REVIEW ARTICLE

Sustenance in Chronic Kidney Disease: Beyond the Calorie Count

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ABSTRACT

Diet and nutrition play key roles in the management of metabolic disorders like hypertension, obesity, hyperlipidemia and diabetes. All these conditions are linked with the pathogenesis of chronic kidney disease (CKD). Patients with CKD frequently exhibit a progressive loss of muscle and fat mass that may not be related to reduced intake alone. This article provides a comprehensive overview of protein-energy wasting (PEW) in CKD, including its etiology and the obesity paradox and the nutritional guiding principles.

Keywords: Chronic kidney disease, protein-energy wasting, nutrition, deficiencies, supplementation

DWINDLING GFR BLOCKING THE EXIT OF NITROGENOUS WASTE

Diet and nutrition have an extremely pivotal role to play in the management of metabolic disorders like hypertension, obesity, hyperlipidemia and diabetes, all of which are bonded stalwartly with the pathogenesis of chronic kidney disease (CKD).

As the glomerular filtration rate (GFR) experiences a downhill movement, the nitrogenous metabolites tend to be retained, resulting in a decreased ability to regulate the levels of electrolytes and water. Alongside this, certain vitamin deficiencies can occur due to dietary changes. Adding up, protein-energy depletion is frequently observed and predicts a pitiable outcome.

THE UNMET NEEDS OF NUTRITION: PROTEIN-ENERGY WASTING

Patients with CKD, particularly more advanced stages, frequently exhibit a progressive loss of muscle and fat mass that may not be related to reduced intake alone. Because malnutrition refers to an intake that is inappropriate for the needs of the individual, it can be misleading to use this blanket term when reduced intake is not necessarily the sole cause of wasting. Protein-energy wasting (PEW) is defined as a state of nutritional and metabolic derangements in patients with CKD that may negatively affect nutritional status and lean body mass, leading to frailty.

PERCEPTION OF PROTEIN-ENERGY WASTING

Protein-energy wasting was proposed in 2007 by the International Society of Renal Nutrition and Metabolism as a notion defining the multifactorial nature of metabolic processes and nutritional consequences of uremia in CKD. PEW involves a hypermetabolic state that promotes protein catabolism, attributed to both metabolic consequences of CKD—including inflammation, oxidative stress, uremia, metabolic acidosis, diminished efficacy of anabolic hormones and a multi-morbid condition—and the catabolic nature of hemodialysis (HD), which can lead to protein losses and muscle and fat wasting (Fig. 1).

Therefore, the reduction in energy and protein intake associated with PEW is often secondary to other factors, rather than a primary consequence of inadequate access to adequate energy and protein to meet nutritional needs, as in primary malnutrition. In clinical practice, the reduction in nutritional intake and causes may be difficult to separate because they are synergistic and may exacerbate each other.

PERPETRATOR OF PROTEIN-ENERGY WASTING IN CHRONIC KIDNEY DISEASE

Understanding the features that have a say in the etiology of PEW is critical to put in the picture,

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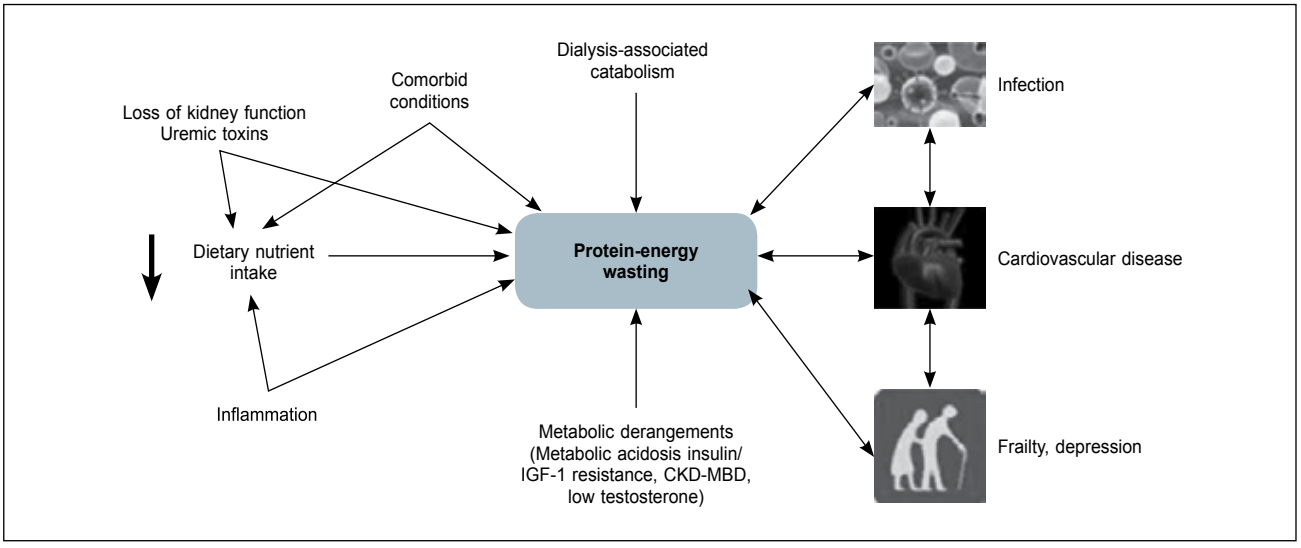

