Screening for muscle wasting and dysfunction in patients with chronic kidney disease

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Skeletal muscle mass and muscle function are negatively affected by a variety of conditions inherent to chronic kidney disease (CKD) and to dialysis treatment. Skeletal muscle mass and function serve as indicators of the nutritional and clinical state of CKD patients, and low values or derangements over time are strong predictors of poor patient outcomes. However, muscle size and function can be affected by different factors, may decline at different rates, and may have different patient implications. Therefore, operational definitions of frailty and sarcopenia have emerged to encompass these 2 dimensions of muscle health, i.e., size and functionality. The aim of this review is to appraise available methods for assessment of muscle mass and functionality, with an emphasis on their accuracy in the setting of CKD patients. We then discuss the selection of reference cutoffs for defining conditions of muscle wasting and dysfunction. Finally, we review definitions applied in studies addressing sarcopenia and frailty in CKD patients and discuss their applicability for diagnosis and monitoring.

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Skeletal muscle tissue is critical for many functions of the body; fundamentally, it is responsible for movement, and loss of muscle mass and quality results in weakness and reduced mobility. However, skeletal muscle is also the largest reserve of protein in the body. During periods of stress, disease, undernutrition, or starvation, it serves as a source for amino acids that maintain protein synthesis in other vital tissues. Skeletal muscle is also the primary site of glucose disposal, and diminished muscle mass therefore plays a role in impaired glucose metabolism. In addition, skeletal muscle is the major consumer of energy and a contributor to the basal metabolic rate in the body.[1]

Research advances during the past several decades have contributed much to our understanding of how chronic kidney disease (CKD), its associated comorbidities (e.g., diabetes, osteoporosis, cardiovascular disease), its complications (e.g., metabolic acidosis, excess glucocorticoid production, inflammation and/or impaired insulin/insulin-like growth factor-1 signaling), and its therapies (e.g., dialysis) all stimulate the loss of skeletal muscle mass (see recent reviews[2–4]). A wealth of studies have consistently informed clinicians on the consequences of accelerated muscle loss, linking surrogates of muscle mass with worse quality of life, depression, malnutrition, cardiometabolic complications, and higher risk of hospitalizations and death in CKD populations.[5–11] In parallel, it has become apparent that CKD is linked to poor muscle function, impaired mobility and exercise capacity, and ultimately poor patient outcomes.[12–14] Skeletal muscle size seems to be the most important predictor of muscle strength or physical performance, but other factors, including neurological aspects, also influence voluntary muscle strength.[15,16] As a consequence, muscle size and function can be affected by different factors and decline at different rates.[16–20] A recent study in patients on hemodialysis (HD) noted that muscle dysfunction was only marginally correlated with muscle atrophy, and patients still showed poorer muscle function than matched controls for a given muscle mass.[21] Old age, comorbidities, physical inactivity, and inflammation are all related to low muscle strength in dialysis patients, but such factors did not fully explain their low muscle mass.[13] Adding to this, disability, being defined as the inability to perform normal daily physical activities, represents a linked but distinct dimension.

Disability may be associated more with muscle strength than muscle mass, but it is associated with mortality independently of both.[22,23]

The links between muscle size, strength, function, and survival have raised awareness of the importance of assessment and monitoring of these different dimensions of musculoskeletal health in patients with CKD. However, assessment of these domains is not free of challenges, and some special considerations are necessary to properly evaluate this unique population. Operational definitions of frailty and sarcopenia have emerged to encompass both dimensions of muscle health (size and functionality) and are being increasingly used in the nephrology literature. The aim of this review is to discuss available methods for assessment of muscle mass and functionality in CKD patients, to describe criteria defining conditions of muscle wasting and dysfunction in these patients, and to consider whether the concepts of sarcopenia and frailty have clinical applicability for diagnosis and monitoring of CKD patients.

METHODS OF ASSESSMENT

Citing Prado and Heymsfield,[24] "if the medical fields have evolved to using sophisticated techniques, we can also advocate for the use of advanced body-composition methodology for assessment of health status of patients beyond simple measurement of body weight." A broad range of methods of assessment exists for both muscle mass and function. Some of them, such as imaging techniques, have been historically inaccessible, but, to date, most hospitals would have them available for clinical diagnostics.

