JGG 2019;67:39-45

Review

Assessment of sarcopenia: from clinical practice to research

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Sarcopenia is the loss of muscle mass and function that occurs in aging. Multiple factors are involved in the pathogenesis of sarcopenia, such as mitochondrial dysfunction, protein synthesis alteration, and poor exercise. Both European (EWGSOP) and American (FNIH) diagnostic criteria are currently available. Sarcopenia could represent the biological substrate of physical frailty. In every older patient presenting compatible clinical features, the presence of sarcopenia should be screened with validated questionnaires such as SARC-F. The DXA evaluation is considered the current gold standard technique both in research and in clinical practice for the assessment of muscle mass. In clinical practice, the measurement of muscle strength by handgrip strength is recommended, while physical performance should be primarily assessed by SPPB test. In this review, we report current strategies to counteract sarcopenia, which consist of adequate protein intake and physical exercise.

Key words: Muscle strength, Muscle mass, Physical performance

INTRODUCTION

The aging process is characterized by alterations of various organs and systems that affect the total homeostatic capacity of the human body. As described for the first time by Irwin Rosenberg in 1989 in Albuquerque (New Mexico, USA), "from a structural and functional point of view, no decline is more dramatic than the one that muscle mass undergoes during the various decades of life", and proposed the term "sarcopenia" to define the loss of muscle mass and function that occurs in aging [1]. The muscle mass and functional decline described by Rosenberg 30 years ago has been clearly documented with large observational studies. Recent findings show that different patterns of muscle mass and physical decline with age are observed for different ages [2]. In general, muscle mass slightly decreased with advancing age. Interestingly, for muscle strength (as measured by hand grip test) and physical performance (as measured by chair stand test) there is stability in the first decades of adulthood, and decrements in the middle years (45+) and late adulthood. In particular, individuals older than 75 years lose approximately 60% of their muscle strength and 30% of their physical function. The linear pattern of age-decline is surprisingly similar in men and women across the entire course of life, and is independent by different race [2].

Biological substrates of sarcopenia

Multiple factors are involved in the pathogenesis of sarcopenia [1] (Fig. 1): (a) constitutional factors, such as male sex, low birth weight, genetic susceptibility; (b) modifications related to the aging process itself. The latter factors can be schematized as follows:

- *muscle cell alterations*: including decreased type II cells – involved in rapid muscle power contraction and with a predominantly glycolytic metabolism -a size reduction of residual muscle cells, loss and disorganization of myofilaments, accumulation of lipofuscin pigments;
- age-dependent decline level of *hormones:* androgens (testosterone and DHEA), estrogen, growth hormone (GH), and decline of insulin sensitivity;

Received: January 25, 2019 - Accepted: March 19, 2019

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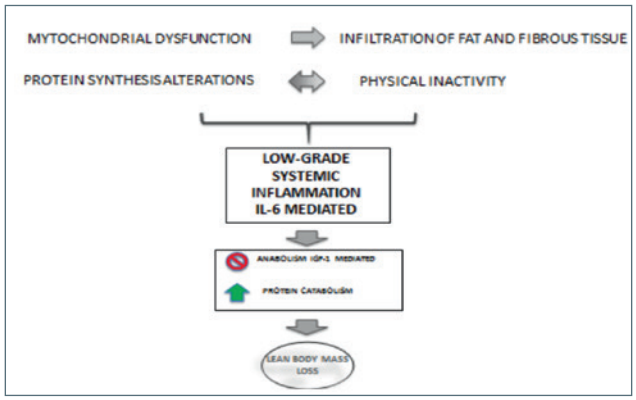

Figure 1. Biological substrates of sarcopenia.

- degeneration of spinal *moto-neurons*, probably due to a "retrograde effect": the muscle, through largely unknown mechanisms, sends negative "remodeling" information to the motor terminal;
- *Mitochondrial dysfunction*: in the muscles of sarcopenic subjects, a significant deletion of the mitochondrial genome has been found caused by errors in DNA replication. The shorter genome replicates faster and induces the formation of malfunctioning or completely inactive mitochondria [3]. This causes a cell energy deficit and the loss of the fiber itself, which is replaced by infiltration of connective and fatty tissue;
- increased *protein turnover*: since an adequate availability of nutrients, there is an imbalance between the ability of the fibers to complete a correct protein synthesis and the rate of degradation [4];
- *poor exercise and/or sedentary lifestyle*: in this connection, current evidence clearly shows that physical exercise may exert a positive impact on muscular physiology through systemic and local effects [7].

