

An update on methods for sarcopenia diagnosis: from bench to bedside

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ABSTRACT

Sarcopenia has been recognized as an age-related syndrome characterized by low muscle mass, low muscle strength, and low physical performance that is associated with increased likelihood of adverse outcomes including falls, fractures, hospitalization, frailty and mortality. Therefore, it is necessary to identify the condition early for applying intervention and prevention of the disastrous consequences of sarcopenia if left untreated. Clinical definition and diagnostic criteria for sarcopenia have been developed in the last years and different tools have been proposed for screening subjects with sarcopenia, evaluating the muscle mass, the muscle strength and the physical performance. In this review we analyzed the diagnostic criteria of sarcopenia and examined the current assessment tools used for the diagnosis and screening of sarcopenia.

Introduction

Aging is characterized by a progressive decrease in skeletal muscle mass, which leads to a loss of muscle strength and function. In 1989 Irwin Rosenberg proposed the term *sarcopenia* (from the Greek $\sigma\alpha\rho\chi\omicron$ muscle, $\pi\epsilon\nu\iota\alpha$ =deficiency, poverty) to define the gradual decline in muscle mass related to age.¹⁻⁴

Some years later, Evans and Campbell⁵ defined sarcopenia as age-related loss in skeletal muscle mass that results in decreased strength and aerobic capacity and thus functional capacity. Baumgartner *et al.* using data from the New Mexico Aging Process Study, were

the first to propose an operational definition of sarcopenia based on measure of lean mass as assessed by dual-energy X-ray absorptiometry (DXA). Based on the measuring of appendicular skeletal muscle mass calculated as the sum of lean mass in the arms and legs divided by height squared, subjects with relative muscle mass more than two standard deviations (SD) below the sex-specific mean of a reference population consisting of 122 young subjects aged 18 to 40 years from the Rosetta Study were defined as *sarcopenic*.⁶

Janssen and colleagues proposed an alternative definition of sarcopenia based on the skeletal muscle mass index (SMI) obtained by dividing the skeletal muscle mass in kg to body weight compared to 100, with the identification of two classes of sarcopenia (class I and class II, for SMI values respectively between -1 and -2 SD and < -2 DS than the average of a reference group of young persons included in the NHANES III).⁷

Together with the decrease in muscle mass and muscle strength, qualitative changes of skeletal muscle tissue occur with aging, being mainly characterized by atrophy of muscle fiber type IIa, fast-twitch⁸ with a progressive decline in the efficiency of the muscle (*i.e.*, muscle strength developed for single functional unit of muscle mass).⁹ At the same time, the muscle atrophy is accompanied by an increase of the connective and adipose tissue within the muscle.¹⁰

The loss of muscle in the elderly is caused by multiple factors, such as the reduced synthesis of anabolic hormones, *i.e.* growth hormone, androgens, estrogens, and insulin-like growth factor-I, and the increase of some inflammatory cytokines especially interleukin- 1β , tumor necrosis factor- α , and

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interleukin-6, which play a catabolic action.¹¹ In this context, in a recent study Rossi *et al.* showed that higher serum levels of anti-inflammatory markers, in particular IL-4 and IL-13, may play a protective role on fat free mass (FFM) and performance maintenance in elderly subjects.

The decrease in physical activity with aging process, the insufficient protein intake and comorbidities are other key factors in the development of strength and muscle mass loss.

A rapid decline in muscle mass has been observed in older people who remain bedridden due to an illness. It has been shown that bedridden patients show an increase of urinary nitrogenous bases excretion due to an increased protein catabolism,^{12,13} and that healthy elderly subjects lose an average of 1 kg of muscle mass in 10 days of bed rest which results in 16% reduction of the isokinetic strength of the knee extensor muscles.¹⁴ This marked loss is three times greater than that observed in healthy young adults after 28 days of bed rest.¹⁵

Epidemiology of sarcopenia

The prevalence of sarcopenia varies between 7 to 50% based on the diagnostic criteria, cutoffs chosen, and methods used to measure lean body mass and muscle strength.^{16,17} A recent systematic review including a final sample of eighteen prevalence papers showed higher prevalence of sarcopenia in institutionalized older adults (14-33%), compared to community dwelling elderly (1-29%) or subjects admitted to acute care hospitals (10%).¹⁸ A prevalence increase was observed with age with no significant differences between men and women.

