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.

Kidney International (2016) ■, ■–■; http://dx.doi.org/10.1016/j.kint.2016.02.025

KEYWORDS: frailty; muscle function; muscle mass; sarcopenia; strength

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Received 5 October 2015; revised 12 February 2016; accepted 17 February 2016

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

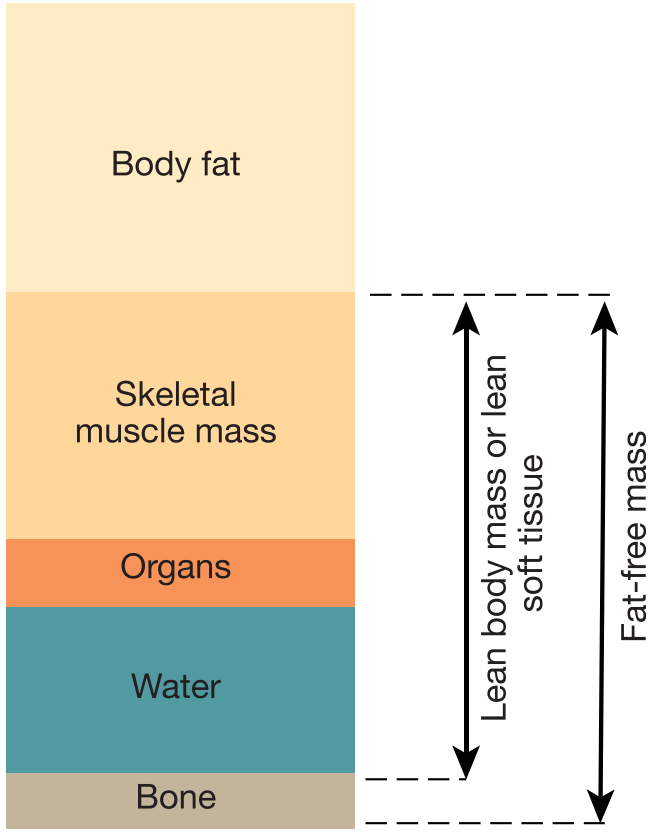

Figure 1 | Body composition compartments; differences in the estimation of fat-free mass and lean soft-tissue/lean body mass. Residual mass considers connective tissue and blood.

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,

Table 1 | Available methods for assessment of muscle mass

Modality	Method	Body compartment assessed	Clinical applicability[a]	Advantages	Disadvantages
Visual signs	Physical examination, component of composite scoring (SGA and MIS)	SMM	↑↑↑	Quick, does not require equipment or in-depth training	High inter- and intraobserver variability, not quantitative. Affected by hydration status
Anthropometry	MAMC Calf circumference APMT	SMM SMM SMM	↑↑↑ ↑↑↑	Widely available, portable, low cost, quick	Low precision, high inter- and intraobserver variation. Affected by hydration status[b]
Estimating equations	Various	SMM	↑↑↑	Usually low cost, readily available	Affected by hydration status. Agreement with direct measures of lean mass has not been tested in CKD patients
Creatinine kinetics	Urinary creatinine excretion	SMM	↑↑	Low cost	Affected by the quality of 24-hour urine collection; influenced by dietary creatine and protein intakes; influenced by creatinine degradation and elimination. Not valid for dialysis patients. Lack of reference values
	Serum creatinine (applied in an equation to estimate LST)	LST	↑↑↑	Low cost, allows routine assessment in dialysis patients	Influenced by the amount of dietary creatine and protein, influenced by creatinine degradation and elimination, the equation has to be validated in other populations; equation directed to hemodialysis patients[c]
Bioelectrical impedance	BIA	FFM	↑↑↑	Widely available, medium cost, low inter- and intraobserver variation, quick, portable	Not a direct measurement of lean mass, equations not validated in CKD patients, amputations and pacemakers preclude its use. In general, affected by hydration status[b]
	BIS	FFM	↑↑↑	Medium cost, low interobserver variation, quick, portable, validated for patients on dialysis	Not a direct measurement of lean mass; amputations and pacemaker precludes its use. Less affected by hydration status as ECW, ICW more accurately estimated[b]
Whole-body counting	Total body potassium	BCM	↓	High precision, not influenced by hydration status	High cost, measures BCM, which is an indirect measure of muscle mass
Neutron activation analysis	Total body nitrogen	Body protein store	↓	High precision, not influenced by hydration status, useful when assessing a multicompartment model to assess body composition	Measures body protein store, which is an indirect measure of muscle mass, radiation exposure (similar to chest X-ray)
Imaging techniques	DXA	LST FFM: LST + bone ASM: LST arms + legs	↓ ↓ ↓	Devices often available in hospitals and research centers, high precision	Radiation exposure, high cost, measures LST, orthopedic implants can create artifacts, measurements affected by hydration status[b]
	CT	Muscle cross-sectional area, muscle density, yielding estimate of SMM	↓	High precision of cross-sectional area and volume, muscle density provides measurements of muscle quality, theoretically not influenced by hydration status	Radiation exposure, high cost, intermachine variations, only provides regional estimates of muscle size (vs. whole body)
	MRI	Muscle cross-sectional area, yielding estimate of SMM		High precision of cross-sectional area and volume, no radiation exposure, theoretically not influenced by hydration status	High cost, intermachine variations, estimates regional muscle size, implanted metal precludes its use

APMT, adductor police muscle thicknesses; ASM, appendicular skeletal muscle mass; BCM, body cell mass; BIA, bioelectrical impedance analysis; BIS, bioelectrical impedance spectroscopy; CKD, chronic kidney disease; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; ECW, extracellular water; FFM, fat free mass; ICW, intracellular water; LST, lean soft tissue; MAMC, midarm muscle circumference; MIS, Malnutrition-Inflammation Score; MRI, magnetic resonance imaging; SGA, Subjective Global Assessment; SMM, skeletal muscle mass.