Methods to assess muscle mass in CKD

The body can be understood as including 2 compartments: fat tissue and nonfat tissue (Figure 1). Body fat encompasses the sum of adipose tissue (collagenous and elastic fibers, fibroblasts, and capillaries) and fat mass (lipids consisting mainly of triglycerides). The nonfat tissue, in turn, can be described using more complex terminology that is at times used incorrectly in the scientific literature: lean body mass (LBM), sometimes also called lean soft tissue [LST]), is the sum of total body water, skeletal muscle mass (SMM), and the fat-free part of organs (i.e., organs and residual mass including connective tissue and blood). When LBM is added to bone-mineral tissues, it results in fat-free mass (FFM).[24] Thus, LBM, FFM, and SMM represent different tissues, and identifying the specific body compartment of interest must precede the choice of method of assessment. For diagnostic purposes, SMM is the ideal compartment to target in the search for muscle abnormalities in CKD.

The accuracy of *all* methods for assessing muscle mass can be affected by CKD-related factors, especially hydration status. In general, for patients with nondialysis-requiring CKD, clinical signs of edema may impede a proper assessment of muscle mass. For patients on dialysis, assessing body composition during the postdialysis period in HD patients when patients are closer to their dry weight or with an empty

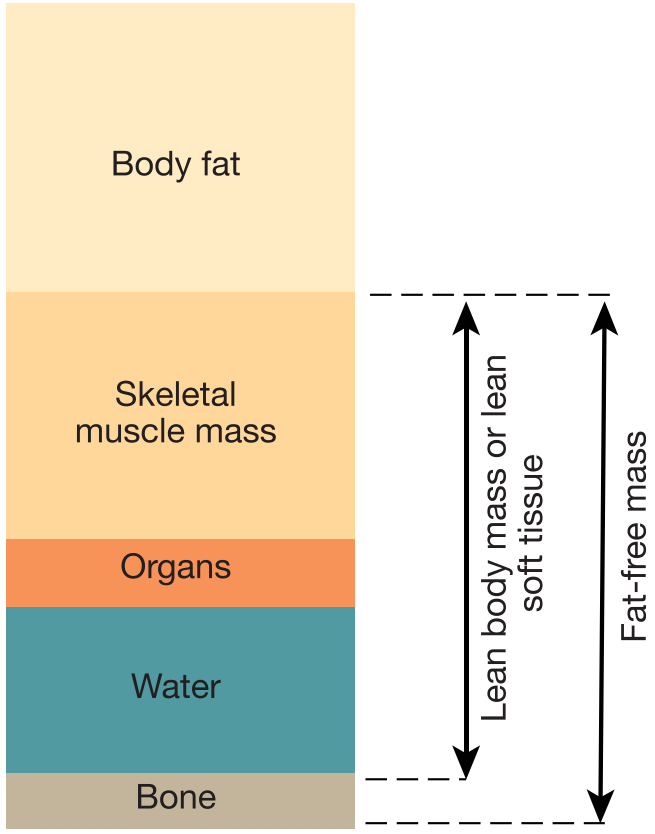

Figure 1 | Body composition compartments; differences in the estimation of fat-free mass and lean soft-tissue/lean body mass. Residual mass considers connective tissue and blood.

cavity in those undergoing peritoneal dialysis can minimize the impact of hydration status. This is particularly important for methods that cannot distinguish between extracellular and intracellular fluid (e.g., dual-energy X-ray absorptiometry [DXA]). Standardized conditions should be considered when possible to allow reproducibility/comparability over time. However, few studies have rigorously evaluated the best timing for body composition assessment in CKD patients. A general important hindrance in current CKD literature is the relative lack of validation studies of these methods.[25] Nuclear-based methods (i.e., total body nitrogen measured by neutron activation and body K^+ content) are considered the reference methods for body composition but have been rarely studied in CKD patients.[26–28] Results obtained by these techniques could be compared with estimates obtained by other techniques in order to assess and rank their validity.

Table 1 describes available methodology for assessing muscle mass, LBM, and FFM. In general, methods that estimate FFM have greater clinical applicability, with lower costs and ease of assessment. However, they tend to also have lower precision. Methods enabling the assessment of LBM and SMM, although more precise, are often accompanied by higher costs, less portability, and the need for a trained/experienced operator, making them more suitable for research purposes. Supplementary Table S1 online[29] offers practical descriptions of the protocols for implementing these methods,