Finally, a long list of chronic diseases (such as cognitive decline, mood disorders, diabetes mellitus, heart failure, liver failure, renal failure, respiratory failure, chronic pain, obesity) is related to sarcopenia, being the systemic inflammation a common pathologic pathway.

Functional aspects

Among the diagnostic criteria of sarcopenia currently available, two are the most used: those developed in 2010 during the European consensus on sarcopenia (EWGSOP) [8], and the more recent ones published in 2014 by the group "FNIH Sarcopenia Project" [9]. Both consensuses underline the importance of functional criteria in addition to the structural ones. The first criteria are based on the detection of decreased muscle mass associated with strength or physical performance decline. The reference values for the diagnosis of sarcopenia developed by the EWGSOP are [10]:

- muscle mass: SMI (skeletal mass index) < 8.87 kg/m^2 for male; < 6.42 kg/m^2 for female;
- pretension force < 30 kg for male; < 20 kg for female;
- physical performance < 0.8 m/s at the 4-meter walking test.

In 2014, as part of the "FNIH Sarcopenia Project" [9], analyzing data produced by 9 studies conducted on populations belonging to the community (for a total of 26,625 participants), a further conceptual step was carried out, with the aim of identifying clinically relevant thresholds of muscle mass and function. As a conceptual assumption, there was a clinical paradigm according to which, starting from a patient with poor physical performance, you can identify in the differential diagnosis "weakness" as the causative agent of this and, subsequently, a reduction of the muscle mass at the base of the weakness itself.

The identification of subjects in whom reduced muscle mass is the main cause of weakness is crucial because they are able to gain significant benefit from the addressed interventions. The reference values for the diagnosis of sarcopenia developed by FNIH are [9]:

- weakness: grip strength < 26 kg for male and < 16 kg for female; alternative grip strength adjusted for BMI < 1.0 for male and < 0.56 for female.
- pppendicular lean body mass (ALM): ALM adjusted for BMI < 0.789 for male and < 0.512 for female; alternative ALM < 19.75 kg for male and < 15.02 kg for female.

The threshold values of the lean mass identified by the "FNIH Sarcopenia Project" as "clinically relevant" are associated with impairment of mobility. In a subsequent research, Studensky also demonstrated that these cut-offs were not only clinically relevant, but also highly predictive of incident disability and mortality [11]. Thus sarcopenia, and not multimorbidity, is strongly associated with adverse outcomes. This fundamental evidence revolutionizes the conceptual terms of the syndrome framework, especially considering that it represents a potentially reversible condition. Hence, it is important to refer to a clear and universal accepted operational definition, in order to develop adequate therapeutic interventions to prevent disability. Interventions will not target a pathology, but functionality, revolutionizing the paradigm so far adopted towards patients in clinical practice.

The updated EWGSOP2 recommendations indicate low muscle strength as the primary parameter of sarcopenia, since this is the most reliable measure of muscle function, similarly to FNIH criteria. The diagnosis has to be confirmed by the detection of low muscle mass. The key conceptual step is represented by the fact that sarcopenia may be the biological substrate of physical frailty and the pathway through which it develops [12].

Sarcopenia may be envisioned as the "organ failure" underlying the clinical manifestations of physical frailty [13]. Therefore, the implementation of this theoretic model will feasibly encourage important advancements over the traditional approaches to this syndrome by enabling the accurate operationalization of the disorder, a clear identification of the affected population, and the rapid translation of findings to the clinical setting. It is important that such a conceptualization renders sarcopenia comparable to other common geriatric conditions, with the great benefit of making the syndrome easily acceptable by health care professionals, public health authorities, and regulatory bodies [14].

According to this conceptual model, sarcopenia relies on a biological substrate at the muscle level (low muscle mass and quality). The clinical manifestations of sarcopenia, such as slow gait speed, impaired balance, and weakness, are also objectively measurable with specific assessment scales [15]. This set of measurable biological substrate, clinical manifestations, and functional performance is similar to the diagnostic path that is usually performed for other common age-related degenerative conditions, such as congestive heart failure, chronic obstructive pulmonary disease, and peripheral artery disease [15]. This implies that older persons with sarcopenia can be easily identified as those with target organ damage (muscle mass), specific clinical phenotype, and impaired physical performance [16].

