EDITORIAL

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Kidney cachexia or protein-energy wasting in chronic kidney disease: facts and numbers

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Abstract

Weight loss and homeostatic disturbances of both energy and protein balances are characteristics of several illnesses including cancer, heart failure, and chronic kidney disease (CKD). Different definitions have been used to describe this deleterious process. The term protein-energy wasting (PEW) has been proposed for CKD patients by the *International Society of Renal Nutrition and Metabolism*. Since its inception, the term PEW has been exceptionally successful, highlighted by 327 original publications referenced in PubMed over 10 years. Using this classification, several studies have confirmed that PEW is among the strongest predictors of mortality in CKD patients [hazard ratio of 3.03; confidence interval of 1.69–5.26 in 1068 haemodialysis patients and 1.40 (1.04–1.89) in 1487 non-dialysed patients across PEW stages 0 to 4]. Based on this classification, prevalence of PEW is 28% to 54% among 16 434 adults undergoing maintenance dialysis. PEW prevalence increases when renal function declines, that is, from $<$2% in CKD stages 1–2 to 11–54% in CKD stages 3–5. A more general definition of cachexia for all chronic diseases proposed by the *Society on Sarcopenia, Cachexia and Wasting Disorders* was also published concurrently. In the CKD area, we found 180 publications using 'cachexia' underlining that some confusion or overlap may exist. The definitions of PEW and cachexia are somewhat similar, and the main difference is that a loss of body weight $>$5% is a mandatory criterion for cachexia but only supportive for PEW. The recent understanding of cachexia physiopathology during CKD progression suggests that PEW and cachexia are closely related and that PEW corresponds to the initial state of a continuous process that leads to cachexia, implicating the same metabolic pathways as in other chronic diseases. Despite the success of the definition of PEW, using a more uniform term such as 'kidney disease cachexia' could be more helpful to design future research through collaborative groups of researchers with focus on cachexia.

Keywords Cachexia; Protein-energy wasting; Chronic kidney disease; Energy intake; Malnutrition

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Protein-energy wasting/cachexia prevalence

Nutritional deficiencies have long been recognized as an adverse effect of chronic kidney disease (CKD) and are associated with reduced physical activity and poor survival.[1–5] However, cachexia is poorly defined and managed in these patients, and a clearer definition of this condition is needed. Indeed, the terms wasting, cachexia, malnutrition, protein-energy malnutrition, and malnutrition–inflammation atherosclerosis (or cachexia) syndrome were used interchangeably, which might have caused confusion. Hence, the exact criteria used to define the prevalence of cachexia and protein-energy wasting (PEW) in CKD were not consistent across studies, making it difficult to aggregate data. Using a nutritional scoring system such as the subjective global assessment or by subjective global assessment or malnutrition–inflammation score, the prevalence of cachexia/PEW was found to be 28–80% of adults undergoing maintenance dialysis[6–9] and as an increasing prevalence

when renal function declines. Indeed, during stages 1–2 CKD, this prevalence is less than 2%[9,10] and in stages 3–5 is estimated to be 11–46%.[10–13] In the last meta-analysis, including 16 434 patients on maintenance dialysis, 25th–75th percentiles range in PEW prevalence was 28–54%.[14] During stages 3–5 in 1778 patients, PEW prevalence was ranging from 11% to 54%.[14]

