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A proposed nomenclature and diagnostic criteria for protein–energy wasting in acute and chronic kidney disease

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The recent research findings concerning syndromes of muscle wasting, malnutrition, and inflammation in individuals with chronic kidney disease (CKD) or acute kidney injury (AKI) have led to a need for new terminology. To address this need, the International Society of Renal Nutrition and Metabolism (ISRNM) convened an expert panel to review and develop standard terminologies and definitions related to wasting, cachexia, malnutrition, and inflammation in CKD and AKI. The ISRNM expert panel recommends the term 'protein–energy wasting' for loss of body protein mass and fuel reserves. 'Kidney disease wasting' refers to the occurrence of protein–energy wasting in CKD or AKI regardless of the cause. Cachexia is a severe form of protein–energy wasting that occurs infrequently in kidney disease. Protein–energy wasting is diagnosed if three characteristics are present (low serum levels of albumin, transthyretin, or cholesterol), reduced body mass (low or reduced body or fat mass or weight loss with reduced intake of protein and energy), and reduced muscle mass (muscle wasting or sarcopenia, reduced mid-arm muscle circumference). The kidney disease wasting is divided into two main categories of CKD- and AKI-associated protein–energy wasting. Measures of chronic inflammation or other developing tests can be useful clues for the existence of protein–energy wasting but do not define protein–energy wasting. Clinical staging and potential treatment strategies for protein–energy wasting are to be developed in the future.

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There has been an increase of mechanisms causing syndromes of wasting, malnutrition, inflammation, and their interrelationships in individuals with chronic kidney disease (CKD) or acute kidney injury (AKI). Currently, there appears to be some confusion regarding the terms and definitions used for conditions associated with loss of muscle and fat tissue, malnutrition, and inflammation in patients with CKD or AKI. Use of non-uniform and ill-defined terminologies may lead to both conceptual errors and misinterpretation of data. The development of a uniform nomenclature, definition, and classification for the presence of loss of muscle and fat tissues (that is, wasting) or the presence of malnutrition and/or inflammation in individuals with kidney disease could lead to benefits by engendering a more systematic and rational approach to both research and the clinical management of such patients.[1–3] Other groups have addressed the need for more exact definitions and stages of illness in kidney disease, including the Kidney Disease Outcome Quality Initiative (KDOQI)[4] and Kidney Disease Improving Global Outcomes (KDIGO).[5–7]

Owing to the foregoing matters, the International Society of Renal Nutrition and Metabolism (ISRNM) convened an expert panel to re-examine the terms and criteria used for the diagnosis of the wasting syndrome, distinct from malnutrition and inflammation in individuals with CKD or AKI. During the biannual conference of the ISRNM in Meridá, Mexico, from 28 February to 3 March 2006, and the annual meeting of the American Society of Nephrology in San Diego, CA, 16–19 November 2006, the panel met to address these issues of nomenclature. The current position paper is the result of these deliberations and expresses the opinion of the clear majority of the panel.

THE SYNDROMES OF MALNUTRITION, INFLAMMATION, CACHEXIA, AND WASTING

Surveys using classic measures of nutritional status indicate that approximately 18–75% of patients with CKD undergoing maintenance dialysis therapy show evidence of wasting.[1,8,9] These syndromes have been referred to as uremic malnutrition,[10,11] uremic (renal) cachexia,[12–15] protein–energy malnutrition,[16–18] malnutrition–inflammation atherosclerosis syndrome,[19–21] or malnutrition–inflammation complex (or cachexia) syndrome.[9,22] In the last 5 years, it has become apparent that many of the measures indicating the presence of wasting and abnormalities in protein–energy nutritional status can also be induced by inflammatory processes.[23–26] Simply stated, malnutrition refers to abnormalities induced by an inadequate diet, whereas wasting refers to abnormalities that cannot be corrected solely by increasing the diet.[2,3] For example, pure malnutrition can be associated with reduced serum albumin concentrations, but marked reductions are unusual, while the presence of inflammation is frequently associated with a decrease in serum albumin, where marked reductions are common.[27] Inflammation may also be associated with an increase in protein catabolism that is presumably related to the elaboration of catabolic or antianabolic proinflammatory cytokines.[28] Thus, malnutrition refers to the presence of a low-nutrient intake or, at least, an intake that is inadequate for the nutritional needs of the individual. In contrast, an increase in proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6 may cause loss of protein stores and also can induce anorexia with reduced nutrient intake.[29] The difference is that inflammation or other problems associated with loss of kidney function (for example, metabolic acidosis or impaired insulin/insulin-like growth factor-1 signaling pathways) can impair protein anabolism independently of whether adequate nutrition is present.[24]