[a]One arrow down: little clinical applicability; 2 arrows up: moderate clinical applicability; 3 arrows up: good clinical applicability.

[b]For patients on HD, assessments should be performed after the dialysis session. For patients on peritoneal dialysis, measurements should performed with empty abdominal cavity.

[c]Serum creatinine should be measured before the dialysis session.

together with specific considerations and adaptations for CKD patients.

Visual signs of muscle wasting and muscle palpation as part of a physical examination[5,30] should not be underestimated and could be considered as an adequate screening tool to identify individuals at risk of muscle wasting and in need of a more thorough assessment. Anthropometric estimates, which include the mid-arm circumference, the mid-arm muscle circumference,[31–33] the calf circumference,[33] or the adductor pollicis muscle thickness,[34,35] are also valid for screening for low muscle mass.[36] Low muscle mass identified by anthropometry has been consistently linked with a worse prognosis in patients with CKD.

LST is a good electrical conductor because it contains water and electrolytes. In contrast, fat, bone, and skin are poor conductors and offer resistance to electrical current. These principles are the basis for the use of bioelectric impedance analysis (BIA) and bioelectrical impedance spectroscopy (BIS), which determine the electrical impedance or resistance to the flow of an electric current through body tissues. The main information derived from BIA is total tissue fluid content, equivalent to total body water and cell mass, which in the limbs mainly reflects muscle.[37] The applications of these devices for volume assessment were recently reviewed,[38] but here we focus on their use for body composition assessment. BIA variables, along with individual's general characteristics (e.g., sex, age, weight, and height), are applied in specific empirical equations to provide estimates of body compartments. There are several bioimpedance techniques generally classified by the frequency of the electric current (single frequency or multifrequency) and by site (whole body or segmental). The more frequently used in the clinical setting are the single frequency BIA (50 kHz), the multifrequency BIA (several frequencies ranging from 5 to 1000 kHz), and the bioimpedance spectroscopy (all frequencies ranging from 0 to 1000 kHz). More recently, single-frequency BIA has been largely replaced by BIS within the CKD and end-stage renal disease (ESRD) research and clinical arenas because of the recognition that it provides more accurate estimates of total body water (TBW) and intracellular water (ICW), particularly when fluid distribution may be altered. In addition, there is an increasing interest in its potential for nutritional assessment, especially for monitoring changes in muscle mass. In BIA, the device provides estimates of TBW, extracellular water, and ICW using empirical equations constructed from population-specific equations, which normally are not released by the manufacturers.[39] TBW is thereafter used to estimate FFM and fat mass. To understand the validity of these empirical equations, we must bear in mind that they were developed for healthy subjects from 1 ethnic group. Subsequent studies have shown that body composition varies also with ethnicity[40] and comorbidity (e.g., type 2 diabetes).[41] Further, these algorithms operate under certain assumptions with regard to the body's compartment models; the 2-compartment (fat mass, FFM) model of body composition assessment assumes that the water component is constant in the body, at the level of 73.2%.[42] The 3-compartment (3-C) model (fat mass, lean-tissue mass, water) incorporates TBW in its assessment, thus controlling for interindividual variation in lean-tissue mass hydration and being more accurate for body composition analysis in CKD patients.

Some manufacturers have introduced multifrequency BIA methods with 3-C models of body composition and the concept of overhydrated fat mass.[43] BIS, on the other hand, provides a precise assessment of the ECW and TBW, given that different tissues contain both different amounts of water and also differ in cell density.[44–46] The *BIS method* uses a whole sweep of frequencies ranging from 5 to 1000 kHz. At very low frequencies, the current passes nearly exclusively round the cells, while at high frequencies the current passes through the cell membranes. This allows differentiation between extracellular and intracellular compartments, and the fat mass and the FFM is then estimated using empirical estimations of the hydration of ICW. Using equations based on the 3-C model, BIS is the bioimpedance method of choice to distinguish lean tissue mass, adipose tissue mass, and TBW and ICW.[46,47] Kaysen *et al.*[25] observed a good correlation in HD patients between BIS estimates of muscle mass and measurements of extracellular volume/body water by isotope dilution techniques. Because overhydration will affect BIA estimates of body composition to a greater extent than BIS,[37,48,49] BIS has become the standard in ESRD.[25] However, even with BIS, which produces estimates of muscle mass that are highly correlated with muscle mass estimated by whole-body magnetic resonance imaging, precision is low.[50] New data suggest that variation in hydration status may play a role in the imprecision, with estimates of lean tissue mass affected by the degree of overhydration.[51]

Although it is more convenient for both patients and staff to undertake bioimpedance measurements before dialysis, overhydration affects body composition estimates. This issue is not unexpected in the case of single-frequency BIA (2-compartment model), and was demonstrated by Di Iorio *et al.*[52] when showing that BIA variables (reactance and resistance) significantly increased during the HD, remained stable during the postdialysis period (15–120 minutes after), and subsequently declined during the interdialysis period (24, 48, and 68 hours after) as hydration increased. Although in theory 3-C multifrequency BIA and BIS should be able to better separate the fluid compartment, 2 recent studies[37,51] also show that postdialysis measures display lower lean tissue mass and lower ICW estimates compared with predialysis measures. For a more reliable and reproducible assessment, we recommend assessing muscle mass at a consistent time relative to hemodialysis sessions if repeated measures are planned, preferably 15 to 120 minutes post-dialysis, when patients are closer to their target weight than when overhydrated. If predialysis BIS measures are used for assessment of body composition, investigators may either focus on ICW per kilogram rather than LBM or should adjust for excess

extracellular water in estimating LBM.[45] The same applies to peritoneal dialysis, with 2 studies demonstrating that multifrequency BIA measurements made in patients with peritoneal dialysate instilled overestimate body water and cell mass, including muscle mass.[48,49] Thus, an empty abdomen is recommended when evaluating body composition using BIA in peritoneal dialysis patients.