Definition of protein-energy wasting and kidney cachexia

The term 'wasting' was proposed by the World Health Organization in 1983 and was defined as an involuntary loss of weight of more than 10% of patient's previous value in absence of an opportunistic infection, cancer, or chronic diarrhea. Wasting or malnutrition were once believed to be invariably caused by inadequate nutritional intake and should be reserved for this situation only. If wasting is often present in CKD in response to anorexia-induced insufficient energy intake, it is not the only component of nutritional alterations. In order to unify the description of the global systemic disorder including the loss of homeostatic control of both energy and protein balances, panels of experts participated in formal consensus processes. A subsequent generic definition of cachexia (for all types of cachexia) was published in 2008 by the *Society on Sarcopenia, Cachexia and Wasting Disorders*.[15] Cachexia was defined as a complex metabolic syndrome associated with underlying illness and characterized by a loss of muscle, with or without loss of fat. At the same time, the *International Society of Renal Nutrition and Metabolism* proposed a specific classification of uraemia-induced wasting disorders in which cachexia was the most severe stage of PEW.[16] This classification became successful and the message fairly well reached the nephrology community. Ten years later, a PubMed literature search (from inception to 12 September 2018) identified 327 CKD publications that used PEW in their title (*Figure* 1). However, during the same period, still in CKD, 180 publications used 'cachexia' underlining that some confusion was still present.

What is the difference between cachexia and protein-energy wasting in chronic kidney disease?

As shown in *Table* 1, the diagnostic criteria for cachexia (proposed by the *Society on Sarcopenia, Cachexia and Wasting Disorders*)[15] and for PEW (proposed by the ISRNM)[16] are similar, but not identical. However, there is no obvious distinction between PEW and cachexia from a pathophysiologic standpoint, and limiting the term cachexia to extreme forms of PEW is perhaps too restrictive. With our understanding of the mechanisms involved in the PEW/cachexia, should these definitions evolve and reconcile?

Body weight and body composition

The main criterion for cachexia (*Table* 1) is either a weight loss >5% in the previous 12 months or a body mass index (BMI) <20 kg/m^2 and does not seem satisfactory in the CKD context because low BMI is not always present at the early stages of nutritional disorders. Indeed, due to a tendency for elevated body weight in CKD, given that the average BMI of US dialysis patients is >25 kg/m2,[17] waiting for a low BMI to consider cachexia would certainly induce a late diagnosis. In this regard, the use of BMI in the PEW definition and cachexia has been challenged.[18] It is the authors' opinion that a specific BMI cut-off level should not be considered anymore in these classifications given racial and ethnic diversities and because the information provided by BMI does not overcome that brought by body weight. By contrast, weight loss is an easy and more sensitive tool to monitor as the primary clinical manifestation of cachexia. Indeed, body composition is difficult to measure with precision in a clinical setting. Body

Figure 1 PubMed search using 'Protein energy wasting (PEW)' or 'cachexia' in chronic kidney disease (CKD) keywords.

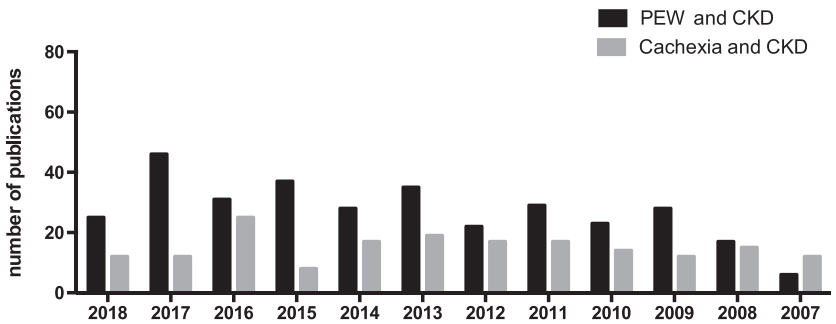

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Table 1 Criteria for the clinical diagnosis of protein-energy wasting (PEW) and cachexia in adults with chronic kidney disease

