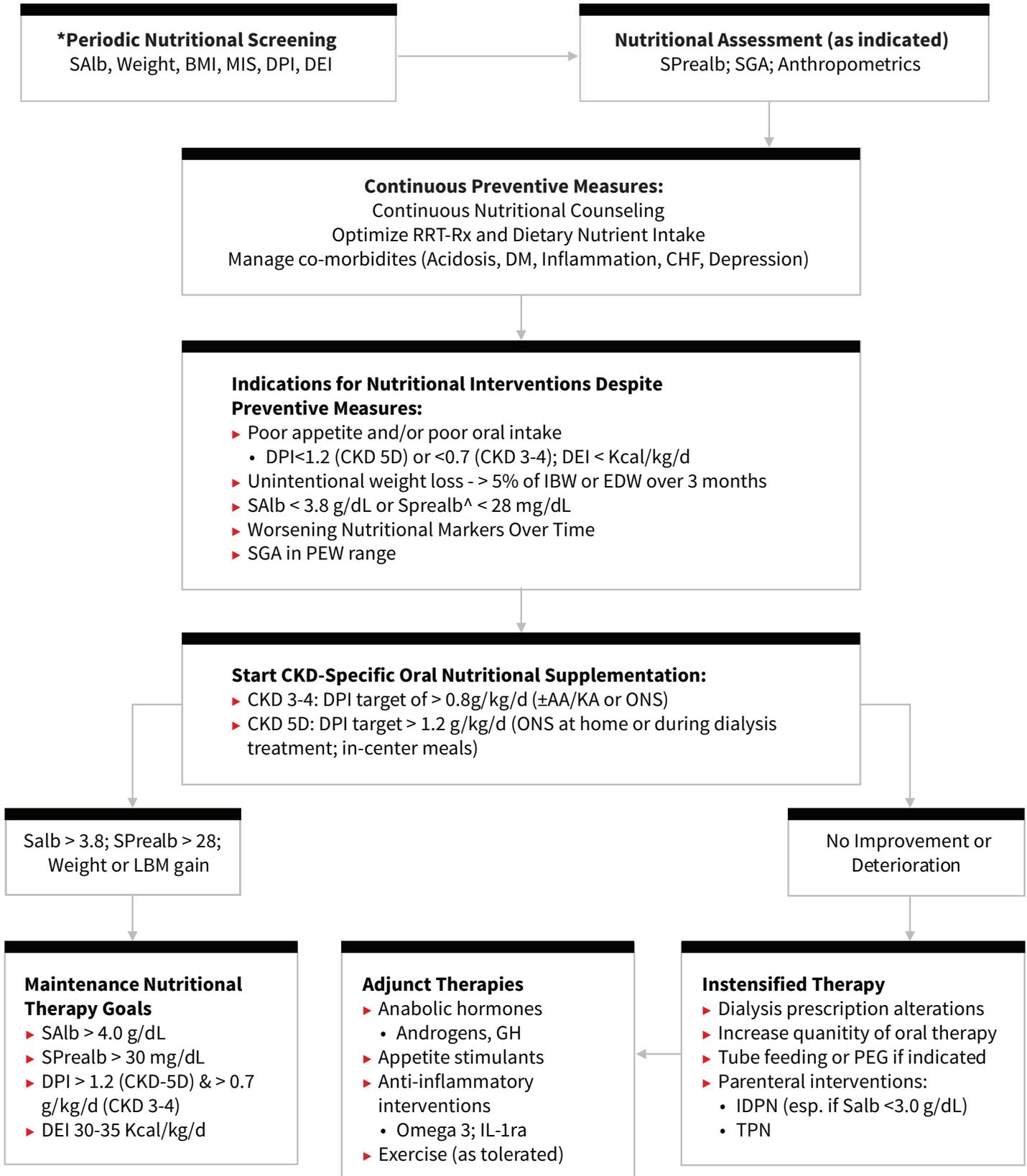In patients who cannot compensate for this increased need, a state of semistarvation ensues, resulting in the development or worsening of protein energy wasting. While the current targets for acceptable levels of dose of dialysis should be adequate to prevent development of protein energy wasting in both HD and PD patients, there are limited data suggesting that a substantial increase in dose of dialysis could result in improvement in overall nutrition status in maintenance dialysis patients.