Equations and algorithms originally developed in individuals without CKD are often used to estimate appendicular skeletal muscle mass (ASM) from body weight, height, hip circumference, and handgrip strength.[53] Also, Janssen *et al.*[54] developed equations to estimate SMM from BIA measurements. Over the past decades, various studies have developed formulas to estimate FFM in CKD patients based on 24-hour urinary creatinine excretion, serum creatinine concentration, or the amount of creatinine in the dialysate.[55–59] The use of these equations is in acceptable agreement with various reference methods, but with considerable under- and overestimation.[55–59] Nevertheless, because these estimates have not included evaluations of creatinine degradation or daily creatinine excretion, this may introduce a source of error.[60] In the absence of methodology to measure LST directly, these algorithms can serve to indirectly estimate LST; however, because of the lack of reference ranges for serum creatinine and urinary creatinine excretion, they would only be appropriate in the context of intraindividual changes in body composition over time.

Imaging methods have higher precision and accuracy for assessment of muscle mass. Computed tomography and magnetic resonance imaging can assess the quantity of muscle in a specific region of the body. Both methods have been applied in studies of patients with CKD to assess muscle cross-sectional area and volume.[7,61–63] In addition, computed tomography allows calculation of muscle density, which provides additional information regarding muscle quality or the degree of intramuscular fat infiltration.[64] DXA is probably the most commonly used imaging technique in the kidney literature. DXA passes 2 X-ray beams of different energies through the body. The difference in attenuation of these 2 X-ray energies is related to the thickness, density, and chemical composition of the object traversed. This information is then applied through different equations to calculate fat mass, LBM, and bone mineral density.[24,64] Because DXA assumes a constant hydration status in the calculation of FFM,[65] fluctuations in the hydration status results in over- or underestimation LBM quantification,[66] which would in turn affect the estimated proportion of body fat.[65] DXA therefore also requires standardizations as close as possible to conditions of dry weight. Although the nephrology community has mainly used DXA to calculate whole-body LBM, recent consensuses[67–71] recommend instead focusing on the lean mass of arms and legs (the so-called appendicular lean mass), which is more intrinsically linked to muscle function and mobility. Heymsfield *et al.*[72] totaled the lean mass of the 4 limbs from a DXA scan and referred to it as ASM, defining the ASM index (ASMI) as ASM/(height)^2 (kg/m^2).

There is a plethora of methods to estimate muscle mass, and each of them has advantages and limitations. Ultimately, the choice of method will depend on practicality, availability, purpose, and the need for specialized personnel. For routine clinical practice, the method chosen should be simple with a low risk of complications that could impair assessments. To that end, in our clinical experience, anthropometric estimates and algorithms such as the one from Janssen *et al.*[54] may be adequate alternatives in the absence of dedicated equipment. These simple tools have been shown to be good proxies of muscle mass and also good prognostic indicators of patient outcomes.[31–35] Because most of these methods are subject to inter- and intraobserver variability, it is important to standardize the protocol conditions and, if possible, to have the same observer make repeated, longitudinal measurements and, as discussed earlier, ensure conditions close to dry weight. We recognize that BIS devices have become increasingly available for routine patient monitoring and as such are promising, noninvasive, portable, and easy to operate tools. Of the various options available, the 3-C models of BIS offer advantages for routine care and monitoring, allowing the detection of short-term body composition changes.[73]

Methods to assess muscle functionality in CKD

A decrease in protein synthesis and/or an increase in protein degradation can have major effects on muscle mass. However, even minor losses of muscle contractile proteins (i.e., myosin and actin) representing muscle quality can be associated with even larger decrements in force due to a reduction in cross-bridge formation during muscle contraction. Even the most sophisticated methods discussed earlier may not detect these subtle changes. Thus, functional deficits may precede noticeable losses in muscle mass. There are many aspects of muscle function that can be measured, including strength, power, endurance, fatigability, and integrated functions in the form of performance tests (Table 2). Choice of appropriate measures will depend on cost, ease of measurement, and the conceptual model being used or tested. Although muscle strength is not the sole determinant of physical performance, weakness is an important potential contributor to poor physical performance. Thus, loss of muscle strength may be the functional parameter most closely tied to loss of muscle mass and weakness of the lower extremities, in turn, the most closely tied to relevant disability, such as difficulty in walking, climbing stairs, and rising from a chair.