Criteria	PEW (ISRNM)	Cachexia (SCWD)
Serum chemistry	Serum albumin <38 g/L Serum prealbumin (transthyretin) <300 mg per 100 mL (for maintenance dialysis patients only) Serum cholesterol <100 mg per 100 mL[a]	Serum albumin <32 g/L Anaemia <12 g/dL Increased inflammatory markers CRP (>5.0 mg/L), IL-6 (>4.0 pg/mL)
Body mass	BMI <23 kg/m^2 Unintentional weight loss over time at least 5% over 3 months or 10% over 6 months Total body fat percentage <10%	BMI <20 kg/m^2 Unintentional weight loss of at least 5% in 12 months
Muscle mass	Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months Reduced mid-arm muscle circumference area (reduction >10% in relation to 50th percentile of reference population) Low creatinine appearance	Reduction of appendicle skeletal muscle index by DEXA (kg/m^2) <5.45 in women and <7.25 in men. Reduced mid-arm muscle circumference area (<10th percentile for age and gender) Fatigue = defined as physical and/or mental weariness resulting from exertion; an inability to continue exercise at the same intensity with a resultant deterioration in performance.
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]	Unintentional low DEI <20 kcal kg^{-1} day^{-1} Unintentional DEI <70% of usual food intake Poor appetite
Definition of PEW/ cachexia	At least three out of the four listed categories (and at least one test in each of the selected category)	Weight loss of at least 5% in 12 months or BMI <20 kg/m^2, plus three of the other criteria

BMI, body mass index; CKD, chronic kidney disease; DEI, dietary energy intake; DPI, dietary protein intake; IL-6, interleukin 6; ISRNM, International Society of Renal Nutrition and Metabolism; SCWD, Society on Sarcopenia, Cachexia and Wasting Disorders.

weight loss remains a valid criterion; in a recent study including almost 5000 patients, a significant weight loss began relatively early during the course of CKD and was associated with a substantially higher risk for death after dialysis therapy initiation.[19] Overall, both classifications have identified a non-voluntary weight loss as a phenotypical criterion based on a robust literature: greater than 5% within the past 6 months or >10% beyond 6 months as recently proposed by the Global Leadership Initiative on Malnutrition.[20] The presence of a critical weight loss (>5% in 6 months) should probably be considered as a major criterion to define cachexia/PEW. By contrast, a more moderate weight loss (<5%) should be considered as one criterion among others.

Muscle wasting (or sarcopenia) is obviously acknowledged as an important feature in the pathophysiology of the cachexia phenotype and predisposes to increased risk of co-morbid complications.[15,21,22] In both definitions, measures of muscle mass by mid-arm muscle circumference area are present. In contrast to PEW, the diagnostic criteria for cachexia emphasize muscle functional measures (such as muscle strength or fatigue). Indeed, muscle strength is an independent predictor of renal outcomes in CKD patients and can be helpful in diagnosing cachexia/PEW in this population.[23,24] In the PEW definition, creatinine appearance is proposed to estimate muscle mass but its accuracy and reproducibility are weak, and in our opinion, this criterion is probably not used much nowadays.[25] Mechanically, an increase in muscle proteolysis by a common transcriptional programme is always present despite the diverse nature of cachexia, primarily through the ubiquitin-proteasome system and the coordinated induction of atrophy-related genes (atrogenes) by FOXO transcription factors.[21,26,27]

There is questioning about the role of fat in cachexia and until now, fat loss is not considered as an important feature of cachexia except in the PEW classification. In epidemiological studies, adipose tissue wasting has been associated with an increased risk of death in different cachexia diseases.[28–30] The discovery about the ability of white adipose tissue to be turned towards the brown adipose phenotype with thermogenesis capacity, leading to increased energy expenditure and lipid mobilization, underlines the importance of this tissue in cachexia. Experimental data also suggest that this phenomenon appears before skeletal muscle atrophy.[31–33] The browning inductors could be similar in different cachexia such as those induced by parathyroid hormone (PTH) in CKD and PTH-related peptide (PTHrP) in cancer.[33] In this situation, PTH/PTHrP-induced fat-derived molecules, that is, adipokines, free fatty acids, or other metabolites, mediate the crosstalk between muscle and fat that contributes in a major way to tissue catabolism. Despite this, there is currently no consensus about the optimal fat mass or fat loss value suggesting the presence of PEW, and fat was not retained in the last nutrition recommendation.[20]