Figure 1. The conceptual model for protein-energy wasting in CKD.
CKD-MBD = Chronic kidney disease-mineral bone disorder; IGF-1 = Insulin-like growth factor 1.

the suitable assessment and treatment strategies (Table 1). Furthermore, adequate nutritional intake will not alter some of the contributing factors, such as hypermetabolism secondary to inflammation, the reduction in anabolic response, the catabolic nature of HD, insulin resistance or frailty associated with reduced physical activity. A multifaceted therapeutic approach for this complex syndrome is therefore necessary.

The prevalence of PEW in dialysis patients ranges from 10% to 70%, depending on the choice of nutritional marker and the population studied. There is also diminished nutritional status before initiation of dialysis, which strongly predicts mortality on dialysis. Several factors contribute to the high incidence of PEW.

There is a spontaneous reduction in nutrient intake that parallels the decrease in GFR and is largely driven by CKD-associated anorexia. This anorexia is caused by impaired taste acuity and diminished olfactory function, medications, autonomic gastroparesis, psychological and socioeconomic factors and inadequate dialysis. Frailty, poverty, advanced age and multiple acute or chronic comorbidities also may contribute to suboptimal intake. Protein and amino acid losses occur during dialysis treatment. Metabolic acidosis and periods of acute or chronic illnesses may induce protein catabolism. This is mediated in large part through the ubiquitin-proteasome pathway of protein degradation.

Chronic inflammation may contribute to both an increase in nutritional needs and anorexia. Alterations in intestinal microbiota and increased permeability of the intestinal barrier may play a pivotal role in the pathogenesis of inflammation. Endocrine disorders, such as insulin resistance (associated with increased muscle breakdown), vitamin D deficiency and increased parathyroid hormone concentrations have long been considered contributors to PEW.

Table 1. Causes of Protein-energy Wasting in CKD

Decreased protein and energy intake
• Anorexia, problem in organs involved in nutrient intake
• Dietary restrictions
• Depression, frailty, dependency
Hypermetabolism
• Increased energy expenditure
• Metabolic acidosis
• Inflammation
• Hormonal disorders
▪ Insulin resistance of CKD
▪ Increased glucocorticoid activity
Decreased anabolism
• Resistance to GH/IGF-1
• Testosterone deficiency
• Low thyroid hormone levels
Comorbidities and lifestyle
• Comorbidities (DM, CHF, depression, CAD, PVD)
• Poor physical activity
• Unhealthy dietary pattern
Dialysis
• Nutrient losses into dialysate
• Dialysis-related inflammation and hypermetabolism

CKD = Chronic kidney disease; GH = Growth hormone; IGF-1 = Insulin-like growth factor 1; DM = Diabetes mellitus; CHF = Congestive heart failure; CAD = Coronary artery disease; PVD = Peripheral vascular disease.

THE OBESITY PARADOX IN CKD: REVERSE EPIDEMIOLOGY

Although there is a high prevalence of PEW in patients with CKD associated with poorer outcomes, paradoxically a higher body mass index (BMI) is associated with better survival. This is termed *reverse epidemiology*.

APPRAISAL OF NUTRITIONAL STATUS

The measurement of nutritional status does not lend itself to one simple test, and a panel of measures is required.