The criterion standard method for measuring lower extremity strength uses isokinetic dynamometers because of their precision. However, this equipment is expensive and bulky. Furthermore, operating the machines requires detailed training, and testing is time-consuming. By contrast, handheld dynamometers are simple, portable, and relatively inexpensive, making them much more attractive for clinical and research use.[74] These considerations make lower extremity strength testing impractical for routine monitoring in the clinical setting. Handheld dynamometers are much more reliable for upper extremity strength testing, particularly for

Table 2 | Available methods for assessment of muscle function

Measure	Rationale	Advantages	Disadvantages	Recommendation
Strength	Closely related to muscle size			
Lower extremity strength		Directly related to relevant measures of physical performance and function, such as walking, stair climbing, standing from a chair	Requires expensive equipment for accurate measurement; more portable measures lack precision	Suitable for research
Handgrip strength		Easy to measure, portable dynamometer, good accuracy and reproducibility; correlated with lower extremity strength and function	May be inaccurate in the setting of arthritis	Suitable for research and clinical application, assess in dominant hand or in nonfistula arm
Power	Closely related to physical performance		Difficult to measure, requires expensive equipment and complex protocols	Suitable for research
Physical performance	Directly related to ability to perform activities of daily living and to quality of life	Most tests are relatively quick and easy to perform, standard protocols available	Related to muscle power, endurance, and neuromuscular control rather than solely to muscle size or strength	
Gait speed		Easy to perform, associated with important clinical outcomes (death, disability, hospitalization, institutionalization), relevant cut points have been established		Suitable for research and clinical practice
SPPB	Includes gait speed, chair stand, and static balance tests	Easy to perform, associated with important outcomes, relevant cut points have been proposed		Suitable for research and clinical practice
Stair climbing			More patients unable to complete testing, less clearly standardized, cut points not established	Not recommended
Timed Up and Go Test		Standard protocols available	Cut points less extensively validated than gait speed, SPPB	Suitable for research, not specifically included in any sarcopenia definitions
6-Minute walk test		Standard protocols available, clinically important difference established (50 m)	Takes longer to perform, related to endurance as well as strength and neuromuscular control, requires more space in the form of an unobstructed course	Suitable as an integrated measure of function and endurance, not included in sarcopenia definitions

SPPB, Short Physical Performance Battery.

grip strength.[75,76] Standard protocols are available for measuring grip strength without a high level of investigator training (Supplementary Table S2 online).[77–81] Although lower extremity strength is more relevant to mobility, grip strength is correlated with lower extremity strength[82] and closely related to mobility outcomes.[82,83] Muscle power is defined as the amount of work generated per unit of time and is perhaps the measure of muscle function that is most closely related to lower extremity function.[84–87] However, because of the need to integrate the measurement of force and velocity, measuring power is more complex than measuring strength and requires sophisticated and expensive equipment. There are numerous tests of physical performance in use in research and clinical practice. Such tasks rely on muscle strength, power, endurance, and neuromuscular control and plasticity. Commonly used physical performance tests include gait speed, chair standing, balance tests, and the Short Physical Performance Battery, which incorporates all 3 as well as the Timed Up and Go Test and the 6-minute walk test, among others. Gait speed, usually over a 3- or 4-m course, has been the most commonly used physical performance measure in clinical studies because it is highly predictive of mortality and other relevant outcomes and because it can be assessed relatively easily.[79] However, gait speed is only moderately correlated with muscle strength in the general elderly population[88,89] and among patients with CKD.[61] For this reason, some have considered gait speed as an outcome measure or validation tool.[90] Similar considerations apply to the Short Physical Performance Battery and Timed Up and Go Test. In general, muscle performance in patients with

CKD is inferior to that in healthy individuals of similar age,[91–94] and poor muscle performance is associated with worse survival among patients with ESRD.[93,95,96] Because the effects of HD on physical performance are unclear, testing should be standardized relative to dialysis treatment in the HD population. Most studies have tested patients before a dialysis session[97] or on a nondialysis day.[91] Standard protocols used in healthy elderly populations can be used among patients with CKD and ESRD, but it may be advisable to limit chair stands to only 5 repetitions and to consider measuring grip strength in a seated position to avoid variability as some patients will be unable to stand. In order to maximize the reproducibility of the measures, it is advisable to follow a standard protocol, explain the procedure clearly to the participant, and have the participant complete a practice test (or in the case of the chair stand, a single practice stand, which also serves as an indication of the safety of the test). We recommend that grip strength and gait speed tests be performed 2 to 3 times with the results averaged. Sit to stand and 6-minute walk tests should be conducted only once because subsequent tests may be affected by participant fatigue. It is important that, particularly for the 6-minute walk, a precise script be followed to provide standard instructions and encouragement.

CLINICAL DIAGNOSIS OF MUSCLE WASTING AND MUSCLE DYSFUNCTION

Challenges with defining reference/normal populations

After quantifying muscle mass and function, clinicians face the challenge of defining whether the resulting measure is appropriate or low. In clinical research, studies have often used cutoffs derived from the population under study (e.g., categorizing based on a certain percentile, such as median and tertiles). Although these cutoffs can serve to estimate associations with other risk factors and outcomes, they cannot be extrapolated to other populations beyond the studied cohort and therefore lack generalizable diagnostic value. Reference populations are needed to define the norms for separating healthy muscle size and function from conditions of wasting and dysfunction, but identifying a normative healthy population is complex. The choice of referent population is not inconsequential[98] because it can yield a severalfold difference; in a study of elderly HD patients, prevalence estimates of low muscle mass ranged from 4% to 74% depending on the method and cutoff applied.[99] Although muscle mass and strength are related to function, both age, sex, and ethnicity are to be taken into account. Furthermore, estimates may also vary in different countries; this regional variability was clearly illustrated in the PURE (Prospective Urban Rural Epidemiology) study,[100] which assessed grip strength in 140,000 individuals from 17 countries of varying incomes and sociocultural settings. Even after standardizing for age, sex, and ethnicity, normative handgrip strength values still differed markedly between countries geographically close to each other or with similar economic development. In addition to population-related variability, additional complexity is introduced when one considers the different methods for assessing muscle mass and strength and the different ways in which they can be indexed to body size. The Foundation for the National Institutes of Health initiative[83,101] has made substantial efforts to develop uniform clinical definitions. By pooling available data from 9 large, mainly North American population–based cohorts, the Foundation for the National Institutes of Health initiative uses a different conceptual approach. Rather than identifying cutoffs that differentiate from young populations, they argue that it is more clinically relevant to instead define muscle mass cutoffs that would capture individuals with low muscle function and vice versa in the elderly age.

