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CLINICAL EVALUATION, BIOLOGICAL MARKERS AND OTHER EVALUATION TOOLS

SARCOPENIA: CLINICAL EVALUATION, BIOLOGICAL MARKERS AND OTHER EVALUATION TOOLS

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Abstract: Sarcopenia is characterized by a lower skeletal muscle quantity, higher fat accumulation in the muscle, lower muscle strength, and lower physical performance. The most commonly used, low cost and accessible methods to assess skeletal muscle mass include dual energy X-ray absorptiometry (DEXA), anthropometry and bioelectrical impedance analysis (BIA). Magnetic resonance imaging (MRI), computerized tomography (CT) and creatinine excretion are the most specific golden standards for assessing muscle mass or cross sectional muscle area. Other available measures include peripheral quantitative computerized tomography (pQCT), ultrasound and neutron activation. Skeletal muscle strength is another important component for the assessment of sarcopenia and muscle quality. Several methods are available for the measurement of muscle strength which include simple dynamometers to measure isometric strength and the most complex isokinetic strength measures of power and torque. Standardized physical performance measures complement the measures of muscle mass for the assessment of sarcopenia. A clinical definition of sarcopenia ought to use methods of assessment that are valid, reliable, specific to skeletal muscle, predictive of future health events, non-invasive, practical, low cost and widely accessible.

Sarcopenia is characterized by a lower skeletal muscle quantity, higher fat accumulation in the muscle, lower muscle strength, lower physical performance, and changes in circulating biological markers. Because sarcopenia has long-reaching definitions, there is a lack of standardized methodologies to assess sarcopenia resulting in inconsistencies in the literature, to the paucity of clinical trials of interventions which primarily target sarcopenia, and to the lack of therapeutic indications for sarcopenia that are accepted by the regulatory agencies in the US and Europe.

Methods for measuring skeletal muscle mass and imaging

The most commonly used, low cost and accessible methods to assess skeletal muscle mass include dual energy X-ray absorptiometry (DEXA), anthropometry and bioelectrical impedance analysis (BIA). Magnetic resonance imaging (MRI), computerized tomography (CT) and creatinine excretion are the most specific golden standards for assessing muscle mass or cross sectional muscle area. Other available measures include peripheral quantitative computerized tomography (pQCT), ultrasound and neutron activation. Table 1 summarizes the advantages and limitations of each of these measurement methods.

The DEXA is one of the most commonly used, widely available and low cost technologies for measuring body composition and muscle mass estimation. However, the accuracy of DEXA for assessing muscle mass in people of different age groups and in some pathological conditions may vary. For example, DEXA may overestimate muscle mass (1) because it does not differentiate between water and bone-free lean tissue, and therefore may lead to an overestimate on muscle mass in older persons who have and extracellular fluid accumulation (2). Despite this limitation, DEXA provides valid estimates of appendicular skeletal muscle mass, (3, 4) and skeletal muscle measures with DEXA are associated with prevalent and incident physical disability (5, 6). Anthropometric measures and BIA are inexpensive and easy to assess, but have limited accuracy and validity (7-9).

MRI and CT are considered the golden standard and the most accurate imaging methods to assess muscle mass, muscle cross sectional area and muscle quality as determined by muscle density and intramuscular fat infiltration. However, the high cost and the operational complexity limit their use in large clinical trials and clinical practice, although the new technology of low-field extremity MRI is allowing less expensive alternatives to this image modality. MRI and CT also assess adipose tissue, which is directly associated with intramuscular fat infiltrates, which in turn may impair muscle function and strength (10). The assessment of muscle density using MRI or CT provides a reliable and valid measure of the fatty degeneration of muscle tissue (11). A lower muscle density indicates a higher intramuscular fat content which may be detrimental for muscle function.

Urinary creatinine excretion is a specific indicator of total body skeletal muscle mass because creatine, which is the precursor of creatinine, originates almost exclusively from skeletal muscle. However, creatinine excretion varies during the day, which may affect the excretion estimate. In addition, this method requires to maintain the subject on a meat-free diet for a few days and a prolonged urine collection is needed (2).