We present currently available tools for measuring muscle mass and physical function in order to better understand their advantages and limits, and their appropriate use in clinical setting.

SCREENING OF SARCOPENIA IN CLINICAL PRACTICE

In every older patient presenting with weight loss, weakness, fatigue, frequent falls, and difficulties in activities of daily living, the presence of sarcopenia should be evaluated. In this regard, the *SARC-F questionnaire* is a simple validated questionnaire should be administered during general medical examination to quickly identify subjects at risk of sarcopenia [17]. It includes 5 questions about difficulties to lift and carry 5 kg, walking across a room, transferring from a chair or bed, climbing 10 stairs, and numbers of falls in the previous year. Despite an uncertain sensitivity, a score ≥ 4/10 is reported to be predictive of sarcopenia and its negative outcomes [18]. This screening test is considered as the first step in the identifications of sarcopenia by the revised version of 2EWGSOP [8].

Other recent studies tested different ways to predict sarcopenia in primary setting, such as probability tables based on low muscle mass by age and BMI, or predictive score charts including variables such as age, handgrip strength, and calf circumference, but these need to be validated [17].

ASSESSMENT OF SARCOPENIA

It follows the list of methods for measuring muscle mass, useful in clinical practice or in research settings.

Assessment of muscle mass

Anthropometric measures – calf circumference, mid-arm muscle circumference

Mid-arm muscle circumference (MAMC = mid-arm circumference – (3.14 X triceps skinfold thickness) and calf circumference have been show to reflect both health and nutritional status, and to predict performance and survival in older people, and have been shown to be correlated with ALM [19]. The WHO Expert Committee considers a calf circumference smaller than 31 cm indicative of low muscle mass [20]. Anthropometry represents the most portable, easy to use, inexpensive tool, therefore it seems to be suitable for screening in primary care.

DXA – Dual energy X-ray absorptiometry

DXA is the most popular technique to estimate body composition, in particular appendicular skeletal lean mass [21]. Based on the attenuation capacity of X-rays in proportion to the composition and thickness of a composite material, DXA is able to measure the body content of soft tissue, fat mass and total body (appendicular and trunk) skeletal mass. Allowing measurement of the three body compartments and the estimation of appendicular skeletal lean mass (ALM) as the sum of the non-bone and non-fat mass of the four limbs (which is used both in EWGSOP and FNIH Sarcopenia project diagnostic criteria), DXA is considered the current reference technique both in research and clinical practice for the assessment of muscle mass [21]. The ALM is demonstrated to be strongly correlated with both MRI and CT measures of skeletal muscle volume. The main advantages of this tool are non-invasiveness (for the small doses of radiation: < 1 μSv for whole body scans) [22], cheapness, rapidity, and low rate of errors (1,2%). Weaknesses include that DXA is not portable, it is unable to assess intramuscular adipose tissue and consequently muscle quality; furthermore, its results could be affected by diseases associated with water retention (e.g. heart, kidney or liver failure), or with extracellular fluid accumulation, due to its inability to differentiate between water and bone-free lean tissue. Finally, the DXA machine usually does not support very tall or very obese people [21].

Magnetic resonance imaging (MRI)
MRI gives high accuracy information about muscle quantity and quality: different tissues have different magnetic properties (such as density of hydrogen atoms and relaxation time), so variations in the radio frequency pulse sequence allow to differentiate adipose tissue and fat-free mass. Its use in clinical practice is limited by difficult access, high costs, long execution time, the need of high trained staff; it is suitable for small-scale research studies [23].

Computed tomography (CT)
CT produces images as maps of pixels which reflect different tissue attenuation (related to electron density): bone, skeletal muscle and adipose tissue have specific range, and this allow their identification in the cross-sectional images. Strengths and weaknesses are very similar to MRI, except for radiation exposure and a shorter time for image acquisition [23].