Given that CKD is prominently a disease of the elderly, considerations should be given to the impact of the aging process on muscle size and function. For clinical diagnoses of

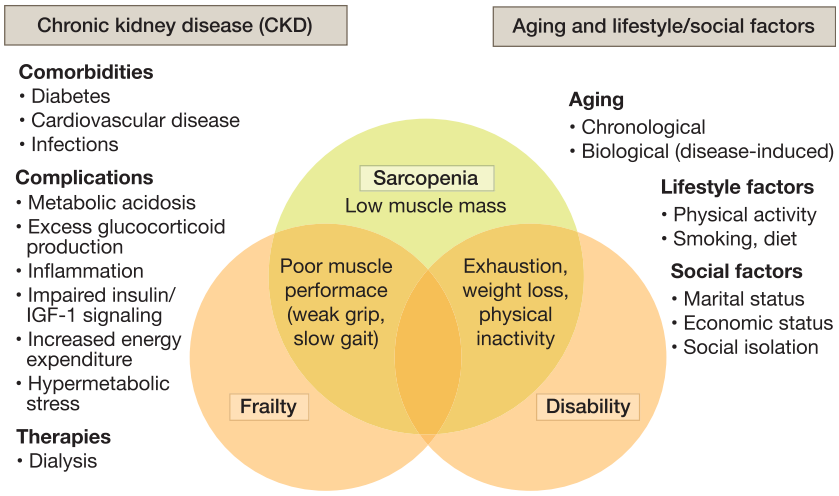

Figure 2 | General and chronic kidney disease–specific causes, as well as conceptual overlapping of the syndromes of sarcopenia, frailty, and disability. IGF-1, insulin-like growth factor.

muscle deficiency, a young reference population is ideal.[102] However, to distinguish disease-associated muscle wasting from age-related changes, referent populations should be defined for each age stratum. In a recent study, data from 11,643 National Health and Nutrition Examination Survey participants who underwent DXA was used to examine the association between low muscle mass and different stages of CKD.[103] The authors found an almost linear crude association between low muscle mass and renal function, but the association flattened when muscle parameters were standardized according to age and sex. This study indicates that low muscle mass is common in advanced stages of CKD, but the strong association of CKD with older age makes it difficult to disentangle age and kidney function, and old age seemed to explain the high prevalence of low muscle mass in these nondialyzed individuals. Nevertheless, identification of healthy elderly referent populations not plagued by overt or subclinical illness is challenging.

Patients at risk of low muscle mass or strength and in need of intervention should be identified on the basis of intra-individual temporal trends in addition to population-derived thresholds. One of the most commonly used criteria for muscle wasting in clinical guidelines is a reduction of muscle mass of 5% over 3 months or of 10% over 6 months, regardless of the method.[36] Although we lack reference ranges for serum creatinine in dialysis patients, decreases in serum creatinine concentrations over time have clinical utility as they likely underscore a loss in muscle stores.[104,105] Similarly, declining physical performance may signal a high-risk state even before accepted thresholds have been crossed. Because the etiology of muscle abnormalities is multifactorial, prudence suggests basing clinical decisions on not 1 indicator but different and complementary nutritional indicators, as well as monitoring patients frequently to assess for evolution.[36]

Sarcopenia and frailty

Sarcopenia and frailty are overlapping geriatric syndromes (Figure 2). They both arise from various interrelated causes and contributors linked to both aging and disease. Irwin Rosenberg[106] initially coined the term sarcopenia to describe the age-related decline in muscle mass. However, in recognition that loss of strength or function often accompanies sarcopenia, it has more recently been defined as including both low muscle mass and low muscle function.[67–71] Frailty, on the other hand, represents a syndrome resulting from cumulative deterioration in multiple physiological systems, leading to impaired homeostatic reserve and decreased capacity to withstand stress.[77,107,108] Frailty is interrelated, but not synonymous, with comorbidity and disability. Frailty and sarcopenia are linked but distinct correlates of

Table 3 | Currently proposed criteria, methods, and reference ranges to diagnose sarcopenia