Inflammation
Systemic inflammation is one of the major contributors to protein

FIGURE 2

Algorithm for nutritional management and support in patients with chronic kidney disease.

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*Periodic Nutritional Screening
SAlb, Weight, BMI, MIS, DPI, DEI

Nutritional Assessment (as indicated)
SPrealb; SGA; Anthropometrics

Continuous Preventive Measures:
Continuous Nutritional Counseling
Optimize RRT-Rx and Dietary Nutrient Intake
Manage co-morbidites (Acidosis, DM, Inflammation, CHF, Depression)

Indications for Nutritional Interventions Despite Preventive Measures:
▶ Poor appetite and/or poor oral intake
  • DPI<1.2 (CKD 5D) or <0.7 (CKD 3-4); DEI < Kcal/kg/d
▶ Unintentional weight loss - > 5% of IBW or EDW over 3 months
▶ SAlb < 3.8 g/dL or Sprealb^ < 28 mg/dL
▶ Worsening Nutritional Markers Over Time
▶ SGA in PEW range

Start CKD-Specific Oral Nutritional Supplementation:
▶ CKD 3-4: DPI target of > 0.8g/kg/d (±AA/KA or ONS)
▶ CKD 5D: DPI target > 1.2 g/kg/d (ONS at home or during dialysis treatment; in-center meals)

Salb > 3.8; SPrealb > 28; Weight or LBM gain

No Improvement or Deterioration

Maintenance Nutritional Therapy Goals
▶ SAlb > 4.0 g/dL
▶ SPrealb > 30 mg/dL
▶ DPI > 1.2 (CKD-5D) & > 0.7 g/kg/d (CKD 3-4)
▶ DEI 30-35 Kcal/kg/d

Adjunct Therapies
▶ Anabolic hormones
  • Androgens, GH
▶ Appetite stimulants
▶ Anti-inflammatory interventions
  • Omega 3; IL-1ra
▶ Exercise (as tolerated)

Instensified Therapy
▶ Dialysis prescription alterations
▶ Increase quanitity of oral therapy
▶ Tube feeding or PEG if indicated
▶ Parenteral interventions:
  • IDPN (esp. if Salb <3.0 g/dL)
  • TPN

energy wasting in patients with CKD (**Figure 1**).[6] Increased levels of proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor–α (TNF-α) play a crucial role in the exaggerated protein and energy catabolism present in individuals with CKD. Proinflammatory cytokines play integral roles in protein breakdown, resulting in muscle atrophy in chronic disease states such as advanced CKD. Recent data in maintenance HD patients clearly indicate exponentially increased protein catabolism, especially in the skeletal muscle compartment, in the setting of exaggerated systemic inflammation. In addition to increasing protein breakdown, chronic inflammation is associated with reduced physical activity and impairment in both insulin and growth hormone actions; it may also contribute to anorexia due to central effects. Small randomized studies suggest that certain anti-inflammatory interventions such as IL-1 receptor blockers, pentoxiyfillin, and fish oil could improve protein catabolism in maintenance dialysis patients.[7]

Metabolic Acidosis

Metabolic acidosis is associated with increased muscle protein catabolism and promotes muscle wasting in patients with advanced CKD by stimulating the oxidation of essential amino acids. Multiple studies have shown improvements in nutrition status associated with oral bicarbonate supplementation in patients with advanced CKD, while some, but not all, observational studies and one randomized clinical trial suggest that the progression of CKD is slower among individuals treated with oral bicarbonate.[8] This finding has led to a suggestion that attempts should be made to maintain a steady-state serum bicarbonate level of at least 24 mmol/L in nondialysis CKD patients. Data on bicarbonate supplementation in maintenance hemodialysis are mixed, although recent epidemiologic data suggest worse outcomes with very high predialysis serum bicarbonate levels, potentially indicating a subset of the HD population with lower dietary protein intake.