In a recent cross-sectional observational study on 730 elderly people, a higher prevalence of sarcopenia was demonstrated in subjects with chronic diseases (heart failure, cognitive impairment, Parkinson's disease, renal failure, peripheral artery disease and hip fracture) and people with low educational level.¹⁹

Health consequences of sarcopenia

Sarcopenia is a subject of increasing interest in the scientific community for its multiple clinical and epidemiological implications. In fact, sarcopenia, which is characterized by progressive loss of skeletal muscle mass and strength, results in physical disability, reduced quality of life, and increased risk of fractures, hospitalization and mortality.²⁰⁻²⁴ A recent multicenter observational study involving 770 hospitalized patients showed a significantly higher in-hospital and 1-year mortality in participants with sarcopenia diagnosed according to EWGSOP criteria.²⁵

Definition and diagnostic criteria

The first definition of sarcopenia was based only on skeletal muscle mass measurement by DXA or bioimpedantometry (BIA).^{6,7,26}

This definition of sarcopenia used in several epidemiological studies has important limitations. In fact, several studies showed that age-related decline in muscle strength is quicker and poorly correlated with the decline in muscle mass. Although muscle mass is an important determinant of muscle strength,²⁷⁻²⁹ age-related loss of muscle mass only partially explains the loss of muscle strength. In a meta-analysis Manini and Clark showed that low lean mass is generally a poor predictor of impaired physical performance, physical disability and functional limitation, outcomes more related to muscle weakness.³⁰

Since 2010, several groups of experts and in particular the European Working Group on Sarcopenia in Older People (EWGSOP) and the International Working Group on Sarcopenia (IWG) have convened with the goal of establishing consensus diagnostic criteria for sarcopenia taking into account also its functional consequences.³¹⁻³³ All the consensus groups agree in stating that a sarcopenia diagnosis should include both low muscle mass and poor muscle function as assessed by either low muscle strength or impaired physical performance.

The EWGSOP established three criteria for a diagnosis of sarcopenia: i) criterion 1: decreased muscle mass; ii) criterion 2: reduction of muscle strength; iii) criterion 3: decreased physical performance.

The documented presence of the criterion 1 associated with criterion 2 or criterion 3, allows a diagnosis of sarcopenia (Table 1).³²

The EWGSOP suggests three different stages of sarcopenia which attest the severity of the condition: *presarcopenia*, *sarcopenia*, and *severe sarcopenia*. The *presarcopenia* is characterized by the loss of muscle mass not associated with strength or physical performance loss. The *sarcopenia* is defined by the reduction in muscle mass associated with strength or physical performance loss. The *severe sarcopenia* is characterized by the presence of the three diagnostic criteria.

Identifying the different stages of sarcopenia can be useful for establishing the treatment and defining appropriate recovery objectives.

More recently, in order to create a new definition of the criteria for sarcopenia validated by larger studies, it was approved *The FNIH Sarcopenia Project* promoted by the Foundation for the National Institutes of Health (FNIH), a public/private partnership made up of representatives of the National Institute of Aging, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the Center for

Drug Evaluation and Research/Food and Drug Administration, several leading academic institutions and six pharmaceutical companies.

The FNIH Sarcopenia Project analyzed results from nine large population studies with longitudinal measures of muscle mass and function (Age, Gene/Environment Susceptibility-Reykjavik Study, Boston Puerto Rican Health Study, 6 clinical trials of the University of Connecticut; the Framingham Heart Study, the Health, Aging, and Body Composition Study, the Aging InChianti study; the Osteoporotic Fractures in Men Study, Rancho Bernardo Study, Study of Osteoporotic Fractures), for a total of 26,625 men and women aged 65 years and older.

The Project recently published a series of five papers³³⁻³⁷ describing rationale, methods, and recommendations resulting from a year-long effort supported by the FNIH Biomarkers Consortium.

Specifically the Sarcopenia Project aimed to determine a level of muscle weakness associated with mobility disability and a degree of muscle mass that identifies muscle weakness and to evaluate whether the criteria for muscle weakness and low lean mass are associated with incident mobility impairment defined as gait speed less than 0.8 m/s. Sex-specific cut-points for handgrip strength that discriminate individuals with mobility impairment³⁴ and cut-points

for appendicular lean mass measured by DXA, that were associated with weakness defined by the previously calculated cut-points,³⁵ were obtained.