Consensus	Criteria	Suggested methodology	Suggested reference ranges for clinically low states
European Working Group on Sarcopenia in Older People[70]	Low muscle mass	ASMI by DXA or SMMI by BIA	ASMI or SMMI: <2 SD below the mean of young adults or by the specific cutoff points: ASMI: Men, 7.26 kg/m^2; women, 5.5 kg/m^2 SMMI: Men: severe, ≤8.50 kg/m^2; moderate sarcopenia, 8.51–10.75 kg/m^2; normal muscle ≥10.76 kg/m^2 Women: severe, ≤5.75 kg/m^2; moderate sarcopenia, 5.76–6.75 kg/m^2; normal muscle ≥6.76 kg kg/m^2
	Low muscle strength and/or function	Handgrip strength Gait speed	Men: <30 kg; women: <20 kg <0.8 m/s
Special Interest Groups "cachexia-anorexia in chronic wasting diseases" and "chronic geriatrics"[69]	Low muscle mass	None suggested	Muscle mass (%), <2 SD below the mean value of young adults of same sex and ethnic background
	Low muscle strength and/or function	Gait speed or geriatric functional tests	Gait speed: <0.8 m/s on the 4-m walking test
International Working Group on Sarcopenia[67]	Low LBMI	LBMI by BIA or DXA; ASMI (by DXA)	LBMI or ASMI: <20th percentile for healthy young adults or ASMI: men ≤7.23 kg/m^2; women ≤5.67 kg/m^2
	Low muscle function	Gait speed or geriatric functional tests	Gait speed: <1 m/s in 4-minute walking test
Foundation for the National Institutes of Health Sarcopenia Project[71]	Low muscle mass	ASMI adjusted for BMI, ASM assessed by DXA	ASM adjusted for BMI: men, <0.789; women, <0.512
	Low muscle strength (weakness)	Handgrip strength	Men: <26 kg; women: <16 kg
Society of Sarcopenia, Cachexia and Wasting Disorders[68]	Low muscle mass	Muscle index (by DXA, CT, MRI, ultrasound, or BIA)	<2 SD below the mean value for young adults of same sex and ethnic background
	Limited mobility	Gait speed	Gait speed: <1 m/s or walking distance <400 m in 6 minutes

ASMI, appendicular skeletal muscle mass index; BIA, bioelectrical impedance analysis; BMI, body mass index; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; LBMI, lean body mass index; MRI, magnetic resonance imaging; SMMI, skeletal muscle mass index.

Table 4 | Summary of studies exploring sarcopenia prevalence in CKD patients

Author	Sample characteristics	Assessment of low muscle mass	Assessment of low muscle function	Prevalence of sarcopenia
Kim *et al.*, 2014[110]	South Korea: 95 prevalent HD; 57% men; age, 64 ± 10 yr	LSTI (BIS) <2 SD of reference young population	HGS <30 kg in men or <20 kg in women	9.5%
Isoyama *et al.*, 2014[13]	Sweden: 330 incident dialysis; 61% men; age, 53 ± 13 yr; GFR, 7 ml/min/1.73 m^2	ASMI (DXA) <7.3 kg/m^2 in men and <5.5 kg/m^2 in women	HGS <30 kg in men or <20 kg in women	20%
Lamarca *et al.*, 2014[99]	Brazil: 102 prevalent HD; 73.5% men; age, 71 ± 7 years	I. ASMI (DXA) <20th percentile of reference young population	HGS <30 kg in men or <20 kg in women	I. 63.3%
		II. ASMI (DXA) <2 SD below means of reference young population		II. 30.6%
		III. FFM (BIA) <20th percentile of reference young population		III. 45.1%
		IV. FFM (BIA) <2 SD below reference young population		IV. 12.7%
		V. FFM (anthropometry) <20th percentile of reference young population		V. 37.3%
		VI. FFM (anthropometry) <2 SD below reference young population		VI. 3.9%
		VII. MAMC <90% of reference population		VII. 31.4%
		VIII. Calf circumference <31 cm		VIII. 20.6%
Pereira *et al.*, 2015[30]	Brazil: 287 nondialysis CKD; 62% men; age, 60 ± 10 yr; GFR, 25 ± 16 ml/min/1.73 m^2	I. MAMC <90% of reference population II. Physical exam from SGA III. SMMI (BIA) <10.76 kg/m^2 in men and <6.76 kg/m^2 in women	HGS <30th percentile of a reference population adjusted for sex and age	I. 9.8% II. 9.4% III. 5.8%

ASMI, appendicular skeletal muscle mass index; BIA, bioelectrical impedance analysis; BIS, bioelectrical impedance spectrometry; CKD, chronic kidney disease; DXA, dual-energy X-ray absorptiometry; FFMI, fat-free mass index; GFR, glomerular filtration rate; HD, hemodialysis; HGS, handgrip strength; LSTI, lean soft-tissue index; MAMC, mid-arm muscle circumference; SGA, Subjective Global Assessment; SMMI, skeletal muscle mass index.

musculoskeletal aging. Frailty results from a large number of causes, not all of which are related to skeletal muscle amount or function. Finally, frailty and sarcopenia overlap, with some aspects of the conditions of protein-energy wasting[22] and cachexia,[109] which are also defined as multifactorial syndromes characterized by body weight, fat and muscle loss, and increased protein catabolism due to underlying disease(s). The difference between protein-energy wasting and cachexia is that the latter encompasses only severe forms of metabolic depletion, whereas protein-energy wasting can refer to mild degrees of depleted protein and energy mass. Etiologically, these conditions encompass a variety of other nutrition-related disorders that do not necessarily relate to musculoskeletal health, including the loss of body fat or diminished appetite. Thus, although cachectic patients are likely also sarcopenic, many sarcopenic patients are not necessarily cachectic.