Intake Composition

Diet history, recall and food diaries are the mainstays for estimation of dietary intake. In addition, a gradual decrease in blood urea nitrogen and reduced phosphate and potassium levels may indicate a decrease in protein intake in dialysis-dependent patients, and low serum cholesterol level may indicate a poor calorie intake. The emission of urea is easily calculated and is often used to estimate adequacy of dialysis.

The protein equivalent of total nitrogen appearance (PNA) can be estimated on HD from interdialytic changes in urea nitrogen concentration in serum and the urea nitrogen content of urine and dialysate.

Index of Body Mass

The BMI (BMI = weight [kg]/height [m^2]) is the most commonly used parameter for nutritional assessment. BMI cannot distinguish muscle from fat mass and is affected by hydration status.

Composition of the Body

An assortment of techniques can make a distinction between body compartments on the basis of physical characteristics, which can provide information about nutritional state (body lean tissue and fat content) and hydration. Skinfold thickness can be used to assess body fat, and muscle mass can be assessed by measurement of mid-upper arm muscle circumference.

Although these anthropometric parameters are inexpensive and relatively easy to measure, they are limited by inconsistency, both on the part of patient and examiner. Sequential measures of bioelectrical impedance are used as an appendage to the day-to-day clinical appraisal of hydration status and body composition management of patients on dialysis.

The Primeval Protein

Fluid status, impaired hepatic function, age and acute inflammatory conditions can affect albumin levels. However, despite its relatively longer half-life (20 days), albumin remains an important measure of nutritional status and health of the patient. Clinically, it may be possible to observe the growth of white nails when there has been a transient period of hypoalbuminemia. Serum transferrin is linked to body iron stores and may be altered with changes in iron status.

NUTRITIONAL GUIDING PRINCIPLES

Guideline campaigners advocate that it is important that dietary restrictions are not gratuitously made obligatory for each and every individual, rather the advice be tailored to the individual and altered as circumstances dictate (Table 2).

DYSREGULATED LIPID COMPOSITION

Although disturbances in lipid metabolism are commonly seen in CKD, there is a paucity of data on the effect of diet therapy in this group. A diet low in fat (particularly saturated fat) with an increased intake of soluble fiber may be helpful in reducing cholesterol levels, although the role of cholesterol lowering in CKD patients is controversial. Losing weight and consuming a diet lower in sugar may improve hypertriglyceridemia, but a balance needs to be struck between healthy eating concepts and nutritional adequacy.

VITAMINS, MINERALS AND TRACE ELEMENTS

Vitamins, minerals and trace elements deficiencies are not uncommon in patients with CKD and it relates to dietary restriction, dialysate losses and the necessity of integral renal function for normal metabolism of certain vitamins. However, the dietary requirements for patients with CKD are not lucid. Protein and potassium restrictions can lead to inadequate intakes of pyridoxine, vitamin B12, folic acid, vitamin C, iron and zinc. The use of recombinant human erythropoietin may increase the requisite for iron and folic acid. In the absence of firm guidance, it is prudent to have a low threshold for commencing water-soluble vitamin preparations. High-dose vitamin C supplements should be avoided in CKD because of the increased risk for secondary tissue oxalate deposition. A review on fat-soluble vitamins in advanced CKD concluded that there is universal agreement that supplementation with vitamin A is generally not recommended (unless a patient is receiving total parenteral nutrition) because

Table 2. Nutritional Recommendations for CKD

Daily intake	Predialysis CKD	Hemodialysis	Peritoneal dialysis
Protein (g/kg ideal BW) (refer to KDOQI for estimation of adjusted edema-free BW)	0.6-1.0 Level depends on the nephrologist's viewpoint. 1.0 for nephrotic syndrome.	Min ≥1.1 Recommendations are in conjunction with an adequate energy intake. Requirements may be higher during illness because of multiple comorbidities or during acute periods of infection, including peritonitis.	Min 1.0-1.2
Energy (kcal/kg BW)	35 (<60 y) 30-35 (>60 y)	35 (<60 y) 30-35 (>60 y) 30-40 kcal/kg ideal BW	35 including dialysate calories (<60 y) 30-35 including dialysate calories (>60 y)
Sodium (mmol)	<100 (more if salt wasting)	<100	<100
Potassium	Reduce if hyperkalemic	Reduce if hyperkalemic	Reduce if hyperkalemic; potassium restriction is generally not required. May need to enhance potassium intake if hypokalemic.
	If hyperkalemic, advice will be to decrease certain foods (e.g., some fruits and vegetables) and giving information about cooking methods.		
Phosphorous	Reduce because of phosphate retention. Monitor levels. Advice will be to reduce certain foods (e.g., dairy, offal, some shellfish) and processed foods with high content of added phosphates, and giving information about the timing of binders with high-phosphorus meals and snacks.		

deficiencies are rare, dialysis losses are minimal and buildup leading to toxicity can occur.

Vitamin E has been suggested to have antioxidant properties and beneficial effects for patients with CKD. Evidences suggest that most dialysis-dependent patients have subclinical vitamin K deficiency, and there is no known toxicity but, its benefits are waiting to get approval from the clinical trials. Novel, orally administered potassium-exchanging compounds are being investigated as possible treatment options for the management of hyperkalemia. Sodium zirconium cyclosilicate and patiromer act by enhancing potassium removal, predominantly through the gastrointestinal (GI) tract.

BENEVOLENT SUPPLEMENTATION

If food fortification advice is insufficient, supplements, in the form of high-protein, high-calorie drinks, powders and puddings, should be considered. Enteral tube feeding is also an option if nutrient intake cannot be increased sufficiently by use of oral supplements.

Renal-specific tube feeds and supplements are available that have lower fluid and electrolyte contents. A systematic review suggested that enteric multinutrient support increases serum albumin concentration and improves total dietary intake in patients receiving maintenance dialysis.

The GI route is the preferred choice for nutritional supplementation. However, intradialytic parenteral nutrition (IDPN) has been used to provide intensive parenteral nutrient therapy with use of concentrated hypertonic solutions infused into the venous blood line three times weekly during HD treatments for patients who cannot tolerate oral or enteral administration of nutrients. IDPN typically provides 800-1200 kcal three times weekly, in the form of glucose and fat emulsion and 30-60 g of protein and so will only supplement rather than provide full nutritional needs.

Intraperitoneal amino acids (IPAAs) can be used in peritoneal dialysis. A 1.1% amino acid solution is substituted for glucose in peritoneal dialysis (PD) fluid, and about 80% of the amino acids are absorbed in a 4-hour period. The long-term effects of IPAAs on nutritional status and clinical outcomes are not known, and the solution is often used primarily to reduce glucose exposure. Expert opinion on the use of these approaches is inconsistent. The Kidney Disease Outcomes Quality Initiative (KDOQI) has suggested that IPAAs (for PD) or IDPN (for HD) should be considered for patients who have evidence of protein

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or energy malnutrition and inadequate protein or energy intake and who are unable to tolerate adequate oral supplements or tube feeding.

HUNGER SYRUPS

Megestrol acetate, a progesterone derivative, moderately improves appetite in HD patients, as shown in small studies. However, megestrol acetate has adverse effects and larger trials are required before recommendations can be made for CKD patients. More studies are also required for ghrelin, anorexigenic hormone and melanocortin-receptor antagonists.

GUT-WELL-MICROBIOME

There is accumulating evidence that the GI tract may be a major source of chronic inflammation in CKD. It is hypothesized that altered diets (low potassium, phosphorus and fiber) may affect the gut microbiome, resulting in overgrowth of bacteria that produce uremic toxins and a leaky epithelial barrier that allows toxins to get into the circulation. It has been suggested that prebiotic and probiotic formulations may lower serum levels of uremic toxins. However, more trials investigating gut-targeted therapeutics are needed before they could be recommended for use in clinical practice.

pH BALANCE

Although some trials have shown no detrimental effect of mild metabolic acidosis, many others have reported that normalization of serum bicarbonate concentration is beneficial for protein nutritional status and bone metabolism. Current guidelines recommend the correction of acidosis in dialysis-dependent patients.

CONCLUSION

Protein-energy wasting is a relatively common metabolic complication inherent to CKD. A worsening of quality-of-life and an increase in the risk for comorbidities, hospitalizations and death accompany the onset and progression of PEW. The cause of PEW is multifactorial, involving undernutrition (insufficient or inadequate nutrient intake) and excess protein catabolism that altogether favors the progressive and continuous loss of energy and fat fuels. This multifactorial nature makes diagnosis difficult; it must be based on the combined interpretation of complementary nutritional screening and assessment tools.

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