Hormonal Derangements

Resistance to the anabolic actions of insulin is a key endocrine abnormality implicated in the loss of muscle mass in chronic disease states including CKD. Enhanced protein catabolism applies to both insulin-deficient and insulin-resistant states. Maintenance hemodialysis patients with suboptimally controlled type 2 diabetes have a higher rate of muscle protein loss than hemodialysis patients without diabetes, a catabolic state that can be detected even in hemodialysis patients with insulin resistance.[9]

Acquired resistance to the anabolic actions of growth hormone is a potential cause of increased net protein catabolism in patients with advanced CKD.

Additional metabolic disorders such as increased parathyroid hormone concentration, low levels of testosterone, and several abnormalities in the thyroid hormone profile might also promote hypermetabolism and decrease protein anabolism, leading to excess net protein catabolism in patients with advanced CKD.

Acquired resistance to the anabolic actions of growth hormone is a potential cause of increased net protein catabolism in patients with advanced CKD. Growth hormone is the major promoter of growth in children and exerts anabolic actions even in adults, such as enhancement of protein synthesis, reduced protein degradation, increased fat mobilization, and increased gluconeogenesis, with insulin-like growth factor–1 (IGF-1) being the major mediator of these actions. Several studies showed that recombinant human growth hormone treatment over 6 months improves fat free mass in MHD patients.

Testosterone levels are also abnormally low among men and women with CKD, especially those treated with maintenance dialysis. Testosterone is an anabolic hormone that induces skeletal muscle hypertrophy by promoting nitrogen retention and stimulating fractional muscle protein synthesis. In dialysis and advanced CKD patients, low testosterone levels are associated with increased mortality risk. In one small clinical trial, nandrolone decanoate, an androgen analogue of testosterone, was associated with significant improvements in nutritional parameters, body composition, and physical functioning. However, its side effects, such as virilization, voice changes, and hirsutism in women and abnormalities in prostate markers in men, and changes in liver enzymes limit its routine clinical use.

TABLE 3

SUGGESTIONS FOR MONITORING NUTRITIONAL STATUS AND THERAPY IN KIDNEY FAILURE

Simple Assessment (monthly)	Findings	Possible Interventions
Body weight	Continuous decline or less than 85% IBW	No restriction
Serum albumin	Below 4.0 g/dl	Consider preventive measures
Serum creatinine	Relatively low pre-dialysis values	No specific intervention needed at this point

Detailed Assessment (as indicated by simple assessment)	Findings	Possible Interventions (simple)
Serum prealbumin	Below 30 mg/dl	Dietary counseling to increase DPI ≥ 1.2 g/kg/d and energy intake 30-35 kcal/d.
Serum transferrin	Below 200 mg/dl,	Consider timely initiation of maintenance dialysis
LBM and/or fat mass	Unexpected decrease	Assurance of optimal dialysis dose
SGA	Worsening	Upper GI motility enhancer in suitable patients

Repeat Detailed Assessment (2 to 3 months from previous)	Findings (any of the markers)	Possible Interventions (moderate to complex)
Serum prealbumin	Below 30 mg/dl	*Nutritional supplements:* Oral, enteric tube feeding, IDPN, AAD
Serum transferrin	Below 200 mg/dl,	*Anabolic interventions:* Anabolic steroids rhGH *(experimental)*
Serum creatinine	Relatively low pre-dialysis values	*Appetite Stimulants:* Megestrol acetate Ghrelin*(experimental)*
LBM and/or fat mass	Unexpected decrease	Anti-inflammatory Interventions: *IL1ra (experimental)*
C-reactive protein	Above 10 mg/l	Fish Oil

PEW, protein-energy wasting; DPI, dietary protein intake; LBM, lean body mass; SGA, subjective global assessment; IDPN, intradialytic parenteral nutrition; AAD, amino acid dialysate; rhGH, recombinant human growth hormone; IL1ra, Interleukin1 receptor antagonist.

