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Editorial

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Distinguishing Between Cachexia, Sarcopenia and Protein Energy Wasting in End-Stage Renal Disease Patients on Dialysis

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Patients with end-stage renal disease (ESRD) receiving dialysis can have altered nutritional status and body composition due to dietary restrictions, level of physical activity, co-morbidities, metabolic alterations and inflammation.[1] As such, weight loss or wasting is common among this population with up to 75% of adults with ESRD undergoing maintenance dialysis displaying some evidence of wasting.[2] There are several forms of loss of lean muscle mass or wasting in ESRD, including 'protein energy wasting', 'cachexia', and 'age-related sarcopenia' and these terms are often used interchangeably alongside 'malnutrition' in current care. Limited understanding of the differences between such terms is arguably a barrier to accurate recognition and management of these disorders in patients with ESRD. For instance, a recent European study of over 700 dietetic participants concluded that only 13% of health care professionals who could differentiate between malnutrition, starvation, cachexia and sarcopenia.[3] Such knowledge is pertinent as for example, loss of muscle mass is a key feature in both sarcopenia and cachexia, but most patients with sarcopenia are not cachectic,[4] as muscle wasting occurs with aging.

Research has informed a disease specific definition (and associated diagnostic criteria) for protein energy wasting (PEW) in renal disease, and while cachexia in ESRD is seen as the severe form of PEW,[5] there remains no consensus definition or diagnostic criteria to differentiate between PEW and cachexia. What distinguishes PEW from cachexia is that the latter relates to only severe forms of metabolic depletion. However, PEW can refer to mild reduction of lean muscle and depletion of energy stores.[6] Alongside, the lack of disease specific definition or diagnostic criteria for cachexia, there is also no such disease specific criterion for sarcopenia in renal disease. The evidence-based development of these terms is essential to enable health care professionals to clearly identify and differentiate between such conditions. This greater understanding of the difference and interplay between cachexia, PEW and sarcopenia in ESRD

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has the potential to inform the development and testing of targeted novel therapeutic treatments aimed at reducing morbidity and mortality.[7] Significant progress has been made defining cachexia and its associated clinical characteristics in patients with cancer. An agreed definition and classification of cancer cachexia[8] has contributed to enhanced standardization of screening, staging assessment and management. This is a model that could be applied to cachexia in other chronic conditions, such as ESRD.

Reflecting the current evidence base, Table 1 outlines the characteristics of age-related sarcopenia, cachexia in chronic illness, and PEW in renal disease. These characteristics and associated pathologies are reviewed elsewhere in the literature,[5,9-11] and while the diagnostic criteria share similarities they are not identical. For example, weight loss is part of the definition of both cachexia in chronic illness and PEW in renal disease, but the duration of the weight loss differs (weight loss of 5% over 6 months in cachexia as opposed to 5% over 3 months in PEW). Additionally, the diagnostic criteria for cachexia in chronic illness emphasizes lean mass functionality (decreased muscle strength and fatigue), which is also common in sarcopenia of old age, although the defining characteristics of sarcopenia emphasize the importance of gait speed which cachexia does not. Furthermore, anaemia is considered a feature of cachexia in chronic illness, but not of PEW in renal disease or sarcopenia of old age.

	Sarcopenia of old age[9]	Cachexia in chronic illness[10]	Protein energy wasting in renal disease[5,11]
(i) Weight	Not stated, but weight gain is expected in obese sarcopenia whereas weight loss can occur otherwise	Oedema-free "unintentional" weight loss of at least 5% in 12 months or less in the presence of underlying illness. In cases where weight loss cannot be documented, a BMI<18.5 kg/m^2 or a drop from higher BMI to a BMI<20 kg/m^2 is sufficient.	Unintentional weight loss over time: 5% over 3 months or 10% over 6 months. Oedema-free BMI<23 kg/m^2 for example, post-dialysis dry weight.
(ii) Biochemistry	Not stated, but it is expected that serum creatinine relative to kidney function declines.	Increased inflammatory markers CRP (>3.0 mg/L), IL-6>3.0 pg/mL). Anaemia (<10 g/dL). Low serum albumin (<3.5 g/dl BGG or <3.2 BCP)	Serum albumin<3.8 g/dl (bromocresol green). Serum prealbumin (transthyretin)<30 mg/dL (for maintenance dialysis patients only; levels may vary according to GFR level for patients with CKD stages 2-5). Serum cholesterol<100 mg/dL
(iii) Muscle and/or fat mass	Low muscle mass<7.23-7.26 kg/m^2 for men and<5.5-5.67 kg/m^2 for women using appendicular lean tissue/height^2 by DEXA[12]	Low fat-free mass index. Lean tissue depletion i.e. mid upper arm muscle circumference<10th percentile for age and gender); appendicular skeletal muscle index by DEXA <5.45 kg/m^2 in females and<7.25 kg/m^2 in males.	Total body fat percentage<10%. Reduced mid-arm muscle circumference area - reduction >10% in relation to 50th percentile of reference population. Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months. Indirect measure of muscle mass, such as serum creatinine.
(iv) Muscle strength	Low muscle strength, handgrip strength<20 kg women and<30 kg men.	Decreased muscle strength (lowest tertile).	Not stated
(v) Functionality	Gait speed<0.8 metres per second.	Presence of 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.	Not stated
(vi) Dietary intake	Not stated, but often some decline in appetite and/or protein and energy is observed.	Anorexia. Limited food intake (i.e. total energy intake<20 kcal/kg /day; <70% of usual food intake) or poor appetite.	Unintentional low dietary protein intake<0.80 g/kg/day for at least 2 months for dialysis patients or<0.6 g/kg/day for patients with CKD stages 2-5. Unintentional low dietary energy intake<25 Kcal/kg/day for at least 2 months.
Diagnosis	Person must have column iii plus column iv or v.	Person must have column i plus three of the remaining five columns ii,iii,iv,v,or vi.	Person must have at least three out of the four columns i,ii,iii and vi and at least one test from each of the selected columns.

Table 1: Defining characteristics of sarcopenia of old age, cachexia in chronic illness and protein-energy wasting in renal disease.

As seen in Table 1, there are both variations and commonalities in the known clinical characteristics of sarcopenia, cachexia and PEW in a renal population. This may be reflective of the poly-symptomatic nature of ESRD. However, it makes the diagnosis of any of the three conditions more complex. Effectively distinguishing between these three conditions in ESRD is important, acknowledging that elements of sarcopenia and PEW may be present in cachexia, as interventional strategies may be very different for each. Work on delineating key clinical characteristics of PEW in renal disease has progressed extensively[13] and cachexia is viewed as a severe form of PEW.[5] However, the diagnostic criteria for cachexia in ESRD, as opposed to PEW, have not been agreed. This is significant as cachexia may involve additional metabolic abnormalities that are potentially amenable to therapeutic intervention.

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What should the next steps be? Adoption of a disease-specific definition of cachexia in ESRD would contribute to standardization of screening, assessment and management strategies that are aimed at improving morbidity and mortality in these patients. Such a definition needs to be derived in such a way to distinguish cachexia from both sarcopenia and PEW, should define a population group with a different prognosis from PEW, and needs to reflect our understanding of the pathophysiology (particularly the role of inflammation) of cachexia in other conditions such as cancer, heart failure and COPD. Such a definition would greatly facilitate screening, diagnosis and development of treatments for this life-limiting complication of end stage renal disease.

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