Biological criteria

To assess nutritional disorders, biological criteria should be able to identify and risk stratify patients with PEW/cachexia, distinguishing the causes and consequences of PEW/cachexia and the underlying diseases that lead to PEW/cachexia. However, some nutritional markers used in cachexia, such as anaemia, are influenced by CKD and cannot be used. There is also no consensus on the role and pertinence of inflammation in the criteria of PEW and cachexia. In the initial definition of PEW, it was proposed that inflammation could be a source of confusion by supposing that PEW was exclusively because of inflammation.[16] The central role of cytokines or inflammation into the pathophysiology of cachexia is still an outstanding question. Numerous experimental and clinical data have highlighted that inflammation acts directly on target tissues as well as through alteration of central nervous system (dysregulation of appetite), neuroendocrine targets (such as the release of adrenal steroids), sickness behaviour (such as anorexia and fatigue), and muscle catabolism.[34]

In cancer cachexia, the important role of inflammation is now indisputably admitted. Numerous pro-inflammatory cytokines are generated through tumour crosstalk with associated stromal cells, and the immune system and inflammation is the cornerstone of cancer cachexia.[35] In CKD, increased serum inflammatory cytokines predispose to the pathogenesis of PEW.[36–38] Accumulating data also suggest that during CKD, specific accretion of uremic toxins may have a direct effect on inflammation stimulation and cytokines production.[39] Therefore, inflammation contributes to PEW/cachexia in several ways, both by direct and indirect mechanisms of muscle proteolysis and by impinging upon and magnifying other causes of PEW in a vicious circle. Therefore, the rationale not to include inflammatory criteria in the PEW criteria might be reconsidered.

Protein and energy intake

An unintentional reduction in dietary energy intake is a criterion of both cachexia and PEW definitions. In the PEW–CKD field, an intake less than 25 kcal per kg body weight is proposed, and for cachexia, it is 20 kcal per kg body weight. It is recognized that there are pitfalls in identifying a decrease in energy intake. In order to help energy intake management, the gap between energy expenditure and energy intake can be estimated from direct measures of resting energy expenditure (indirect calorimetry) and indirect measures by records of dietary intake.[40] However, this is not routinely performed and until now, there is no consensual value of a 'low' energy intake. The other main difference is protein intake, which has only been considered in the PEW definition. Although it is generally accepted that the protein needs of cachectic patients are increased, the existing international guidelines on

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the optimal amounts of protein and amino acid intakes are vague.[41] This suggests that protein intake could be integrated in the cachexia criteria and is not specific of the uremic condition. For instance, a low protein diet is suggested for the management of CKD with normal nutrition status.[42]

Conclusion

Assessment of protein and energy status is a broad and complex topic, in particular in CKD. No consensus is available on the definition of and methods for measuring skeletal muscle depletion, reduced food intake, and the biological indicators of altered metabolism. The aim of PEW nomenclature was to unify terminology to describe a cachectic disorder that occurs in many patients with CKD. The implementation of this classification was a great success, and contrary to the generic cachexia definition proposed by Evans and co-workers,[15] PEW has been validated to predict mortality in several cohorts of CKD patients.[5,43] In addition, using a generic vs. a specific definition in the kidney disease population has not been performed so far. We do not know whether this may improve diagnosis and management of adverse outcomes in these patients. However, differences between PEW[16] and cachexia[15] are very limited (*Table* 1) and without strong justification. Initial triggers of cachexia may be different between chronic diseases but the catabolic pathway and physiopathology are very similar and induce a comparable phenotype. We would like to suggest that PEW is cachexia and should be termed 'kidney disease cachexia' as a continuum with PEW first followed by cachexia. Substituting PEW by kidney disease cachexia might be less confusing to describe a similar phenomenon observed in other cachectic diseases as seen in cancer.[22] Finally, cachexia definition should evolve to better describe the reality and take into account fat loss and insufficient protein intake. Future research will undoubtedly demonstrate and confirm that criteria of cachexia are similar and helpful in monitoring nutritional disorders in CKD.

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All authors declare that the submitted work has not been published before (neither in English nor in any other language) and that the work is not under consideration for publication elsewhere.

The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017.[44]

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