Adapted with permission from Pupim LB, Cuppari L, Ikizler TA. Nutrition and metabolism in kidney disease. *Semin Nephrol*. 2006; 26:134-157.

Energy Metabolism and Requirements

The minimum energy requirement of patients with CKD is not well defined (**Table 2**). An individual's energy requirement is dependent on resting energy expenditure, activity level, and effects of other ongoing illnesses. Resting energy expenditure is elevated in maintenance dialysis patients compared to age-, sex-, and body mass index– matched normal controls and further increases during the HD procedure when catabolism is at a maximum due to amino acid losses into the dialysate.[10] Several comorbid conditions also lead to hypermetabolism, including systemic inflammation, uncontrolled diabetes mellitus, and hyperparathyroidism, further increasing energy requirement in patients with CKD. For earlier stages of CKD, energy requirements likely are similar to those of the general population. Among stage 4 and 5 CKD patients, the recommended energy intake is 35 kcal/kg body weight/day for those who are less than 60 years of age and 30-35 kcal/kg body weight/day for individuals 60 years and older.

Lipid Metabolism and Requirements

Dyslipidemia is common in CKD patients, and abnormalities in lipid profiles can be detected in patients once kidney function begins to deteriorate. The presence of nephrotic syndrome or other comorbid conditions such as diabetes mellitus and liver disease as well as the use of medications altering lipid metabolism (e.g., thiazide diuretics, beta-blockers) further contribute to the dyslipidemia seen in patients with CKD.

In maintenance hemodialysis patients, the most common abnormalities are elevated serum triglycerides and very-low-density lipoproteins, and decreased low-density (LDL) and high-density (HDL) lipoproteins. The increased triglyceride component is thought to be related to increased levels of apoCIII, an inhibitor of lipoprotein lipase. A substantial number of chronic hemodialysis patients also have elevated lipoprotein (a) [Lp(a)] levels. Patients treated with PD exhibit higher concentrations of serum cholesterol, triglyceride, LDL cholesterol, and apolipoprotein B even though the mechanisms that alter the lipid metabolism are similar to those of maintenance hemodialysis patients. This finding is thought to be related to increased protein losses through the peritoneum, possibly by mechanisms that are operative in the nephrotic syndrome and the glucose load supplied by dialysate causing increased triglyceride synthesis and hyperinsulinemia. PD patients also exhibit higher concentrations of Lp(a).

Assessment Of Nutritional Status In CKD Patients

A variety of parameters have been used to determine nutrition status in CKD patients. An approach that incorporates continuous screening combined with more detailed assessment techniques is preferred for these patients as well as for the general population [**see Table 3**].[11] Some are easy to perform, readily available and inexpensive, while others are sophisticated, not available in many centers, and either expensive or carry an unfavorable cost-benefit ratio. For example, a monthly nutritional screening can be easily performed at nearly any clinic or hospital by measuring serum albumin, serum prealbumin, serum transferrin, and bioimpedance values. However, if the goal is to precisely and longitudinally follow changes in body composition, one may want to use anthropometry, dual-energy x-ray absorptiometry, and even more sophisticated methods, if available. For all indirect methods, repeated measures and technical standardization are extremely important to reduce variability of results.

Prevention And Treatment Of Protein Energy Wasting

Given the importance of adequate nutritional status and the large number of factors that can result in protein energy wasting, especially in later stages of CKD, prevention and therapeutic strategies should involve a multidisciplinary approach to reduce protein and energy catabolism, prevent further losses, and restore negative balance [see **Figure 2**].[12] Prescribing dietary nutrient intake appropriate for the stage of kidney disease (**Table 2**) is critically important. Many

Many maintenance dialysis patients will continue their predialysis diets while receiving kidney replacement therapy; this is inappropriate.

maintenance dialysis patients will continue their predialysis diets while receiving kidney replacement therapy; this is inappropriate, and it is important that dietary protein and calorie intake increase to meet requirements after dialysis initiation. Critical and often simple and straightforward steps to minimize the risk for the development or worsening of protein energy wasting include combating the catabolic effects of kidney replacement therapy, treating obvious causes of systemic inflammation, and managing comorbid conditions such as metabolic acidosis, diabetes, and depression. Managing food intake by either dietary counseling or positive reinforcement is crucial, particularly for patients treated with maintenance dialysis. Renal dietitians play a critical role in providing the majority of educational support and monitoring patient outcomes.