Bioeletric impedance analysis (BIA)
BIA allows to quantify body compartments based on their different electrical conductivity: water rich tissue, such as skeletal muscle, are less resistant to the passage of an electrical current than lipid-rich adipose tissue [21]. Whole-body bioelectrical impedance measurement, in particular the resistance caused by the total water across the body, is taken between the right wrist and ankle with the subject in a supine position. The muscle mass is calculated through the Janssen equation (Skeletal muscle mass (kg) = [(height 2/BIA resistance X0.401) + (gender X 3.825) + (age X-0.071)] + 5.102).
Although BIA is a portable, easy to use, non-invasive, unexpensive tool, there is a poor correlation between BIA and DXA measurements (36), probability due to the fact that BIA measurements are very sensitive to subjects' conditions such as hydration, recent activity and time being supine, body temperature, intra and inter-instrumental variability, and electrode positioning.
Thus, BIA is suitable for screening of sarcopenia in community dwellers and bedridden patients [23].

Muscle ultrasonography (US)
The US beam propagates through and is reflected back to the transducer by tissues, according to their acoustic impedance; therefore, US allows the determination of thickness and cross-sectional areas of superficial muscle, and estimates muscle architecture parameters such as muscle volume, fascicle length, and pennation angle (which represents the angle of the muscle fibres relative to the force-generating axis, directly affecting both the force production and the muscle excursion) [24]. Although the major issue that must be taken into consideration is the impact on the measurements result of the applied pressure on the probe, an excellent intra and inter rater reliability for US measurements of quadriceps muscle layer thickness has recently been reported. In addition, US is portable and radiation-free, being promising for muscle mass assessment in clinical and research settings [24].

Other approaches to estimate muscle mass
Neutron activation (NAA). A stationery neutron beam passes over the subject lying on bed. A gamma detection system capturs gamma rays emitted by excited atomic nuclei, in turn excited by interaction with neutrons. Although very accurate in estimating muscle mass, this technique is not recommended for its high costs and radiation exposure [21].
Electrical impedance miography (EIM). It is based on the interpretation of muscle as a set of resistances and capacitances [21]. Resistances, determined by intra and extracellular matrices, increase when muscle cross sectional area reduces; capacitances, constituted by cell lipid bilayer membranes, also increase in case of muscle loss. These quantitative parameters are measured by applying, through separated electrodes, a high-frequency/low-intensity electrical current. EIM is a non-invasive, painless tool to measure muscle mass, but it requires high trained personnel. Hence, is not applicable in daily clinical practice [21].
Serum and urinary creatinine. Creatine is a widely present amino acid in skeletal muscle [21]. Creatine is non-enzymatically converted in creatinine at a relatively constant rate per day (about 2%) and excreted in urine. So, serum creatinine or 24-h creatinine excretion could be assumed to be proportional to the absolute amount of muscle mass [21]. Measurement could be affected by many factors such as renal failure. Some Authors suggested that, in the presence of stable renal function, it could be considered a reliable indicator of muscle mass, meat intake (accurate assessment would require a meat-free diet for about 1-2 weeks), inaccurate 24-h urine collection, conversion rate influenced by pH and temperature. Although predictive equations of creatinine excretion taking into account sex, weight, race and age have been developed, the absence of a normal range of reference does not make this technique currently applicable.
Deuterated creatinine (D3-creatine) dilution method. According to the non-enzymatic transformation just described above, urine excretion of D3 creatinine can be quantified after an ingestion of oral dose of deuterated creatine, considering it an indirect measure of skeletal muscle mass [21]. Although it is a complex technique that can only be used for research purposes, the estimation of muscle mass with this method showed excellent concordance with MRI measurements of muscle mass

in rats and humans. Some researchers have tested the possibility of using muscle turnover circulating products (such as those of collagen types II and IV), as muscle mass biomarkers, but further studies are needed.