Absolute appendicular lean mass emerged as the single best discriminator of weakness (low grip strength). Taking into account the obesity influence on the relationship between lean mass and muscle strength, alternative cut-points for appendicular lean mass standardized to body mass index (BMI) were proposed as a discriminator of weakness.

Low appendicular lean mass standardized to BMI was associated with a more modest increased risk of mobility impairment compared to low grip strength, whereas low absolute appendicular lean mass was not associated with mobility impairment.³²

Among those classified as weak by the low grip strength criteria, the risk of mobility limitation did not differ between those with and without low lean mass, indicating that weakness is the primary determinant of future mobility problems. Nevertheless, the investigators noted that among those with weakness there was likely a subgroup for whom low lean mass was the underlying cause of their weakness, and these individuals could be targeted for treatment with therapies that increase muscle mass. Thus, the Sarcopenia Project recommended a set of sex-specific, empirically-derived cut-points for low absolute grip

Table 1. Different definitions of sarcopenia.

	European Working Group on Sarcopenia in Old People (EWGSOP) (Cruz-Jentoft AJ)	International working group on sarcopenia (IWG) (Fielding RA)	Special interest Group: Cachexia-anorexia in chronic wasting disease (Muscaritoli M)	Sarcopenia with limited mobility: an international consensus (Morley JE)
Definition	Syndrome characterized by a progressive generalized muscle strength and mass loss with increase risk of unfavorable events such as physical disability, reduced quality of life and increased mortality	The loss of muscle mass and strength associated with aging	The term <i>sarcopenia</i> originally referred solely to the loss of muscle mass with age, and as such, is an almost universal phenomenon Current <i>sarcopenia</i> definitions incorporate not only muscle mass but also elements such as strength and function	Reduced muscle mass, with limited mobility
Criteria	1. Low muscle mass + 2. Low muscle strength <i>or</i> 3. Low physical performance	1. Low muscle mass (<i>i.e.</i> a percentage of muscle mass 2 standard deviations below the mean measured in young adults of the same sex and ethnic background) 2. Low walking speed (<0.8 m/s over 4 meters gait speed test)	1. <i>Recommended cutoff for weakness: grip strength (GSMAX) <26 kg for males and <16 kg for females</i> <i>Alternate: grip strength adjusted for BMI (GSMAXBMI) <1.0 for males <0.56 for females</i> 2. <i>Recommended cutoff for low muscle mass: ALM adjusted for BMI (ALM/BMI) <0.789 for males <0.512 for females</i> <i>Alternate: ALM <19.75 kg for males <15.02 kg for females</i>	1. ALM corrected for height squared of more than 2 standard deviations below that of healthy persons between 20 and 30 years of age of the same ethnic group 2. Walking speed <1.0 m/sec o <400 m at the 6 min walking test

ALM, appendicular lean mass; BMI, body mass index.

strength and low appendicular lean mass standardized to BMI as potential criteria for clinically relevant weakness and low lean mass, respectively, in older men and women (Table 1).

Qualitative changes occurring in sarcopenic skeletal muscle

Within aging, the total number of motor units (motor neuron and muscle fibers associated) decreases with a prevalent loss of fast-twitch muscle-skeletal fibers (type IIa); the remaining fibers, both type I and type II fibers, undergo atrophy, histologically detectable with a reduction of their section area.³⁸

The age-related decrease in the number of neurons, at cortical, medullary and peripheral levels, is an important causal factor of motor units' depletion. As an adaptation mechanism, new neuro-muscular junctions are generated between the residual nerve endings and the muscle fibers that have undergone denervation (type I and type II), generating new motor units in which a single motor neuron innervates both slow and rapid twitch muscle fibers. The result of this process is the loss of muscle efficiency (that is, of the muscle strength developed for each functional unit of muscle mass). This set of modifications determines an important deterioration in physical performance with a 30-35% decrease in muscle strength.³⁹

Further, another morphological aspect consists in lipid infiltration both within adipocytes located between the muscle fibers and at the cytoplasmic level of the muscle cells themselves (intramyocellular fat).⁴⁰

At ultrastructural level, mitochondrial dysfunction causes excessive production of reactive oxygen species causing accumulation of mitochondrial DNA damage; this can trigger apoptosis with subsequent programmed death of the entire fiber by the release of cytochrome c into the cytosol, or by the production of pro-apoptotic proteins.^{41,42}