The pQCT uses a portable CT scanner to measure cross-sectional area and density of bone, muscle and adipose tissue of the extremities (10). B-mode ultrasonography is an alternative

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Table 1
Methods to assess skeletal muscle mass and muscle imaging

	Method	Advantages	Limitations
Golden Standard	Magnetic resonance imaging (MRI)	• High resolution • Cross-sectional measurement of lean and fat mass areas in a specific part of the body • Assessment of muscle quality	• High cost • Time-consuming image analysis • High space requirements • Technically difficult to perform
	Computerized tomography (CT)	• Cross-sectional measurement of lean and fat mass areas in a specific part of the body • Assessment of muscle quality	• Exposure to radiations • Time-consuming image analysis • High space requirements • Technically difficult to perform
	Creatinine excretion	• Measure directly related to total body muscle mass	• Time-consuming • Diet restrictions the days before the urine collection • Results not immediately available • Complicated procedure • Daily variation of creatinine excretion
Widely Used Measures	Dual energy X-ray absorptiometry (DEXA)	• Low cost • Widely available • Sensitive and accurate method • Estimates of lean, fat, and bone tissues in the entire body or in specific parts of it • Does not require highly trained personnel	• No information about muscle quality • Space requirements • Exposure to low dose radiation • Possible biased results due to limited differentiation between water and bone-free lean tissue
	Bioelectrical impedance analysis (BIA)	• Low cost • Minimal maintenance • Portable • Results immediately available • Does not require highly trained personnel	• Results based on body resistance • No measure of muscle quality • Affected by hydration status • Lower accuracy compared to other methods (i.e., MRI, CT, DEXA)
	Anthropometry	• Low cost • Easy to assess	• Very limited accuracy • No information about muscle quality • Nutritional status and comorbidities can easily bias the results
Other Measures	Peripheral quantitative computerized tomography (pQCT)	• Cross-sectional measurement of lean and fat mass areas in a specific part of the body • Assessment of muscle quality • Portable • Does not require highly trained personnel	• Images of a body part which may not be applicable to different body districts • Limited accuracy compared to MRI or CT • Originally designed to evaluate bone parameters, it has lower application on muscle • Exposure to low dose radiation
	Ultrasound	• Low cost • Can assess specific muscles • Valid and reliable	• Needs trained personnel • Difficulties assessing muscle quality • Does not assess total body skeletal muscle mass
	Neutron activation	• Estimate of overall skeletal muscle mass	• High cost • Limited validity • Exposure to radiations • Technically difficult to perform • No information about muscle quality • No information about specific body districts (e.g., limbs)

low cost methodology for assessing the muscle size of individual muscles, but this technique requires highly trained personnel (12). Another method to estimate the whole body muscle mass is the in vivo neutron activation analysis combined with the 40K whole body counting (13). This method is based on the difference in the potassium-to-nitrogen ratio between the skeletal muscle and the non-skeletal muscle tissues. If total body potassium (from the 40K whole body counting) and total body nitrogen (from prompt-γ neutron activation analysis) are known, these ratios can be derived and

applied to predict the skeletal muscle mass. However, this method is expensive and needs to be validated compared to CT (1).

Muscle strength

Skeletal muscle strength is another important component for the assessment of sarcopenia and muscle quality (8, 14, 15). Several methods are available for the measurement of muscle strength which include simple dynamometers to measure isometric strength and the most complex isokinetic strength measures of power and torque. In well-functioning older men and women enrolled in the Health Aging and Body Composition (Health ABC) study, the mid-thigh muscle area is associated with a higher risk of mobility disability, but such an association is not independent of lower knee extension strength and skeletal muscle density (16). In the same cohort, low muscle mass does not explain the strong relationship between strength and mortality, suggesting that muscle strength may be more important than muscle mass in estimating the risk of events (17). Hand grip and quadriceps strength have similar predictive value for mortality (17-19). In the InChianti cohort isometric hand grip strength is strongly correlated with lower extremity muscle power, knee extension torque, and calf cross-sectional muscle area, (20) suggesting that sarcopenia is a systemic condition rather than being limited to single muscles or body compartments, such as lower extremities. Because muscle strength measures of various body compartments are highly correlated, these data also suggest that grip strength measured with a hand held dynamometer may be a good surrogate measure of other more complex measures of skeletal muscle strength in the lower extremities.

