Techniques for the diagnosis of sarcopenia

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Summary

Sarcopenia is an age-related process of skeletal muscle loss associated with declining physical performance, highly prevalent among older subjects, with a negative prognostic effect on falls, disability and mortality risk. Modern approaches to sarcopenia case finding and diagnosis are based on physical performance measures, while assessment of muscle mass represents the second diagnostic step. Muscle mass can be quantified at different levels of body composition, with a complexity increasing from atomic detection to anatomic measure. In the choice of measuring method, different factors have to be taken into account, including validity, simplicity, cost and specific purpose (clinical versus research). Some methods, such as MRI and CT, have high validity but are complex and costly. Bioelectrical impedance analysis is inexpensive and easy to perform in most settings, being the preferred method for clinical practice. Dual energy X-ray absorptiometry has intermediate cost and complexity with good reproducibility, and is more reliable for research setting. Other methods, such as administration of tritium (D3)-marked creatine and measurement of urinary D3-creatinine, are still in a preclinical phase of development. For all methods the issue of normative data does exist and needs to be solved, in order to reliably identify homogeneous populations with sarcopenia, to be targeted in clinical practice and intervention studies.

KEY WORDS: sarcopenia; skeletal muscle; physical performance; elderly; diagnostic methods.

Sarcopenia: epidemiological and clinical relevance, from research to clinic

Sarcopenia, defined as an age-related progressive and generalized loss of skeletal muscle mass and strength, has been associated with impaired mobility, functional decline and disability, falls, and mortality in elderly people (1). Age-related muscle loss is the result of a progressive atrophy and loss of type II muscle fibers, motor neurons and muscle lipid infiltration. Muscle mass decreases at a rate of 3-5% per decade after the age of 30 year and its rate of decline accelerates further after the age of 60 (2).

The prevalence of sarcopenia increases with aging and differs across different settings and clinical conditions. In a milestone study, where estimates of skeletal muscle mass were obtained in a large sample of individuals of various ages living in the community, prevalence was 15-24% in 60-70-year-olds and over 50% in subjects aged 80+ (3). Figures close to 70% have been reported in nursing home residents (4). Undernutrition and reduced physical activity can accelerate age-related muscle loss, and the frequency and severity of sarcopenia increase sharply in the presence of several co-morbidities, including osteoporosis, type 2 diabetes mellitus and other endocrine diseases, neurodegenerative disorders, advanced organ failure, and chronic inflammatory states, resulting in the so called "secondary sarcopenia" (5). Although the specific meaning of this term in respect to other wasting syndromes may be questioned, its popularity in recent literature appears to legitimate its use. Due to the high risk of serious negative health outcomes, including disability and death, sarcopenia is considered a major contributor to healthcare costs and even a small reduction of its prevalence might be expected to produce relevant savings in health-care resources (6).

For these reasons, in the last decade an increasing number of phase II clinical trials have tested the ability of a variety of interventions, including physical exercise, dietary supplementation, and pharmacological (mainly hormonal) treatments to reduce sarcopenia, with promising but still limited evidence of efficacy (7). One of the major issues that must be faced to obtain stronger evidence, to be ultimately translated into clinical practice, is the availability of a consensus on sarcopenia definition and case finding, as well as of reliable, valid, non-injurious, and affordable measures of muscle mass for the diagnosis of sarcopenia.

Approach to sarcopenia definition and case-finding

The European Working Group on Sarcopenia in Older People (EWGSOP) developed a clinical definition and consensus criteria for the diagnosis of sarcopenia, relying on specific and easily identifiable parameters (5). The variables to be measured to this purpose are muscle mass, strength, and physical performance. The EWGSOP recommends defining sarcopenia as the presence of both low muscle mass and low muscle function

(strength or performance) and using gait speed and assessment of grip strength with handheld dynamometry for case-finding: if gait speed and/or grip strength are reduced below 0.8 m/sec and the age- and gender specific cut-off, respectively, the diagnosis needs confirmation by muscle mass measurement with dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance, computerized tomography, magnetic resonance imaging or, as second choice, anthropometry, depending on local availability and purpose (research or clinical) of the diagnosis. The EWGSOP also identified a grading for sarcopenia in pre-sarcopenia (decreased muscle mass with normal strength and physical performance), sarcopenia (decreased muscle mass with decreased strength or performance), severe sarcopenia (decreased muscle mass, strength and performance).
According to the US guidelines, issued by the International Working Group on Sarcopenia (IWGS) (8), the diagnosis of sarcopenia should be suspected in older subjects who are non-ambulatory or who cannot rise from a chair unassisted or, if ambulatory, show a low gait speed (<1.0 m/sec). The measurement indicated for instrumental confirmation of low muscle mass is DEXA. The lack of the criterion of reduced muscle strength is probably the cause of the lower prevalence of sarcopenia diagnosed according to IWGS criteria in comparison to EWGSOP (9).
However, it should be noted that, unlikely the classic diagnostic approach (10), in both sets of criteria the identification of low muscle mass is not *per se* sufficient for a diagnosis of sarcopenia. On the other hand, at least over the age of 80 years, the prevalence of sarcopenia diagnosed according to the EWGSOP algorithm is similar to that obtained with the sole muscle mass decline.