The relative contributions of malnutrition or inflammation to mortality are obscured because many indicators of malnutrition and inflammation are identical (e.g., low serum albumin and prealbumin concentrations, protein intake, and even body weight-for-height measures, such as body mass index (BMI)).[30] Moreover, loss of muscle and fat stores and inflammation are likely to increase the risk of death from cardiovascular or cerebrovascular disease (possibly by promoting vascular endothelial damage[26,31–33]).

PROTEIN–ENERGY WASTING

Protein–energy wasting (PEW) is the state of decreased body stores of protein and energy fuels (that is, body protein and fat masses). This abnormality is often associated with diminished functional capacity related to metabolic stresses. Protein or energy depletion can result from an inadequate diet (for example, anorexia nervosa), but in kidney disease, in contrast to anorexia nervosa, there are conditions resulting in loss of lean body mass not related to reduced nutrient intake. These include nonspecific inflammatory processes; transient, intercurrent catabolic illnesses;[34] nutrient losses into dialysate;[35–37] acidemia;[38–40] endocrine disorders such as resistance to insulin,[41] growth hormone,[42] and insulin-like growth factor-1;[43] hyperglucagonemia;[44] hyperparathyroidism;[45] and loss of blood into the hemodialyzer, into feces or by blood drawing.[46] It is possible, but not proven, that malnutrition may also predispose to inflammatory states as shown in animal models.[47] Thus, we believe that the most desirable term for describing the syndrome of depletion of protein mass and/or energy fuel supplies is 'protein–energy wasting'. Since protein wasting and energy wasting may occasionally occur separately from each other, the term 'protein wasting' or 'energy wasting' may be used to indicate the isolated occurrence of only one of these phenomena. Potential causes and consequences of PEW are depicted in Figure 1.

CACHEXIA

Recently, the word 'cachexia' has been suggested as a term to denote PEW included in the setting of kidney disease.[12–15,48] Cachexia refers to a very severe form of PEW, often associated with profound physiological, metabolic, psychological, and immunological disorders.[49] 'Cachexia is a complex syndrome that often develops as a serious complication of various chronic diseases.'[50,51] 'Cachexia carries a very poor prognosis and almost no therapies for its treatment are approved, apart from that for acquired immune deficiency syndrome (AIDS)-induced cachexia.'[50,51]

The difference in PEW compared to cachexia is that the latter encompasses only severe forms of metabolic depletion, whereas PEW can refer to mild degrees of depleted protein and energy mass. It would seem to be a contradiction to classify mild protein or energy depletion as cachexia. Modified terms such as 'latent cachexia' neither describe the body mass or composition of an individual nor mechanistically denote metabolic processes and are not recommended,[48] whereas cachexia may be used for severe forms of PEW (Figure 1).

OTHER TERMINOLOGIES

Other terms used to indicate the existence of 'malnutrition' in patients with kidney disease include uremic malnutrition,[10,11] protein–energy malnutrition,[16–18] malnutrition–inflammation atherosclerosis syndrome,[19–21] and malnutrition–inflammation complex syndrome.[9,22] Because 'malnutrition' may indicate both undernutrition and overnutrition,[52,53] there is an additional interpretational problem when it is used to