Criteria and reference values for sarcopenia. Although consensus groups agree on the importance of this syndrome, they have failed to agree on a common definition (Table 3). Differences in these operational definitions stem from the choice of methodology for estimating muscle mass and function as well as the reference population cutoffs, with <2 SD below the mean and less than the 20th percentile being the most commonly used. Studies that have used these definitions in the setting of CKD are few and are listed in Table 4. The prevalence of sarcopenia ranged from 6% to 10% among nondialysis-dependent CKD patients[30] and from 4% to 64% among HD patients.[13,99,110] Although differences in patient selection based on age, sex, or country of origin may partially account for the differences in prevalence, the wide variation is also a direct consequence of the choice of criteria for defining sarcopenia. Furthermore, the clinical implications of sarcopenia in CKD are thus far ill defined. Pereira *et al.*[30] tested 3 working definitions in relation to the risk of mortality, finding that only one of them (combining BIA-estimated muscle mass and handgrip strength values) was associated with mortality on multivariate analysis. Isoyama *et al.*[13] observed that the predictive mortality value of low muscle strength alone (handgrip) was similar to the combined entity of low muscle (DXA) mass and function.

Criteria and reference values for frailty. Operational definitions of frailty also vary, but 3 general approaches have emerged. First, a subjective *clinical frailty scale* has been proposed, which is a 7- to 9-point scale score that ranges from "very fit" to "terminally ill."[111] Second, a *deficit accumulation approach* in which an individual's impairments and conditions are summed to create a frailty index[112]; finer gradations of frailty can be obtained if many conditions are included in the index. Third, a physical *frailty phenotype* characterized by weight loss, exhaustion, low physical activity, and poor physical performance has been proposed.[82] These frailty constructs differ fundamentally in their conceptual framework; the first 2 approaches include comorbidity and disability as part of frailty, whereas the frailty phenotype encompasses frailty, comorbidity, and disability as overlapping conditions, in which frailty and comorbidity are independent risk factors for disability.[108] In this view,

Table 5 | Studies on the prevalence of frailty among patients with CKD and ESRD, including definitions employed for its assessment

Reference	Population	Weight loss	Exhaustion	Physical activity	Gait speed	Grip strength	Prevalence
Studies in the ESRD population							
Johansen *et al.*, 2007[115]	Incident dialysis	Malnourished according to provider assessment	SF-36 Vitality	Inactive (single question about frequency of activity)	SF-36 PF scale	SF-36 PF scale	67.7%
Bao *et al.*, 2012[116]	Incident HD	No	SF-12 Vitality	Human Activity Profile	SF-12 PF	SF-12 PF	73%
McAdams-Demarco *et al.*, 2013[117]	Prevalent HD	Yes	CES-D	MMLTA	Over 15 ft	Yes	41.8%
Johansen *et al.*, 2014[97]	Prevalent HD	Yes	CES-D	MMLTA	Over 15 ft	Yes	30%
Johansen *et al.*, 2014[118]	Prevalent HD	Yes	SF-36 Vitality	MMLTA	SF-36 PF	SF-36 PF	53%
Painter and Kuskowski, 2013[119]	Prevalent HD	BMI ≤18.5 kg/m^2	SF-36 Vitality	Detailed self-report of no activity beyond self-care	SF-36 PF >6 m	SF-36 PF Chair stand test (5 repetitions)	78% 24%
Studies of populations or subpopulations with CKD							
Shlipak *et al.*, 2004[120]	Community-dwelling elderly with Scr ≥1.3 in women or ≥1.5 in men	Yes	CES-D	MMLTA	>15 ft	Yes	15%
Wilhelm-Leen, *et al.*[12]	Adults eGFR <45 ml/min/1.73 m^2 from NHANES III	BMI ≤18.5 kg/m^2	Self-report of difficulty walking short distances	Self-report of "less active" than peers	>8 ft	Self-report	20.9%
Roshanravan *et al.*, 2012[121]	Stages 1-4 CKD (mean eGFR 51 ml/min/1.73m^2)	Yes	SF-36 Vitality	Self-reported exercise <1x/week	Yes	Yes	14%
Dalrymple *et al.*, 2013[122]	CHS participants with eGFR <45 ml/min/1.73 m^2	Yes	CES-D	MMLTA	>15 ft	Yes	24%
Reese *et al.*, 2013[123]	CRIC participants	Yes, >5% in 1 yr	CES-D	MESA questionnaire	>15 ft	Yes	7%

BMI, body mass index; CES-D, Center for Epidemiologic Study Depression Scale; CHS, Cardiovascular Health Study; CKD, chronic kidney disease; CRIC, Chronic Renal Insufficiency Cohort; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis; MESA, Multi-ethnic Study of Atherosclerosis; MMLTA, Modified Minnesota Leisure Time Activity questionnaire; NHANES, National Health and Nutrition Examination Survey; PF, physical functioning; Scr, serum creatinine; SF-36, Medical Outcomes Study Short Form 36-Item Survey.

comorbidities can be thought of as the aggregation of clinically manifest diseases present in an individual, whereas frailty is an aggregate of subclinical losses of reserve across multiple physiological systems.[108] It has been suggested that these fundamental differences in the conceptualization of frailty are the hurdles that have kept experts from coming to an agreement on a single definition of frailty.[113]

Although other frailty constructs have been applied in the CKD population,[114] the frailty phenotype has been the dominant approach for the nephrology community (see the following), perhaps because the population is defined on the basis of a disease and because of the long-standing understanding that muscle atrophy and physical dysfunction are common and important.[2–4] The most widely accepted and validated frailty phenotype was proposed by Fried *et al.*[78] and contains 5 equally weighted criteria: weight loss, exhaustion, low physical activity, weak grip strength, and slow gait speed. Patients meeting any 3 of these 5 criteria are considered frail. Although the cutoff points in the original Fried frailty phenotype were determined arbitrarily as the lowest sex-specific quintiles (adjusted for body mass index in the case of grip strength and height in the case of gait speed), it is recommended that standard, normative criteria are used rather than population-specific cutoff points,[70] and the absolute Fried cut points have been adopted as normative cut points. The use of normative cut points is particularly important when applying these definitions to populations whose characteristics differ markedly from those in which they were developed, such as patients with chronic diseases such as CKD and individuals younger than 65 years of age.