When dietary counseling to improve nutritional status is unsuccessful, other forms of supplementation such as enteral (including oral protein, amino acid, and energy supplementation, nasogastric feeding tubes, percutaneous endoscopic gastrostomy or jejunostomy tubes) and intradialytic parenteral nutrition (IDPN) may be considered. Only a limited number of low quality studies evaluating the effects of oral or enteral supplementation in CKD patients not on maintenance dialysis are available. Furthermore, most of these studies demonstrate only a variable degree of success. It is usually a challenge to determine whether an oral or enteral form of supplementation is necessary and effective if administered in

Two recent large-scale observational studies reported significant survival benefit associated with oral nutritional supplement administration during hemodialysis in hypoalbuminemic hemodialysis patients.

CKD patients not on maintenance dialysis. In these patients, recommendations that are developed for other comorbid conditions such as diabetes mellitus, frailty, and old age should be used while taking into account the implications of stage of kidney disease, especially in terms of mineral and electrolyte content of the supplementation.

In certain maintenance dialysis patients, where the standard measures are unable to prevent loss of protein and energy stores, nutritional supplementation is a suitable next step. In general practice, the gastrointestinal route is always preferred as the primary choice for nutritional supplementation. Oral supplementation should be given two to three times a day, preferably 2 hours before or after main meals and/or during HD. Oral supplementation can provide an additional 7 to 10 kcal/kg per day of energy and 0.3 to 0.4 g/kg per day of protein. A minimum spontaneous dietary intake of 20 kcal/kg per day of energy and 0.4 to 0.8 g/kg per day of protein to meet the recommended dietary energy intake and dietary protein intake targets is required.

Although there are no well-designed, large sample size, prospective studies, the beneficial nutritional effects of these supplements have been reported primarily on serum

biomarkers such as albumin, prealbumin, and transferrin, as well as gains in body weight and lean body mass. Improvements in markers of quality of life and physical functioning have also been reported. In prospective randomized studies examining hospitalizations and death, the statistical power to appropriately assess the efficacy of these interventions is mostly lacking while two recent large-scale observational studies reported significant survival benefit associated with oral nutritional supplement administration during hemodialysis in hypoalbuminemic hemodialysis patients. The limitations of these studies include a retrospective design, convenience sampling, and residual confounding from unmeasured variables. A pragmatic cluster randomized clinical trial is underway to answer this question.

For patients who are unable to tolerate nutritional supplementation by mouth, nasogastric, percutaneous endoscopic gastrostomy (PEG) or jejunostomy tubes can be considered. Although most of the studies reported beneficial nutritional effects of intradialytic parenteral nutrition (IDPN) administration in maintenance hemodialysis patients with overt protein energy wasting, a relatively large sample sized, prospective, randomized, controlled study comparing IDPN

plus an oral nutritional supplement (ONS) versus ONS alone showed similar improvements in nutritional parameters, with no additional benefit for hospitalization or death rates.[13] Concerns regarding increased infectious complications, greater fluid volume requirement, and high cost remain as the barriers for the frequent use of IDPN. Hence, parenteral provision of nutrients should be reserved as an approach for individuals who cannot tolerate oral or enteral administration of nutrients. Studies using amino acid dialysate (AAD) in PD patients have provided conflicting results. In studies that suggested benefit from AAD, serum transferrin and total protein concentrations increased and plasma amino acid profiles tended toward normal with one or two exchanges of AAD per day. On the other hand, exacerbations of uremic symptoms as well as metabolic acidosis are potential complications of AAD.

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