Assessment of muscle strength

Hand grip strength

The measurement of muscle strength by handgrip strength is currently recommended in clinical practice. For this aim, the gold standard is the use of a Jamar dynamometer, an isometric instrument composed of a hydraulic gauge, an adjustable handle and a display that indicates (in kg) the peak of strength reached during the test [25]. The standard exam is performed with the subject seated, and the grip size is adjusted for the first test hand. The examiner has to explain the test: the patient has to squeeze the hand grip as hard as he can with the forearm at the thigh level, taking a breath in before starting, and blowing out the air during the performance. Six measures should be taken (3 per each arm) and the highest reading must be reported as the final result. This test presents some limitations in relation to the presence of arthritis, tendonitis, carpal tunnel syndrome, and surgery on hand or wrists in the previous three months. In these cases, physicians can use a pneumatic dynamometer to assess muscle strength.
In the case that sarcopenia could be viewed as a clinical biomarker to identify persons with a high risk of disability and negative-related outcomes, hand grip strength, absolute or adjusted for BMI, assumes fundamental importance because it "*can be considered a composite measure of muscle mass and muscle function and, at the same time, as an important discriminator of mobility limitation*" [8]. Considering this and the fact that it is portable, inexpensive and easy to perform, there is an urgent need to standardize reference values stratified for age, gender and ethnicity.

Leg extension strength

It is another test that measures lower body muscle isometric strength. The participant sits with its lower legs hanging down (knee angle 90°). A resistance is fastened around the right lower leg of the participant, who must try to extend this leg with maximum strength and hold that position for 3 seconds. The score is given in kilograms of force. After one practice trial, the best score of three trials is recorded. The main disadvantage consists in the need of an adequate equipment and trained staff.

Assessment of physical performance

Short Physical Performance battery (SPPB)

Physical performance should primarily be assessed by Short Physical Performance Battery (SPPB) test. It estimates the lower body function and is highly correlated with disability and negative outcomes such as hospitalization, institutionalization and mortality, because it "*provides an accurate picture of the biological age of an older person. At the same time, the SPPB is strongly related with the quantity and quality of skeletal muscle, and is therefore able to capture the core of Physical Frailty and Sarcopenia"* [13].
The SPPB test includes balance tests, gait speed test, and chair stand test. In the balance tests, the participant first tries to stand for about 10 seconds with his feet together side by side, then with the side of the heel of one foot touching the big toe of the other foot for about 10 seconds, and finally with the heel of one foot in front of and touching the toes of the other foot for about 10 seconds. During the three tests, the patient could extend arms or move the body to maintain the balance, but not move the feet. The second test measures the 4 meters gait speed. The patient could use a cane and has two tries. The final test is the "chair stand test": the subject stands up straight as quickly as he can five times without stopping in between, keeping arms folded across the chest. The performance is considered good if chair stand time is ≤ 11.19 seconds. A total score < 9 is indicative of poor physical performance.

Time up and go test (TUG)

The patient is seated in a chair. When the examiner says "go" the patient must get up, walk three meters (appropriately marked on the floor) at its usual gait, go back and sit again. The patient can use a walking aid if necessary. Time is recorded. Time ≥ 12 seconds to complete the TUG is considered an indication of poor physical performance.

Six minutes meters walking test

The patient must walk for 6 minutes along a corridor with a flat surface. The corridor must be at least 30 meters long. Before and after the test, heart rate and blood pressure should be monitored. The six-minute walk distance in healthy adults has been reported to range from 400 m to 700 m. Age and sex-specific reference standards are available to identify individuals with poor physical function.

400 meters walking test

The test is performed by asking the patient to walk for 400 meters along a corridor having a flat surface [13]. The patient could use a walking aid if necessary; the patient could stop at most 10 times. Each stop can last a maximum of 60 seconds, otherwise the test is interrupted. At the beginning and at the end of the test it is necessary to record the heart rate and the arterial

pressure. At the end of the test, the examiner must also investigate the perception of fatigue and the severity of the breathlessness with the Borg scale. A time ≥ 15 minute to complete the 400-m walking test is considered an indicator of poor physical performance.

CONCLUSIONS

In clinical practice, EWGSOP2 new guidelines recommend the use of the SARC-F questionnaire for screening. If it is positive, muscle strength should be measured by grip strength and chair stand test. The evidence of low muscle strength (probable sarcopenia) is enough to search the causes and start intervention. Low muscle quality or quantity should be detected to confirm the presence of sarcopenia; in this regard EWGSOP2 advise the use of DXA and BIA methods in usual clinical care, and DXA, MRI or CT in research. The measures of physical performance (SPPB, TUG and 400-m walk tests) should be used to assess severity of sarcopenia.

Conflict of interest

The author declare no conflict of interest.

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How to cite this article: Martone AM, Marzetti E, Calvani R, et al. *Assessment of sarcopenia: from clinical practice to research*. Journal of Gerontology and Geriatrics 2019;67:39-45.