Also, the oxidative stress that occurs into sarcoplasmic reticulum can lead to apoptosis by release of calcium in the cytoplasm with consequent activation of the effector caspases. Regarding the sarcomeric structures, in addition to a significant decrease in the total amount of myosin per single fiber, there is accumulation of post-transcriptional modifications, such as the glycation of proteins, with impairment of the correct interrelation between actin and myosin, reduction of the efficacy of the muscle contraction.⁴³

Methods for muscle mass evaluation

Several methods have been proposed for muscle mass evaluation. Although BIA and anthropometry may be easily applicable in the clinical field, they are

often considered inaccurate methods for muscle mass evaluation.⁴⁴ In contrast, DXA that estimates appendicular and total body lean mass, and computed tomography (CT) which measures muscle cross sectional area are considered more reliable and reproducible methods.

Among regional measures of muscle mass, the mid arm circumference measured at the midpoint of the upper arm and recorded to the nearest 0.1 cm was the most frequently used. However, this method was limited by the assumption for its use, that the midarm is circular, the triceps skinfold thickness is twice the average fat diameter at the middle of the upper arm.⁴⁴ Sex-specific equations have been previously proposed containing corrections for bone contributions, resulting in average intra-rater error of 7% to 8% in the calculated midarm muscle area. By using this formula in obese subjects an average 50% error was observed.⁴⁵

More recently Lee *et al.* proposed a predictive equation using upper-arm girth adjusted for skinfold, thigh circumference corrected by anterior thigh skinfold and height, and calf circumference corrected by skinfold thickness.⁴⁶

$$\text{SMM} = \text{S} (0.00744 \text{ CAG}^2 + 0.00088 \text{ CTG}^2 + 0.00441 \text{ CCG}^2) + 2.4 \text{ Sex} - 0.048 \text{ Age} \quad (1)$$

where CAG is corrected upper-arm girth adjusted for skinfold thickness, CTG is thigh circumference corrected for anterior thigh skinfold thickness, CCG is calf circumference corrected for skinfold thickness, S is stature in m, age is in years, sex is 1 for male and 0 for female, and race is -2 for Asians, 1.1 for African American, 0 for white or Hispanic.

Bioelectrical impedance analysis is widely used for assessing muscle mass. This method relies on the conduction of a low electrical current and allows measuring two parameters: resistance (R) and reactance (Xc). Reference body composition data to validate the BIA-based measurements were derived from anthropometric assessment and CT measurements of muscle and fat area, and several equations have been proposed for muscle mass estimation.⁴⁴

Roubenoff and colleagues developed the following BIA equations to quantify FFM:⁴⁷

$$9.1536 + 0.4273 \text{ height}^2/\text{R} + 0.1926 \text{ weight} + 0.0667 \text{ Xc for men} \quad (2)$$

$$7.7435 + 0.4542 \text{ height}^2/\text{R} + 0.1190 \text{ weight} + 0.0455 \text{ Xc for women} \quad (3)$$

where height is in cm, age in years and R in ohm; sex: male=1, female=0.

Alternative regression equations, the most used in studies conducted in elderly populations, were

proposed and validated in a multiethnic sample of 388 men and women aged 18 to 86 years by Janssen to estimate skeletal muscle mass (SMM):⁴⁸

$$\text{SMM} = 0.401 (\text{Ht}^2/\text{R}) + 3.825 \text{ Sex} - 0.071 \text{ Age} + 5.102 \quad (4)$$

where R is resistance (ohm) determined at 50 kHz, Ht is height (cm), sex is male =1 and female =0, and age is in years.

The inhomogeneous composition of body compartments, cross-sectional areas variability, FFM hydration fraction, presence of edema and differences in conductor lengths from limbs and trunk limits the use of BIA equations from one population to another and the same equation cannot be used indifferently in populations with different age, BMI or hydration status.⁴⁹ However bioelectrical impedance does not require a prolonged training and is a widely available and inexpensive instrument for routinely use.

DXA is a radiologic technique that offers the opportunity to directly measure muscle, fat and bone mass. This technique, originally developed for bone mineral content assessment, has been refined for assessment of soft tissue composition. DXA exposes the patient to a much less amount of X-ray compared with CT.⁵⁰

Validation studies for DXA indicate good agreement with CT and multicompartiment models, considered as reference methods.

Second generation DXA are equipped with fan-beam technology that allows much less time to complete whole-body composition and bone density scan with improved precision.⁵¹ Fan beam machine has been used frequently in clinical trials and also in the National Health and Nutrition Survey IV. