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Recent advances in the pathophysiology and management of protein-energy wasting in chronic kidney disease

Kosaku Nitta* and Ken Tsuchiya

Abstract

Protein-energy wasting (PEW) is a syndrome that consists of metabolic and nutritional abnormalities that often occur in chronic kidney disease (CKD), and PEW has been found to be associated with increased morbidity and mortality. A review was conducted to identify publications detailing the pathophysiology and management of PEW in CKD. The International Society of Renal Nutrition and Metabolism (ISRNM) has recently published the consensus statement of current knowledge regarding the etiology of PEW in CKD. Although insufficient food intake due to poor appetite and dietary restrictions contributes to the development of PEW, many other factors must be present for PEW to develop. The others include uremia-induced alterations such as increased energy expenditure, chronic inflammation, metabolic acidosis, and endocrine disorders that lead to a state of hypermetabolism and result in excess muscle and fat catabolism. In addition, comorbid conditions associated with CKD, low physical activity, frailty, and dialysis itself also contribute to the development of PEW. Serial assessments of the nutritional status of CKD patients by means of several scoring tools, including the Subjective Global Assessment (SGA), Malnutrition Inflammation Score (MIS), Geriatric Nutritional Risk Index (GNRI), and PEW diagnostic criteria, are recommended to diagnose and manage PEW. This review summarized recent advances in the etiology and evaluation of PEW of CKD patients. However, there are few treatment options for PEW with proven efficacy in terms of improved quality of life, morbidity, and mortality. Proposed therapeutic interventions need to be evaluated in randomized controlled trials to determine whether they improve clinically relevant outcomes.

Keywords: Malnutrition, Protein-energy wasting, Mortality, Chronic kidney disease

Background

The concept of protein-energy wasting (PEW) was proposed by the International Society of Renal Nutrition and Metabolism (ISRNM) in 2007 [1]. PEW is a syndrome that consists of nutritional and metabolic abnormalities that are common in patients with chronic kidney disease (CKD), especially in those with end-stage renal disease (ESRD), and it is associated with high morbidity and mortality. Although insufficient food intake due to poor appetite and dietary restrictions contributes to malnutrition, the pathophysiology of PEW cannot be fully explained by undernutrition. As shown in Table 1, PEW is thought to be attributable to many factors, including aging, hypercatabolic status, increased resting energy expenditure (REE), uremic toxins, malnutrition, chronic inflammation, and acidosis [2]. This review article summarizes recent advances in the pathophysiology and management of PEW in CKD patients.

Pathophysiology of PEW

Undernutrition and appetite loss

Low energy and/or protein intake was found to be associated with a significant decline in nutritional parameters such as the serum albumin levels and a higher increased risk of morbidity and mortality in patients with advanced CKD [3, 4]. Although restriction of dietary sodium, phosphate, potassium, and fluid intake prevents complications, dietary therapy may not be effective when dietary restrictions are unaccompanied by a dietitian's instruction in regard to alternative food

* Correspondence: knitta@kc.twmu.ac.jp
Department of Medicine, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

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Table 1 Phathogenesis of PEW in CKD patients

Causes
1. Decreased protein and energy intake
a. Anorexia
b. Dietary restrictions
c. Alterations in organs involved in nutrient intake
d. Depression
2. Hypermetabolism
a. Increased energy expenditure
(1) Inflammation
(2) Increased circulating proinflammatory cytokines
b. Hormonal disorders
(1) Insulin resistance of CKD
(2) Increased glucocorticoid activity
3. Metabolic acidosis
4. Decreased physical activity
5. Decreased anabolism
a. Resistance to GH/IGF-1
b. Low thyroid hormone levels
6. Comorbidities
a. Diabetes mellitus
b. Chronic heart failure
7. Dialysis procedure
a. Nutrient losses into dialysate
b. Dialysis-related inflammation
c. Dialysis-related hypermetabolism

choices and/or strategies to ensure adequate nutrient intake [5, 6].

Appetite loss often leads to inadequate protein and energy intake and contributes to poor quality of life [7, 8], and the prevalence of appetite loss among ESRD patients has been reported to be 35 to 50 % [9, 10]. A spontaneous decrease in food intake occurs during a progressive decline in kidney function, and the decline is correlated with accumulation of nitrogen-derived uremic toxins [11, 12]. Factors that affect food intake involve not only metabolic disturbances but abnormalities of the digestive system [13].

Decreased energy intake results in reduced insulin secretion, which stimulates the gluconeogenesis from glycogen and increases fatty acid mobilization, and it contributes to a reduction in basal metabolic rate [14]. Muscle mass is preserved because of increased insulin sensitivity, and diets containing as little as 0.55 g/kg/day of protein may be well tolerated [15]. However, serum prealbumin and albumin levels have increased half-life, and their concentration as a result of moderate calorie or protein restriction does not change [16, 17].

Hypermetabolism

Increased REE

The REE of CKD patients is usually normal but it increases from 12 to 20 % during a hemodialysis (HD) session [18] or when there are comorbidities such as poorly controlled diabetes [19], severe hyperparathyroidism [20], and cardiovascular disease (CVD) [21]. Increased REE is frequently mitigated by decreased physical activity, which leads to a reduction in total energy expenditure [22, 23].

Chronic inflammation

Chronic inflammation induces muscle insulin resistance via activation of intracellular NADPH oxidases [24], and the inflammatory response is associated with an increase in REE. Inflammation causes a decline in the serum albumin level and a reduction in the synthesis and half-life of serum albumin [25]. The increased oxidative stress induced by inflammation is associated with muscle insulin resistance, muscle wasting, and atherosclerotic disease [26]. Thus, chronic inflammation causes an increase in REE and oxidative stress, leading to muscle loss.

Inflammatory markers have been reported to be increased in conditions associated with muscle loss, including in CKD [27–29]. Muscle loss due to inflammation has been found to be related to increased inflammatory cytokine production [29]. A previous study showed that high circulating interleukin (IL)-6 levels contribute to inflammatory muscle protein losses that are triggered by alteration of IL-6 signaling due to interaction with acute-phase proteins such as serum amyloid A, to impair insulin/insulin-like growth factor (IGF)-1 signaling via the transcription 3 activator [30]. In uremic skeletal muscle, IL-6 has also been linked to increased caspase-3 activity as the initial step in loss of muscle protein [31].

Tumor necrosis factor (TNF)-related weak inducer of apoptosis (TWEAK), a member of the TNF superfamily [32], binds to its receptor, Fn14, which is linked to signaling pathways involved in the regulation of nuclear factor kappa light-chain enhancer of activated B cells (NF-κB) and to apoptotic cascades, and a significant interaction between soluble TWEAK and IL-6 has been found to be in the prediction of mortality and reduced muscle strength in HD patients [33].

Humoral factors

Impairment of insulin/IGF-1 Resistance to insulin, IGF-1, and growth hormone has been implicated as a mechanism of muscle loss in adult CKD patients. Insulin or IGF-1 binds cell surface receptors that activate similar downstream signaling pathways, which act to prevent loss of muscle protein [34]. Because myofiber shrinkage and satellite cell fusion are regulated by insulin and IGF-1, the insulin/IGF-activated signaling pathways determine the balance

between protein synthesis and degradation, and changes in the balance lead to overall changes in muscle mass.

The effect of low insulin concentrations on muscle mass has been clearly described. The net protein anabolic effect of insulin involves a reduction in proteolysis more than increased protein synthesis. The alterations in glucose metabolism that occur in association with hyperinsulinemia and decreased tissue sensitivity to insulin are partially correctable by HD [35, 36]. HD patients with type 2 diabetes have a higher rate of muscle protein loss than in the absence of diabetes [37]. Moreover, the greater insulin resistance correlates with muscle protein breakdown in nondiabetic HD patients [38]. Insulin resistance is a major target of intervention in PEW. For example, treatment with an insulin sensitizer (PPARγ agonist, rosiglitazone) suppressed muscle proteolysis in insulin-resistant mice [39]. It is not surprising that rosiglitazone treatment has been found to be associated with significantly lower all-cause mortality and higher serum albumin levels among insulin-free, but not insulin-requiring, diabetic HD patients [40].

Uremia, inflammatory cytokines, metabolic acidosis, glucocorticoids, and angiotensin (ANG)-II share a common mechanism as causes of muscle wasting: impairment of insulin/IGF-1 actions by altering the signaling through the phosphatidylinositol 3-kinase (PI3-kinase)/Akt pathway [41, 42]. Dysfunctional PI3-kinase/Akt activity also results in activation of caspase-3, an apoptotic protease that degrades actin from actomyosin complexes [43], and a byproduct of this proteolytic reaction is a characteristic actin fragment that has been shown to serve as a biomarker of muscle wasting in HD patients [31].

Low thyroid hormone levels There are no available data which can distinguish whether low thyroid hormone levels in CKD patients with PEW are an adaptation that reduces REE and minimizes protein catabolism or an insufficient adaptation participating in the wasting syndrome [44]. Low triiodothyronine levels in CKD stage 5 patients are associated with systemic inflammation and endothelial dysfunction and with high all-cause and cardiovascular mortality [45–48]. The correlation between triiodothyronine levels and mortality rates was weaker after adjustment for serum C-reactive protein and albumin levels as surrogate PEW markers [49]. Thus, even if low thyroid hormone participates in the PEW process, the changes in thyroid hormone levels may act as intermediate links among inflammation, metabolic acidosis, PEW, and mortality and not as a primary cause.

Metabolic acidosis

Metabolic acidosis is a key mechanism in the starvation response, and it induces the release of branched chain amino acids from muscle during ketosis. It also causes insulin resistance, which leads to loss of muscle mass. Acidosis does not alter insulin/IGF-1 receptor binding, but it inhibits intracellular signaling. Metabolic acidosis induces increased adrenal glucocorticoid production, and adrenalectomized rats exhibit much less muscle wasting that is reserved by glucocorticoid replacement. Glucocorticoids induce insulin/IGF-1 resistance in skeletal muscle by altering the same signaling pathways that are affected by acidosis, but they act on slightly different signaling molecules within the pathways [50]. It is noteworthy that prevailing evidence from other CKD comorbidities, including ANG II and inflammation, indicates that insulin/IGF-1 resistance and elevated serum glucocorticoid levels are the physiological responses that cause both the increase in protein catabolism and suppression of protein synthesis [51, 52]. Investigating this coordinated response may provide additional evidence in regard to how insulin/IGF-1 signaling controls muscle wasting.

Comorbidities

Typical comorbidities associated with CKD or ESRD contribute to a catabolic process and to the development of PEW. In view of the high prevalence of diabetes mellitus in CKD patients, it may be the most important comorbidity. Pupim et al. [53] showed that diabetes is an important predictor of the lean body mass loss of dialysis patients and that reduced insulin signaling as a result of insulin absence or resistance results in increased muscle protein breakdown [37]. Diabetes also causes CVD and neuropathy, both of which contribute to infection, muscle atrophy, and diabetic gastroparesis. According to these complications, long-term diabetic dialysis patients no longer require hypoglycemic therapy, and the poor outcomes in this subgroup with "burnt-out diabetes" may be the result of PEW [54].

CVD, especially congestive heart failure (CHF), is another common comorbidity [55]. Inadequate cardiac output drives neurohumoral responses associated with PEW, including increased serum glucocorticoid and ANG II levels and enhanced sympathetic nerve activity. Right ventricular heart failure with passive congestion of the liver and gut wall edema is associated with alterations in nutrient absorption, appetite loss, and gut mucosal barrier function [55, 56].

CKD mineral bone disorder (CKD-MBD) is a comorbid condition associated with PEW. PEW contributes to CKD-MBD, because body weight loss, inflammation, and physical inactivity lead to bone loss. Certain conditions associated with CKD such as protein loss and appetite loss can predispose these patients to reduced vitamin D levels. Low circulating vitamin D levels, a decrease in klotho, and an increase in fibroblast growth factor-23 levels stimulate parathyroid hormone synthesis, thereby contributing to the development of secondary hyperparathyroidism [57].

Vitamin D and/or parathyroid hormone have long been considered contributors to PEW, and vitamin D appears to play a role in some key molecular pathways involved in PEW and muscle regulation [58]. There is a positive association between hypogonadism and 25-hydroxyvitamin D levels, suggesting an additional mechanism by which vitamin D may regulate muscle mass in males [59].

Low physical activity and frailty

Decreased physical activity is likely to play a major role in the pathophysiology of PEW in association with increased CVD mortality, because some CKD patients with low physical activity are at increased risk of progression to CKD secondary to obesity, diabetes, and hypertension, which lead to CVD. In addition, some common comorbidities in CKD patients are associated with decreased ability to exercise. Furthermore, certain complications of CKD, including anemia, volume overload, and muscle wasting, limit exercise ability. Patients with G3–G5 CKD have a lower median peak oxygen consumption level, and it limits exercise by some patients enough to impair activities of daily living [60]. Muscle weakness as measured by grip strength and maximum gait speed is common in G5 CKD [61]. Lack of exercise can increase inflammatory markers in association with decreased muscle mass, may be associated with mortality [62].

Dialysis procedure

Recent studies have reported how dialysis treatment affects protein and energy homeostasis. Amino acid and protein loss during dialysis sessions combined with low nutrient intake result in low nutrient availability for muscle synthesis [63, 64]. Catabolic effects of HD therapy on protein homeostasis are profound. The net protein breakdown has been related to (1) an absolute decline in amino acid levels due to dialysis losses, (2) imbalances in amino acid levels, and (3) activation of the inflammatory cascade [65]. Fortunately, concurrent amino acid supplementation can prevent or reverse these adverse effects in HD patients [66–68], providing an opportunity for the treatment of PEW.

Evaluation of PEW

Serial assessments of the nutritional status of CKD patients by means of several scoring tools, including the Subjective Global Assessment (SGA), Malnutrition Inflammation Score (MIS), Geriatric Nutritional Risk Index (GNRI), and PEW diagnostic criteria, are recommended to diagnose and manage of PEW. These tools are reliable, and they are useful to determine predictors of outcomes in CKD patients.

Subjective Global Assessment (SGA)

Baker et al. reported the finding that a general clinical assessment was a reproducible and valid tool of evaluating nutritional status, a process later referred to as the Subjective Global Assessment (SGA) tool [69]. A more detailed description of the semiquantitative scoring system of SGA, which is based on the medical history and physical examination, was later published by Detsky et al. [70]. As shown in Table 2, the medical history consisted of 5 components: weight loss during the preceding 6 months, gastrointestinal symptoms, food intake, functional capacity, and comorbidities. The physical examination consisted of 2 components: loss of subcutaneous fat and muscle wasting. Each component was scored on a scale from 0 to 3, representing normal to severely abnormal. Each of these features were graded separately as A, B, or C, reflecting well-nourished to severely malnourished categories.

A proposed modified SGA tool emerged from the CANUSA (Canada-USA) study in 1996 in which the following 4 items were scored on a 7-point Likert-type scale, with lower scores assigned to poor nutritional status: 1 = weight loss during the past 6 months, 2 = anorexia, 3 = subcutaneous fat, and 4 = muscle mass; and scoring was as follows: 1 to 2 = severe malnutrition, 3 to 5 = moderate to mild malnutrition, and 6 to 7 = normal nutrition [71]. A modified quantitative SGA called the Dialysis Malnutrition Score (DMS) was proposed in 1999 by Kalantar-Zadeh et al. [72] and consists of 7 components: weight change, dietary intake, gastrointestinal symptoms, functional capacity, comorbidities, subcutaneous fat, and muscle wasting.

Malnutrition inflammation score (MIS)

Because of the recognition of the role of inflammation in causing PEW and in an attempt to make their scoring system more comprehensive and quantitative, the same group revised the criteria for the 7 DMS components and added 3 new items: body mass index, serum albumin level, and total iron-binding capacity (Table 3). This new score was called the Malnutrition Inflammation Score (MIS) [73].

Geriatric Nutritional Risk Index (GNRI)

It has been pointed out that there are simpler and more objective nutritional assessments that have been developed for special situations such as hospitalized, postoperative, and elderly patients. These methods include the Mini Nutritional Assessment Short Form, Nutrition Risk Score, Malnutrition Universal Screening Tool, Malnutrition Screening Tool (MST), and Geriatric Nutritional Risk Index (GNRI) [74, 75].

The GNRI was proposed because current methods of nutritional evaluation used several subjective assessments

Table 2 Evaluation of subjective global assessment (SGA)

Clinical parameters (Select appropriate category with a checkmark, or enter numerical value where indicated by "#.")

A. History

1. Weight change

Overall loss in past 6 months: amount = # _____kg; % loss = # _____

Change in past 2 weeks: _____increase,

_____no change,

_____decrease.

2. Dietary intake change (relative to normal)

_____No change,

_____Change _____duration = #_____weeks

_____type: _____suboptimal liquid diet, _____full liquid diet _____hypocaloric liquids, _____ starvation.

3. Gastrointestinal symptoms (that persisted for >2 weeks)

_____none, _____nausea, _____vomiting, _____diarrhea, _____anorexia.

4. Functional capacity

_____No dysfunction (e.g., full capacity),

_____Dysfunction _____duration = # _____weeks.

_____type: _____working suboptimally,

_____ambulatory,

_____bedridden.

5. Disease and its relation to nutritional requirements

Primary diagnosis (specify)

_____

Metabolic demand (stress): _____no stress, _____low stress,

_____moderate stress, _____high stress.

B. Physical (for each trait specify: 0 = normal, 1+ = mild, 2+ = moderate, 3+ = severe).

_____loss of subcutaneous fat (triceps, chest)

_____muscle wasting (quadriceps, deltoids)

_____ankle edema

#_____sacral edema

_____ascites

C. SGA rating (select one)

_____A = Well nourished

_____B = Moderately (or suspected of being) malnourished

_____C = Severely malnourished

Table 3 Components of the malnutrition inflammation score (MIS)

Malnutrition Inflammation Score			
(A) Patient's related medical history			
1- Change in end dialysis dry weight history:			
0	1	2	3
No decrease in dry weight or weight loss <0.5 kg	Minor weight loss (≥0.5 kg but <1 kg)	Weight loss more than 1 kg but <5 %	Weight loss >5 %
2- Dietary intake:			
0	1	2	3
Good appetite and no deterioration of the dietary intake pattern	Somewhat sub-optimal solid diet intake	Moderate overall decrease to full liquid diet	Hypo-caloric liquid to starvation
3- Gastrointestinal (GI) symptoms:			
0	1	2	3
No symptoms with good appetite	Mild symptoms, poor appetite or nauseated occasionally	Occasional vomiting or moderate GI symptoms	Frequent diarrhea or vomiting or severe anorexia
4- Functional capacity (nutritionally related functional impairment):			
0	1	2	3
Normal to improved functional capacity, feeling fine	Occasional difficulty with baseline ambulation, or feeling tired frequently	Difficulty with otherwise independent activities (e.g., going to the bathroom)	Bed/chair-ridden, or little to no physical activity
5- Comorbidity including number of years on dialysis:			
0	1	2	3
On dialysis less than 1 year and healthy otherwise	Dialyzed for 1–4 years, or mild comorbidity (excluding MCC[a])	Dialyzed >4 years, or moderate comorbidity (including one MCC[a])	Any severe, multiple comorbidity (2 or more MCC[a])
(B) Physical exam (according to SGA criteria):			
6- Decrease fat stores or loss of subcutaneous fat (below eyes, triceps, biceps, chest):			
0	1	2	3
Normal (no change)	Mild	Moderate	Severe
7- Signs of muscle wasting (temple, clavicle, scapula, ribs, quadriceps, knee, interosseous):			
0	1	2	3
Normal (no change)	Mild	Moderate	Severe
(C) Body mass index:			
8- Body mass index: BMI = Wt (kg)/Ht^2 (m)			
0	1	2	3
BMI ≥20 kg/m^2	BMI 18–19.99 kg/m^2	BMI 16–17.99 kg/m^2	BMI <16 kg/m^2
(D) Laboratory parameters:			
9- Serum albumin:			
0	1	2	3
Albumin ≥4.0 g/dL	Albumin 3.5–3.9 g/dL	Albumin 3.0–3.4 g/dL	Albumin <3.0 g/dL
10- Serum TIBC (total iron-binding capacity): ♣			
0	1	2	3
TIBC ≥250 mg/dL	TIBC 200–249 mg/dL	TIBC 150–199 mg/dL	TIBC <150 mg/dL
Total score = sum of above 10 components (0–30)			

[a]MCCs (major comorbid conditions) include CHF class III or class IV, full-blown AIDS, severe CAD, moderate to severe COPD, major neurological sequelae, and metastatic malignancies or s/p recent chemotherapy

♣Suggested equivalent increments for serum transferrin are: > 200 (0), 170-199 (1), 140-169 (2) and < 140 (3) mg/dL

and judgments, and assessment by a well-trained staff is necessary to obtain consistent results across examiners and institutions. Furthermore, the other methods were somewhat time-consuming and cumbersome. As shown in Table 4, the GNRI was intended to be a more simple method of assessing nutritional status that was based on only 3 objective parameters, body weight, height, and serum albumin levels, whose values are used to calculate

Table 4 Assessment of geriatric nutritional risk index (GNRI)

Formula
GNRI = [14.89 × albumin (g/dL)] + 41.7 × (body weight/ideal body weight)]

Ideal weight in this study was calculated from the Lorentz equations for men and women differently, as in the original GNRI equation

the index by the following formula: GNRI = (14.89 × albumin g/dL) + [41.7 + (body weight/ideal body weight)] [75]. Yamada et al. reported the finding that the GNRI was a useful tool for assessing the nutritional status not only of elderly patients but also of HD patients [76].

A simple PEW score

Moreau-Gaudry et al. recently reported a new PEW scoring system based on simple, readily available parameters and showed that it can predict survival in maintenance HD patients with acceptable accuracy [77]. As shown in Table 5, the PEW score includes 1 parameter from each major group generally identified as interfering with CKD patients' nutritional status: (1) biological parameters (serum albumin), (2) body composition (body mass index), (3) muscle mass (serum creatinine/body surface area), and (4) nutrient intake (normalized protein catabolic rate). Muscle mass, which accounts for the major part of body mass, is strongly associated with survival. They chose to use the predialysis serum creatinine level normalized to body surface area. However, the reliability of this score has not been validated.

Diagnosis of PEW

The clinical diagnostic criteria proposed for PEW in CKD are listed in Table 6. The expert panel of the ISRNM recommended that 4 main established categories be recognized for the diagnosis of PEW: biochemical criteria; low body weight, reduced total body fat, or weight loss; a decrease in muscle mass; and low protein or energy intake. At least 3 of the 4 listed categories (and at least 1 test result in each of the selected categories) must be satisfied for the diagnosis of CKD-related PEW. Ideally, each criterion should be documented on at least 3 occasions, preferably 2 to 4 weeks apart [78].

Among the biochemical criteria, it is recommended that at least 1 indicator be included when making the clinical diagnosis of PEW: serum albumin level <3.8 g/dL, serum transthyretin level <30 mg/dL, or serum cholesterol level <100 mg/dL. There appears to be a consensus among other organizations to recommend serial nutritional assessment by SGA in HD patients. As'habi et al. have recently reported the comparison of various scoring methods for the diagnosis of PEW in HD patients [79]. They investigated the cutoff points for the diagnosis of mild-to-moderate and severe PEW based on DMS and MIS and the sensitivity, specificity, accuracy, and area under receiver operating characteristic curve analysis of these scores in comparison with SGA. The results of their study indicated that the DMS and MIS were almost similar to SGA for identifying PEW in HD patients.

Table 5 Definition of a simple protein-energy wasting score

Serum albumin (g/dL)	≤3.8
Body mass index (kg/m^2)	≤23
SCr/BSA (μmol/L/m^2)	≤380
nPNA (g/kg/day)	≤0.8

nPNA normalized protein nitrogen appearance, *Scr/BSA* predialysis serum creatinine/body surface area (using postdialysis body weight)

Table 6 A proposed criteria for the clinical diagnosis of PEW in CKD patients

Criteria
Serum chemistry
Serum albumin <3.8 g/dL[a]
Serum prealbumin (transthyretin) <30 mg/dL (for maintenance dialysis)
Serum cholesterol <100 mg/dL[a]
Body mass
Body mass index (BMI) <23[b]
Unintentional weight loss over time: 5 % over 3 months or 10 % over 6 months
Total body fat percentage <10 %
Muscle mass
Reduced muscle mass 5 % over 3 months or 10 % over 6 months
Reduced mid-arm muscle circumference area[c] (reduction >10 % in relation to the 50th percentile of reference population)
Creatinine appearance[d]
Dietary intake
Unintentional low dietary protein intake <0.80 g/kg/day for at least 2 months[e] for dialysis patients or <0.6 g/kg/day for patients with CKD G2-5
Unintentional low dietary energy intake <25 kcal/kg/day for at least 2 months

At least three of the four listed categories along with at least one test in each of the selected categories must be satisfied for the diagnosis of CKD-related PEW. Each criterion should be documented on at least three occasions, preferably 2–4 weeks apart

[a]Not valid in abnormally great urinary or gastrointestinal protein losses, liver disease, or cholesterol-lowering medications

[b]A lower BMI might be favorable in certain Asian populations

[c]Measurement must be performed by a trained anthropometrist

[d]Creatinine appearance is influenced by both muscle mass and meat intake

[e]Can be assesed by dietary diaries and interview, or for protein intake by calculation of normalized protein equivalent of total nitrogen appearance (nPNA or nPCR) as determined by urea kinetic measurements

Management of PEW

Multiple treatment strategies against the etiologies may be required to prevent or reverse PEW [78].

Individualized, continuous nutritional counseling, optimization of the dialysis regimen, prevention or correction of muscle wasting, and management of comorbidities (e.g., metabolic acidosis, diabetes, infection, CHF, and depression) are the most essential preventive measures. Oral or parenteral nutrition supplements together with appetite stimulants and muscle-enhancing agents should be prescribed for patients whose protein and energy stores are not sustained despite those efforts.

Dietary interventions

As shown in Table 7, dietary protein intake of 0.6–0.8 g/kg/day and energy intakes of 30–35 kcal/kg/day have been recommended for patients with stage G3b-5 CKD (estimated glomerular filtration rate (GFR) <45 ml/min/1.73 m^2 body surface area (BSA)), because there is evidence that a low-protein diet (LPD) slows the progression of advanced CKD to ESRD and may mitigate uremia [80]. However, it is difficult to implement proper protein restriction for CKD patients, and inadequate energy intake is considered a common reason for protein restriction failure and may lead to PEW [80]. Partly because of this concern, an LPD has not been widely used in clinical settings in the USA, Europe, and some industrialized nations. To address this issue, Wu et al. conducted an open-label randomized controlled study of energy supplementation in patients with stage G3-4 CKD on an LPD. They found that a supplement packet containing 40 g of maltodextrin and 5 g of oil creamer at breakfast significantly decreased protein intake estimated by 24-h urinary urea excretion by a mean of 0.13 g/kg/day and resulted in lower urinary protein excretion and a higher estimated GFR [81]. Their findings indicated that energy supplementation may improve adherence to LPD in addition to preventing the development of PEW.

Another study that combined epidemiologic and experimental investigations revealed that the effect of protein intake on health may vary according to age [82]. In this analysis of the National Health and Nutrition Examination Survey III, participants aged 50–65 years who had reported high protein intake were found to be at higher risk of all-cause death and cancer death, and high protein intake was found to be associated with lower all-cause and cancer mortality in the group of 65 years of age and over. The results of mouse model studies also convincingly supported these findings. Since the elderly patients account for a significant proportion of CKD patients, these findings suggest that nephrologists and dietitians should take the patients' age into consideration when deciding the extent to which dietary protein should be restricted, because elderly CKD patients are generally frail and at higher risk of death than of progression to ESRD.

In contrast to nondialysis CKD patients, much higher protein intake (>1.2 g/kg/day, i.e., twice as high as for nondialysis CKD patients) is recommended for ESRD patients on dialysis for the following three reasons: first, there is no need to mitigate uremia by protein restriction after starting the patient on dialysis, second, dialysis ameliorates the metabolic acidosis induced by protein intake, and third, the dialysis procedure further stimulates protein catabolism [78]. Indeed, low protein intake, as reflected by a low normalized protein catabolic rate or low protein nitrogen appearance, is associated with high mortality in this population, and protein intake does not reach the recommended level in many patients [83, 84]. Oral or parenteral nutritional supplementation should be prescribed when dialysis patients exhibit evidence of malnutrition despite standard preventive measures. Several studies have demonstrated that standard preventive measures improve nutritional parameters such as lean body mass and the serum albumin concentration [85], and the results of recent observational studies have suggested that oral nutritional supplement use results in a decrease in hospitalization rates [86] and mortality [87].

Phosphate control

Phosphate is considered a uremic toxin. Indeed, hyperphosphatemia is an established risk factor for CVD and

Table 7 Recommended minimum protein, energy, and mineral intakes for chronic kidney disease (CKD) and maintenance dialysis patients

	Nondialysis CKD	Hemodialysis	Peritoneal dialysis
Protein	0.6–0.8 g/kg/day	>1.2 g/kg/day	>1.2 g/kg/day
	Illness 1.0 g/kg		Peritonitis >1.5 g/kg
Energy	30–35[a] kcal/kg/day	30–35[a] kcal/kg/day	30–35[a] kcal/kg/day including kcal from dialysate
Sodium	80–100 mmol/day	80–100 mmol/day	80–100 mmol/day
Potassium	<1 mmol/kg if elevated	<1 mmol/kg if elevated	Not usually an issue
Phosphorus	800–1000 mg and binders if elevated	800–1000 mg and binders if elevated	800–1000 mg and binders if elevated

Greater than 50 % of high biological value protein (that is, complete protein sources, containing the full spectrum of essential amino acids) is recommended
[a]Based on physical activity level. In sedentary elderly adults, recommended energy intake is 30 kcal/kg/day. All recommendations are based on ideal body weight. Regular follow-up supports compliance

death in CKD patients [88], and phosphate binders, especially binders that do not contain calcium, mitigate vascular calcification and thus decrease the rate of CVD and death [89]. Interestingly, although the dietary protein levels of ESRD patients are generally correlated with their dietary phosphate content and associated with serum phosphate concentration [90], high serum phosphorus concentrations are consistently associated with high mortality among HD patients [91], in contrast to the abovementioned association of protein intake with death.

This discrepancy may be explained by the link between phosphate and PEW. In a study on rats with adenine-induced CKD, Yamada et al. [92] showed that dietary phosphate induces systemic inflammation and oxidative stress dose-dependently without affecting kidney function and resulted in the development of phenotypes of PEW that included weight loss, hypoalbuminemia, and decreased urinary creatinine excretion. Moreover, a high phosphate diet caused vascular calcification and premature death. Administration of lanthanum carbonate, a non-calcium-containing phosphorus binder, ameliorated almost all of these pathological changes. Thus, the results of the study reinforced the importance of phosphate management in CKD highlighting the novel association between hyperphosphatemia and PEW. However, neither phosphate binders nor dietary restriction can be advocated as a means of preventing or treating PEW until similar data become available for humans. Indeed, phosphate restriction is potentially harmful for ESRD patients on dialysis, because it is often accompanied by a reduction in protein intake, which results in adverse outcomes caused by the development of PEW [78].

Exercise

Dialysis patients often exhibit extremely low physical activity, and the resultant muscle disuse is an underrepresented risk factor for muscle wasting [93, 94]. This finding is important, because exercise interventions can prevent or even reverse muscle wasting. Indeed, a recent systematic review of the literature confirmed that progressive resistance training induces skeletal muscle hypertrophy, increases muscular strength, and improves their health-related quality of life of CKD patients [95]. A single randomized trial found that the anabolic and strength responses are similar between healthy participants and hemodialysis patients [96]. Although the long-term effect of resistance exercise training on clinically relevant outcomes is yet to be determined, it is well tolerated, effective, and cost-free and should be encouraged as a potential preventive measure against PEW. In advanced CKD, bicarbonate supplementation might enhance the anabolic effects of progressive resistance training by mitigating exercise-induced lactic acidosis [97].

Dialysis procedure

Dialysis adequacy has been considered a target measure to prevent and treat PEW in maintenance dialysis patients, and the minimum dialysis dose has been recommended to maintain optimal dietary nutrient intake. On the other hand, few studies have directly evaluated the effect of increased dialysis dose on nutritional parameters. The results of the National Cooperative Dialysis Study showed an association between lower protein intake and higher time-averaged urea concentrations, suggesting a relationship between underdialysis and appetite loss [98]. Several subsequent studies have suggested that protein nitrogen appearance is dependent on the type and the dose of dialysis [99, 100]. However, none of these retrospective and/or cross-sectional studies demonstrated a cause-effect relationship between dialysis dose and nutritional status. In the HEMO study, the higher delivered dialysis dose (eKt/V 1.53 ± 0.09) neither prevented nor reversed the declines in several indices of nutritional status in maintenance HD patients as compared with the conventional dialysis dose (eKt/V 1.16 ± 0.08). Thus, it can be concluded that what is currently considered adequate dialysis in various guidelines is sufficient to maintain the nutritional status of HD patients [101]. Increasing the dialysis dose beyond these targets has not been shown to improve nutritional status.

Dialysis membrane characteristics may have important implications for the nutritional management of maintenance HD patients. Middle molecules, such as β2-microglobulin, are more efficiently removed by high-flux dialyzers than low-flux dialyzers, although no significant differences in most of the nutritional parameters studied were found between the two groups in the HEMO trial [102]. The European MPO trial investigated the effects of high-flux versus low-flux dialysis in maintenance HD patients. Although there was no difference in the patient group as a whole, there was a nominally significant survival benefit in the group with baseline serum albumin levels <40 g/L and in the group with diabetes mellitus that were randomized to high-flux dialysis [103].

The effects of an increase in dialysis frequency on various outcome measures have been reported by nonrandomized studies and suggest that daily dialysis increases appetite, protein and energy intake, body weight after hemodialysis, interdialytic weight gain, the serum albumin level, normalized protein nitrogen appearance, and the serum cholesterol [104]. However, the results of the FHN trial showed no appreciable differences in nutritional markers between subjects randomized to 6×/week in-center hemodialysis versus standard 3×/week in-center HD [105]. Hemodiafiltration has also been promoted as an efficient method of removing uremic toxins, but no randomized prospective studies have been published of the effects of hemodiafiltration on nutritional parameters [106].

Conclusions

Recent studies have shown that advances in knowledge of how inflammation, insulin resistance, oxidative stress, glucocorticoids, and metabolic acidosis modify the response to reduced protein and energy intake to understand the pathophysiology of PEW. Although HD therapy improves uremia, residual metabolic derangements, inflammation, and comorbid conditions, the dialysis itself is insufficient to treat PEW. Evaluating reduced protein and energy intake and comorbidities separately enable to clarify the pathogenesis of PEW. Evaluation, prevention, and treatment of PEW should involve individualized approaches specific to the CKD population. Nevertheless, there are few treatment options with proven efficacy in terms of quality of life, morbidity, and mortality. Proposed therapeutic interventions need to be evaluated in randomized controlled trials to determine whether they improve clinically relevant outcomes.

Competing interests

The authors have no conflicts of interest to declare.

Authors' contributions

Nitta planned the study, searched the literature, and prepared the article. Tsuchiya searched the literature and assisted in the article preparation. All authors read and approved the final manuscript.

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