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]

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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