Physical performance

Standardized physical performance measures complement the measures of muscle mass for the assessment of sarcopeni (21). Physical performance measures are correlated with body composition and skeletal muscle parameters, (22, 23) and predict relevant health-related outcomes, such as mortality, morbidity, institutionalization and disability (24-27). The Short Physical Performance Battery based on gait speed, chair stands and balance tests, (25) the 400 m walk test (24) and the 6 min walk (28) test are among the most widely used and validated measures. Other useful physical performance measures include the stair climb test, (28) the lift and carry task, (28) the car task,28 the Performance Activities of Daily Living (PADL), (29) the task modification (MOD) scale for assessing compensatory strategies for completing daily tasks, (30) the musculoskeletal impairment index, (31) and the multidimensional physical performance test (32).

Biological markers

The adipose tissue produces several pro-inflammatory cytokines, such as tumor necrosis factor (TNF-alpha), interleukin (IL-6), and IL-1, all of which are associated with aging, obesity and sarcopenia (33-35). The pro-inflammatory cytokines are involved with cachexia, anorexia of aging, (36) and are detrimental to the skeletal muscle (37). Several studies have shown independent associations of pro-inflammatory cytokines with lower muscle strength, lower physical performance, and higher risk of disability in older persons (35, 38-41).

Oxidative damage biomarkers have also relevant associations with sarcopenia. Oxidized low-density lipoprotein (oxLDL), a marker of lipoprotein peroxidation, is an independent predictor of incident mobility limitation (42). Protein carbonyls, markers of oxidative damage, are associated with lower grip strength in older adults (43, 44). On the other hand, antioxidants, such as intake of carotenoids and vitamin C, and plasma levels of alpha- and gamma-tocopherol are inversely associated with measures of sarcopenia (45-47).

Several other biomarkers have shown significant associations with measures of sarcopenia. Anemia is associated with lower muscle strength and physical performance in older persons.48 Low serum albumin is associated with poor grip strength in older men and women (49). Low plasma selenium concentration is associated with reduced muscle strength (50). Higher circulating levels of uric acid are prospectively associated with higher handgrip and knee extension torque strength in older persons (51). Higher magnesium concentrations are significantly associated with indexes of muscle performance, including grip strength, lower-leg muscle power, knee extension torque, and ankle extension strength (52). Vitamin D plays an important role in the skeletal muscle metabolism, and persons with low serum 25-hydroxyvitamin D level have poor muscle mass measured with DEXA and diminished lower grip strength (53).

In summary, several studies have shown that pro-inflammatory cytokines, markers of oxidative damage and a broad range of other biomarkers have strong and independent associations with several measures of sarcopenia. However, such markers are also associated with a wide range of other diseases and conditions. Because these markers have little specificity for skeletal muscle and strength loss, they may have limited utility for the assessment of sarcopenia. The measurement of circulating ubiquitin proteasome (54-56) and plasma caspase (57) may be more specific markers of muscle protein breakdown, however, to our knowledge these circulating markers have not been studied in association with age-related sarcopenia.

Conclusions

Currently there is no standardized and established quantitative definition of sarcopenia based on skeletal muscle

mass, strength and/or physical performance, which is used in clinical practice or as an accepted therapeutic indication. Once the standardized methodology for the clinical assessment of sarcopenia is established, normal and abnormal values of the measurement need to be determined. Normal values of biological or physiological measures can be based on cut-points from standard deviations of a reference population or on quantiles distribution in a population. A clinically more relevant approach to define sarcopenia should be based on cut-points of muscle mass or muscle quality levels determined by expert consensus according to the risk for future health-related events, such as mortality, (1)7 morbidity or incidence of physical disablity (5).

A clinical definition of sarcopenia ought to use methods of assessment that are valid, reliable, specific to skeletal muscle, predictive of future health events, non-invasive, practical, low cost and widely accessible. In this respect, sarcopenia expressed as muscle quality assessed by means of a combined measure of muscle mass with DEXA and measure of grip strength with a hand-held dynamometer seems a very promising approach, as both these methodologies share most of the abovementioned characteristics.

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