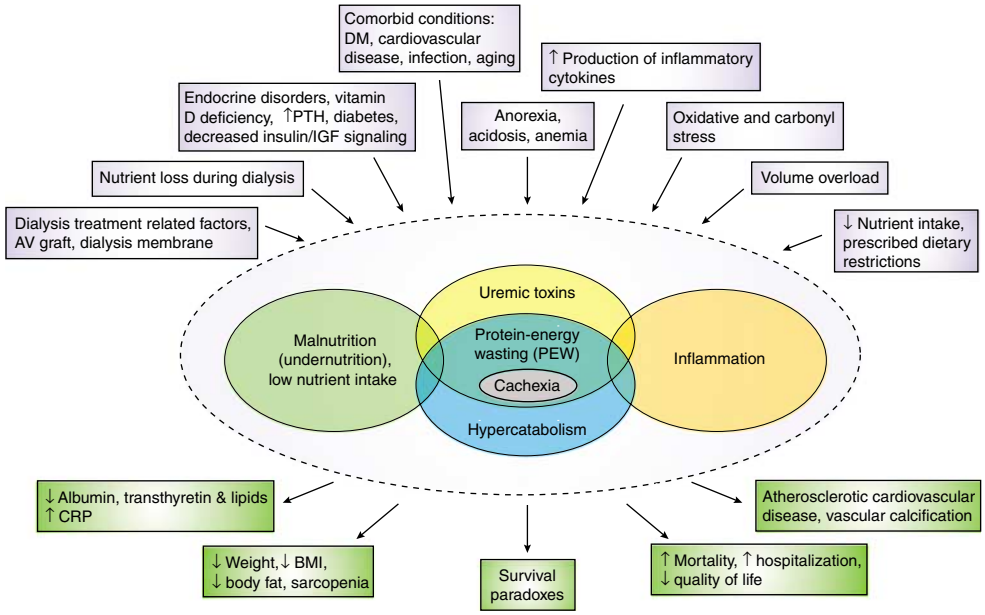

Figure 1 | Schematic representation of the causes and manifestations of the protein–energy wasting syndrome in kidney disease.

describe the wasting syndrome occurring in acute kidney disease or CKD.[53] Clearly characterizing the entire wasting syndrome as malnutrition will lead to underrecognition of the role of other contributing factors such as hypercatabolism, inflammation, acidemia, or oxidative stress.[3]

Some investigators have suggested classifying the wasting syndrome based on the presence or absence of coexisting inflammation.[20] Oxidative stress may also contribute to kidney disease-related wasting.[54,55] However, we believe that labeling the problems of patients with kidney disease as 'inflammatory wasting' may erroneously imply that the PEW syndrome is due exclusively to inflammation.

KIDNEY DISEASE WASTING

Individuals with CKD or AKI are at increased risk for PEW, and the term, kidney disease wasting (KDW), emphasizes this common association. However, there are many causes of PEW in individuals with kidney disease, and KDW does not provide any insights into the different causes of PEW. In addition, some patients may develop severe PEW before they develop kidney failure.

For example, a new onset maintenance dialysis patient who has been severely depressed psychologically all of his adult life, who has eaten poorly for the last 5 years, and who has chronic PEW can be diagnosed with KDW even though the cause of his PEW is not related to kidney disease. Similarly, a patient with CKD stage 4 and advanced AIDS or vasculitis can be cachectic, but the PEW is not caused by kidney disease. The connotation that many people will infer from the term KDW is that the protein–energy malnutrition is at least partly caused by kidney disease. The same disassociation may be found between patients with AKI and causes of PEW. For example, the causes and medical management of PEW in a young, previously healthy individual who develops pancreatitis, sepsis, and AKI may be quite different from those of an individual 85 years old with chronic congestive heart failure, chronic obstructive pulmonary disease, pneumonia, septicemia, and AKI. For these reasons, the clear majority of the panel members prefer PEW to KDW for most circumstances. The panel believes that the term KDW is not a suitable substitute for PEW but simply implies that PEW is likely to occur in people with CKD or AKI. Figure 1 contains a schematic representation of PEW and its complex interrelationships with several conditions that may lead to or aggravate PEW in kidney disease.