Techniques supporting the diagnosis of sarcopenia

Levels in the assessment of body composition

Changes in body composition occur as part of the normal ageing process and include a relative increase in fat mass (FM) in relation to fat-free mass (FFM) (11). Methods for analysis of body composition aim at dividing body mass into components on the basis of differing physical properties. Muscle mass is a part of FFM and can be quantified at five-level model of body composition, with a complexity increasing from atomic to anatomic level (12).
At an *atomic level*, the main components of skeletal muscle are oxygen, hydrogen, carbon, nitrogen, and ions such as potassium and phosphorus. A large percentage of body potassium (60% on average) is distributed in skeletal muscle, and whole-body potassium is often used as a measure of muscle mass, which is only suitable for estimates of whole-body muscle mass (13, 14).
Measures of skeletal mass at a *molecular level* are provided by DEXA, which allows quantification of three body components (bone mineral, fat, and bone-mineral-fat-free mass), based upon differential tissue attenuation of x-ray photons. DEXA allows also separation, for each of these three components, of whole-body scans into regional measures of upper and lower extremities (12, 13).
At a *cellular level*, estimates of total body muscle can be obtained from endogenous metabolites of skeletal muscle, such as creatinine, 3-methylhistidine, urinary creatinine excretion, and D3-creatine. Creatinine is produced at a relatively constant daily rate from non-enzymatic changes in creatine (15), whereas 3-methylhistidine derives from the breakdown of actomyosin (16). Creatinine concentration in 24-h urine has been proposed as an indirect measure of body skeletal muscle mass, but many factors, such as diet, exercise, infection, trauma, renal insufficiency, and also age-related decrease in creatine production, limit its accuracy to this purpose. A new method has been recently proposed, so far only in pre-clinical studies, based on dilution of orally administered tritium-marked creatine (D3-creatine) and measurement of urinary D3-creatinine. Unlike 24-h creatinine excretion, this method requires collection of a single urine sample under isotopic steady state of creatinine enrichment (17). Estimation of total muscle mass with this method assumes that D3-creatine is found only in skeletal muscle and that its turnover is relatively constant, assumptions that hold true only partially. Dietetic factors may modify the non-muscular sources of these markers, whereas changes in renal handling of these metabolites change their turnover rate. These factors limit the general use of endogenous metabolites in the assessment of muscle mass.
Accurate measures of both *anatomic and fat-free skeletal muscle* are obtained with two imaging techniques, such as computerized tomography (CT) (18) and magnetic resonance imaging (MRI) (19). Typically, these methods provide regional estimates of skeletal muscle by means of cross-sectional images, which allow also to detect muscle infiltration from adipose tissue and to quantify fat-free skeletal muscle. Total muscle area and fat-free skeletal muscle area, calculated from cross-sectional images, can be integrated from head to toe, to calculate total muscle and fat-free skeletal muscle volumes: as for other organ volumes derived from CT and MRI, these measures are considered highly reliable. Fat-free skeletal muscle normally declines with ageing, but its decline is accelerated in the presence of poor nutritional status and, in particular, diminished body protein reserves, as observed in diseases leading to overt malnutrition and cachexia.
At a *whole-body level*, bioimpedance analysis (BIA) is a simple, low cost technique to quantify regional muscle mass which was shown to be particularly useful in epidemiological research (20). Furthermore, regional and total body morphological estimates of skeletal muscle can be obtained, based on conventional, time-honored anthropometric measurements or, more modernly, on ultrasounds (21, 22).

Specific methods

The characteristics of the methods for the assessment of muscle mass and the diagnosis of sarcopenia are compared in the following Table 1.

Table 1 - Characteristics of techniques for the diagnosis of sarcopenia.

	Anthropometry	BIA	DEXA	CT/MRI	Ultrasound
Simplicity	+++	++	+	-	+
Low cost	+++	++	+	-	+
Validity	-	+	++	+++	?
Clinical application	+	+	+	-	-
Research application	-	+	++	+++	?

Antropomethry

Anthropometry is a simple technique, easily applied in clinical practice or in large population-based surveys. Skinfold thickness measurement allows estimation of body fat, and

limb circumferences are assumed to reflect limb muscle and protein nutritional state. Yet, significant inter-observer variability may limit sensitivity for detecting changes. Moreover, skinfold anthropometry measures only subcutaneous fat and not visceral fat (21), which is an independent risk factor for several conditions, such as diabetes, cardiovascular disease, and cancer (23-25).