Table 5 summarizes available literature exploring the prevalence of frailty in the CKD population.[12,97,115–123] Several studies have made modifications to the frailty phenotype in order to study existing cohorts in which the measures of some or all criteria differ from those originally proposed. For instance, self-reported physical function[115,116] or different physical performance tests[119] were substituted for gait speed and/or grip strength criteria; low body mass index was substituted for weight loss[119]; or different instruments were used to estimate physical activity or assess exhaustion.[115,116,119] Such a lack of uniformity limits comparison between studies and leads to a wide range of the reported prevalence of frailty.[97,116,117,119] Nevertheless, all studies found a prevalence that is substantially higher than

what has been observed among community-dwelling elders, even when patients younger than 65 years of age have been included. Two relatively recent studies applied the Fried frailty phenotype without modification to dialysis cohorts and reported a similar prevalence of frailty (30% and 41.8%).[97,117] However, other studies have reported a higher prevalence, ranging from 53% to 78% among patients with ESRD.[97,116,117,119] The prevalence appears to be generally lower among individuals with CKD than among those with ESRD, and there appears to be a graded association, with a higher prevalence of frailty among individuals with a lower estimated glomerular filtration rate.[122] Attention has focused on the difference between self-reported physical function and physical performance measures as an explanation for the differences in the prevalence of frailty across studies, with a higher prevalence of frailty observed when self-reported function is used.[118,119] However, other modifications may also have an important impact on the prevalence. In particular, the percentage of underweight patients (based on low body mass index) is considerably lower than the percentage that reports weight loss. In addition, the percentage that is below the 20th percentile for physical activity also varies considerably based on the instrument used, even when norms from healthy younger individuals are applied. Thus, although it is clear that the prevalence of frailty is high among patients with CKD and ESRD, the widely varying definitions used and the paucity of outcome studies to date limit our ability to determine the most useful way of defining frailty. A recent study showed that physical frailty assessed using patients' self-reported physical functioning and directly measured physical performance both identified patients at higher risk of mortality, although the physical performance–based measure performed slightly better.[124] To conclude, although more research is needed, we believe that available evidence suggests that measures of physical frailty may be preferred in the dialysis population, particularly if the goal is prediction of the risk of adverse outcomes, as the deficit accumulation approach includes comorbidities and other variables that would often be included individually in risk-prediction models.

Constructs with clinical applicability or theoretical artifacts? Application of the geriatric syndromes of frailty and sarcopenia among patients with CKD has greatly contributed to increase awareness and attention to the problem among nephrologists. However, there is no consensus regarding operational criteria for diagnoses, which hinders their applicability at the bedside. As such, they still remain theoretical constructs. At present, no validation study has been performed in CKD patients, and it is premature to recommend which consensus definition best fits the assessment of sarcopenia or frailty in this patient population. As previously mentioned, we believe that it is important that cut points for frailty/sarcopenia criteria be based on normative data rather than arbitrary cut points within the study population. Although we recognize that substitution of individual components may be necessary, we believe that caution should be exercised when comparing the prevalence of frailty or sarcopenia across populations if components and cut points are not identical. Furthermore, we suggest that researchers should avoid characterizing individual components of the phenotype (e.g., slow gait speed as frailty or low muscle mass alone as sarcopenia) because this practice goes against the fundamental principle that these are multidimensional syndromes and can lead to considerable confusion in the literature.

This review discussed how estimating muscle loss and dysfunction require rigorous considerations for the pathophysiological peculiarities of CKD. It has shown how available estimates and associated outcomes of sarcopenia and frailty in CKD studies vary dramatically as a consequence of differences in definitions and criteria. The derivation of consensus definitions of sarcopenia and physical frailty as well as identification of appropriate diagnostic cutoffs should be an urgent priority. As a next step, prospective studies should determine whether these cutoffs identify groups of (older) adults with mobility problems who are likely to benefit from interventions designed to maintain or improve mobility. Such improvement may have a positive impact on life expectancy, but also equally important in this multimorbid geriatric population, on quality of life. Many studies suggest that interventions are beneficial in addressing 1 or more components of sarcopenia or frailty in CKD patients, but the quality of the evidence is low for most of them.

DISCLOSURE

BL is employed by Baxter Healthcare Inc. All other authors declared no competing interests.

ACKNOWLEDGMENTS

JJC acknowledges support from the Stockholm County Council, the Swedish Heart and Lung Foundation, and the Westman Foundation. KLJ receives support from the National Institute for Diabetes and Digestive and Kidney Diseases of the National Institutes of Health. The Karolinska Institutet Diabetes Centre, Swedish Medical Research Council, and Westmans Foundation support the research of PS. LC receives support from the National Council of Technological and Scientific Development (CNPq) and from the Oswaldo Ramos Foundation. Baxter Novum is the result of a grant from Baxter Healthcare to the Karolinska Institutet.

SUPPLEMENTARY MATERIAL

Table S1. Procedures and considerations for assessing muscle mass in CKD patients

Table S2. Procedures and considerations for assessing muscle function in CKD patients

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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