DIAGNOSIS OF PEW

There are several clinical, nutritional, and biochemical parameters that may be indicative of PEW in individuals with kidney disease. The expert panel recommends that four main and 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 intakes (Table 1). The panel recognizes additional measures of nutrition and inflammation, including some currently under development, which can be regarded as potential clues to the existence of PEW (Table 2).

Among biochemical indicators that can be used for the diagnosis of PEW, serum albumin is known to have strong and consistent outcome-predictability of mortality in epidemiologic studies of dialysis patients.[62–66] Although low serum albumin is often associated with severe clinical disease states, the epidemiological relationship to mortality is based upon the low serum albumin *per se* and poor outcome. It follows

from Table 1 that a low serum albumin concentration is not necessary or sufficient for the diagnosis of PEW, although it is often present in this condition. Serum prealbumin, also known as transthyretin,[67,68] and cholesterol have also been studied as nutritional markers in CKD patients.[67,69–71] The expert panel recommends that at least one biochemical indicator be included when making the clinical diagnosis of PEW (Table 1). The level of serum C-reactive protein or other inflammatory markers, including such circulating proinflammatory cytokines as interleukin-6, may also be persistently increased in PEW,[31,33,72] but these measurements should not be used as part of the criteria for the diagnosis of PEW (Table 2).

Among indicators of body mass, BMI is the most commonly used measure of weight-for-height[73–75] and may be used to assess PEW. However, BMI can be heavily influenced by fat mass or hydration status. Nonetheless, a low BMI is a consistent predictor of poor outcome and high death risk in maintenance dialysis patients.[76,77] The ISRNM panel recommends that a BMI less than 23 $kg\,m^{-2}$ is a marker of PEW. The panel also recognizes that the threshold for this criterion may need further adjustment; especially in some populations, such as those from southeast Asia, a low BMI may not indicate pathology.[78,79] We also note that these suggested values of BMI should not be expanded to recommendations for the general population, because obesity should be avoided. Notably, the World Health Organization recommends a BMI range between 18.5 and 25 $kg\,m^{-2}$ as the normal range for the general population.[80]

Unintentional weight loss or reduction in BMI of any degree should suggest the presence of PEW in individuals with kidney disease. Currently, the expert panel recommends that a loss of 5% of non-edematous weight within 3 months or an unintentional loss of 10% of non-edematous weight over the past 6 months should be considered an indicator of PEW, independently of weight-for-height measures.

The panel considered the use of body fat as a percentage of weight as an additional criterion for wasting, because BMI is strongly, but not solely, influenced by body fat.[81] Moreover, a decrease in body fat in epidemiologic studies has been

Table 1 | Readily utilizable criteria for the clinical diagnosis of PEW in AKI or CKD

Criteria
Serum chemistry
Serum albumin <3.8 g per 100 ml (Bromcresol Green)[a]
Serum prealbumin (transthyretin) <30 mg per 100 ml (for maintenance dialysis patients only; levels may vary according to GFR level for patients with CKD stages 2–5)[a]
Serum cholesterol <100 mg per 100 ml[a]
Body mass
BMI <23[b]
Unintentional weight loss over time: 5% over 3 months or 10% over 6 months
Total body fat percentage $<10\%$
Muscle mass
Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months
Reduced mid-arm muscle circumference area[c] (reduction $>10\%$ in relation to 50th percentile of reference population)
Creatinine appearance[d]
Dietary intake
Unintentional low DPI $<0.80\,g\,kg^{-1}\,day^{-1}$ for at least 2 months[e] for dialysis patients or $<0.6\,g\,kg^{-1}\,day^{-1}$ for patients with CKD stages 2–5
Unintentional low DEI $<25\,kcal\,kg^{-1}\,day^{-1}$ for at least 2 months[e]

AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease; DEI, dietary energy intake; DPI, dietary protein intake; GFR, glomerular filtration rate; nPCR, normalized protein catabolic rate; nPNA, normalized protein nitrogen appearance; PEW, protein–energy wasting.
At least three out of the four listed categories (and at least one test in each of the selected category) must be satisfied for the diagnosis of kidney disease-related PEW. Optimally, each criterion should be documented on at least three occasions, preferably 2–4 weeks apart.
[a]Not valid if low concentrations are due to abnormally great urinary or gastrointestinal protein losses, liver disease, or cholesterol-lowering medicines.
[b]A lower BMI might be desirable for certain Asian populations; weight must be edema-free mass, for example, post-dialysis dry weight. See text for the discussion about the BMI of the healthy population.
[c]Measurement must be performed by a trained anthropometrist.
[d]Creatinine appearance is influenced by both muscle mass and meat intake.
[e]Can be assessed by dietary diaries and interviews, or for protein intake by calculation of normalized protein equivalent of total nitrogen appearance (nPNA or nPCR) as determined by urea kinetic measurements.

Table 2 | Other potential tools (including those still in development) for assessment of PEW in individuals with CKD stages 3–5 or AKI

Appetite, food intake, and energy expenditure
Appetite assessment questionnaires
Population-based dietary assessments: food frequency questionnaires
Measuring energy expenditure by indirect or direct calorimetry
Body mass and composition
Weight-based measures: weight-for-height
Total body nitrogen
Total body potassium
Energy-beam-based methods: DEXA, NIR, BIA, and Vector
Bioimpedance Analysis
Underwater weighing and air displacement weighing
14 kDa fragment of actomyosin
Microarrays
Muscle fiber size
Relative proportions of muscle fiber types
Muscle alkaline soluble protein
CT and/or MRI of muscle mass
Laboratory markers
Serum biochemistry: transferrin, urea, triglyceride, bicarbonate
Hormones: leptin, ghrelin, growth hormones
Inflammatory markers: CRP, IL-6, TNF-α, IL-1, SAA
Peripheral blood cell count: lymphocyte count or percentage
Nutritional scoring systems
SGA and its modifications, including DMS[56,57] and CANUSA version[58]
MIS[59]
Other scoring tools: Wolfson *et al.*,[60] Merkus *et al.*[61]

BIA, bioelectrical impedance analysis; CANUSA, Canada–USA study-based modification of the SGA; CRP, C-reactive protein; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; DMS, dialysis malnutrition score; HD-PNI, hemodialysis prognostic nutritional index; IGF-1, insulin-like growth factor-1; IL, interleukin (e.g., IL-1 and IL-6); MIS, malnutrition–inflammation score; MRI, magnetic resonance imaging; NIR, near infrared interactance; SAA, serum amyloid A; SGA, subjective global assessment of nutritional status; SUN, serum urea nitrogen; TNF-α, tumor necrosis factor-α.

associated with an increase in the risk of death in maintenance dialysis patients.[82–84] But, the majority of the expert panel members agree that a total body fat below 10% in individuals who are not overtly muscular may be hazardous; there is no consensus on this point and a value suggesting the presence of PEW would be body fat below 10% of weight.[82–84]

A reduced muscle mass appears to be the most valid criterion for the presence of PEW (Table 1).[85,86] A popular term, sarcopenia, has been used to describe the loss of muscle mass that occurs in elderly patients. Hence, sarcopenia, by this definition, should not be applied to the PEW of patients with kidney disease unless this loss of muscle mass occurs in an elderly individual.

It is often difficult to diagnose low muscle mass or muscle loss accurately.[87] Currently, there are no clinically useful, uniform and reproducible measures of lost muscle mass and methods for assessing the presence of accelerated muscle protein catabolism.[88] Some studies have suggested indirect measures of muscle mass, such as serum creatinine, obtained immediately before a hemodialysis treatment in maintenance hemodialysis patients, or the creatinine appearance (net creatinine generation)[89–92] (Table 1). The term 'creatinine appearance' rather than 'creatinine generation' is used because some creatinine is degraded in the intestinal tract[93] and the rate of creatinine degradation increases in patients who have very elevated serum creatinine concentrations. Thus, without isotopic kinetic studies to quantitate the rate of creatinine degradation or synthesis, it is not possible to assess the absolute rate of creatinine generation. We therefore recommend the term creatinine appearance, which can also be estimated by measurement of creatinine in 24 h urine collection and in the collected spent dialysate. The term 'urea nitrogen appearance,' rather than 'urea generation,' has been used for the same reasons.[94]