Bioelectrical impedance analysis (BIA)
BIA is a simple and portable technique, highly acceptable to patients and easy to be performed at bedside. BIA involves passage of a small AC electrical current through the body. As current is conducted by body water, impedance is inversely related to total body water, thus allowing calculation of total muscle mass, which is the largest water-rich tissue in the body (26). This method is very simple and of rapid application, does not require skilled staff, is relatively inexpensive, and does not expose patients to radiation. However, it has a major drawback, since muscle mass measurements can be distorted by hydration status and presence of edema. To avoid possible variability of results, it is essential that BIA measurements be performed in a careful, standardized fashion, ideally at the same time of the day for sequential measurements.

Dual energy X-ray absorptiometry (DEXA)
DEXA is a clinically applicable and well-tolerated technique. It measures the relative attenuation of two different energy X rays by the body. Measurement time is short and radiation exposure minimal. It derives a three-component model of body composition, comprising fat, bone mineral, and lean tissue. It also allows regional analysis, particularly limb lean tissue and body fat distribution, thus allowing the measure of both total muscle mass and appendicular muscle mass, the latter being calculated as the sum of muscle mass of all four limbs. Recent data suggest that the calculation of percentage skeletal muscle mass (total muscle mass/weight x100) provides a higher estimate of sarcopenia prevalence and is more associated with obesity status in comparison with appendicular muscle mass (9). Though less costly than CT and MRI, DEXA is relatively expensive, requires patients to travel to a center and must be applied by specialized personnel: therefore, so far it cannot to be considered a routine test in clinical practice, whereas it is highly appropriate for a research setting.
Cut-off points available for diagnosis of sarcopenia depend upon the measurement technique chosen and on the availability of reference studies. EWGSOP recommends use of normative (healthy young adult) rather than other predictive reference populations, with cut-off points at two standard deviations below the mean reference value (5).
Example of cut-off point using DEXA as measurement method:

- Skeletal muscle mass index (SMI), defined as appendicular skeletal muscle/height^2 (kg/m^2). A SMI two standard deviations below the mean of young adults provides the gender-specific cut-off point for sarcopenia (3);
- Appendicular lean mass divided by height squared (aLM/ht^2) and appendicular lean mass adjusted for height and body fat mass. The gender specific 20th percentile was arbitrarily chosen as the cutoff point for each method (27).

Example of cut-off point using BIA as measurement method:

- Skeletal muscle mass (SM) equation: SM/height^2. A SM equation two standard deviation below mean of young adults (28).

Computer tomography (CT) / Magnetic resonance imaging (MRI)
CT and MRI scanning provide anatomical details and, in particular, can be used to assess skeletal muscle volume. Moreover, they are the only techniques that can directly assess abdominal visceral fat content (11). They allow calculation of segmental and total muscle mass, and assessment of fat infiltration in the muscle, which impacts on muscle quality and force development. These methods are very expensive, are not easily accessible, and are not routinely indicated to study muscle mass, but have been used mainly for research purposes. They require a highly specialized staff, specific software, and a relatively large amount of time. A further limitation of CT includes radiation exposure.

Ultrasound
Ultrasound is simple, easily applied in clinical practice or large population surveys. It is widely available equipment and useful for bed-ridden or mobility impaired individuals but does not measure muscle mass and is operator-dependent. Ultrasound evaluates muscle mass and also its quality, as enhanced echo intensity represents changes caused by increased intramuscular fibrous and adipose tissue (29). Recently, some research groups have used computer-aided gray scale analysis to evaluate the quality of skeletal muscle. There is limited experience in sarcopenia studies.

Conclusions and future prospectives

Techniques for the diagnosis of muscle mass are a cornerstone for the diagnosis of sarcopenia and allow identification of sarcopenic elderly subjects among older subjects with poor physical performance, which not necessarily depends on abnormal muscle mass or strength (9). Several techniques are available for measurement of muscle mass: the ideal technique should combine reliability and validity, affordable cost, total body and regional assessments, and virtual absence of risks for both the participant and the operator. Anthropometry, although easy to assess and useful in clinical practice, has a very limited accuracy and can be biased by nutritional status and comorbidity. Conversely, CT and MRI are precise and measure direct physical property of muscle but they are hospital-based, expensive, time-consuming in acquisition processing and therefore only adequate for research aims. A more realistic clinical method for measurement of muscle mass is DEXA, but in many countries this technique is only available clinically for measurement of bone density. BIA is an inexpensive, portable body composition technique that, if properly applied, can provide reliable estimates of skeletal muscle mass. For both BIA and DEXA, the issue of normative data does exist and is crucial for the definition of sarcopenia in individual cases.
In a recent systematic literature review, validity, reliability, and feasibility of different diagnostic tools for the screening and diagnosis of sarcopenia in community-dwelling older people were assessed (30). To measure muscle mass, strength and physical performance in general practice or home settings, BIA, handheld dynamometry, and gait speed over a short distance are probably the optimal choice, since these approaches can be easily applied in the community and require limited, not expensive, and easy to use and transport equipment. However, as the validity of BIA is not optimal, DEXA measurement, if available, is preferable for

measurement of muscle mass in subjects whose muscle strength and/or physical performance are below normal.

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