The accuracy and reproducibility of serum creatinine as an indirect measure of muscle mass is not very precise, especially in dialysis patients receiving different doses of dialysis.[77] Nonetheless, in many diseases, there is clinical and prognostic importance when loss of muscle mass is documented and hence, the panel agrees that it should be included as a clinical criterion for the diagnosis of PEW. Emphasis is placed on assessing the loss of muscle mass because of the limitations of assessing changes in body weight in patients with impaired salt and water regulation, and on the fact that there are many pitfalls in diagnosing the adequacy of the diet.[95,96]

Bioelectrical impedance analysis (BIA) has become a commonly used technique for estimating body water and, by inference, muscle mass[97] (Table 2). The BIA phase angle has been correlated with mortality rate in maintenance hemodialysis (MHD) patients.[98] Vector Bioimpedance Analysis has been reported as a more sensitive and accurate method for estimating the state of hydration in chronic dialysis patients.[99] Multifrequency sum of segments bioimpedance may be more sensitive for estimating muscle mass.[100] The near infrared interactance is a simple method to assess percent body fat via light emission using near infrared spectroscopy on the biceps of the dominant arm and has high correlation with hydrostatic densitometry.[101] Near infrared measurements of body fat have been shown to correlate significantly with other nutritional measures[102,103] and predict survival[84] in maintenance hemodialysis patients.

The panel recognizes that diminished appetite (anorexia) can be associated with PEW and may herald a poor clinical outcome.[29,104] Hence, an unintentional reduction in dietary protein intake less than about 0.80 g per kg body weight per day in maintenance dialysis patients and dietary energy intake less than about 25 kcal per kg body weight can be associated with PEW.[4] It is also recognized that there are pitfalls in identifying a decrease in energy intake.[95,96] We recognize that these criteria are quite conservative, and most maintenance dialysis patients will have dietary protein needs and most CKD and maintenance dialysis patients will have energy requirements that are substantially higher than these values.[4] We also note that the amount of dietary protein needed for patients with stages 3–5 CKD who are not being treated by maintenance dialysis therapy should be considered to be an exception to this rule.[105,106]

In recent years, nutritional scoring systems have been recommended as practical tools for the diagnosis of malnutrition in individuals with kidney disease (Table 2). The KDOQI expert panel for nutrition[4] as well as the European Best Practice Guidelines Wave II have recommended serial assessments by Subjective Global Assessment of Nutrition (SGA) in CKD patients who undergo maintenance dialysis treatment.[56,107] There are additional nutritional scoring systems, some of which are modified versions of the SGA.[56] Currently, there is no consensus about the relationship of these subjective assessments to the diagnosis of PEW. These scoring systems should be considered as potential clinical markers of PEW status (Table 2) but not as definitive diagnostic indicators of this syndrome.

CONCLUSIONS AND FUTURE STEPS

The purpose of our position paper is to advance a unifying and practical terminology for the PEW syndrome of loss of protein mass and energy stores that occurs in many patients with CKD or AKI. There are a large number of disorders that can cause PEW in patients with kidney disease, including the presence of an inadequate diet, the presence of inflammation, oxidative stress, acidemia, nutrient losses into dialysate, altered responses to anabolic hormones, increased levels of unexcreted toxins, and blood loss. It is hoped that a systematically defined nomenclature and diagnostic criteria for PEW in CKD and AKI will help to clarify thinking and communication, enhance the effectiveness of patient care, and promote more incisive research in this field. Many questions about the description, classification, and treatment of KDW need to be addressed: (1) Can nutritional intervention improve the biochemical and clinical disorders related

to PEW (Table 1)? (2) What is the PEW scoring system that most effectively predicts morbidity and/or mortality? (3) Is there a gender impact on appetite, wasting, inflammation, and outcome? (4) If therapeutic interventions are effective at improving indicators of PEW, will clinical outcomes, including survival, also improve? Randomized, well-designed, controlled trials will be required to answer these and similar questions concerning PEW in AKI and CKD.

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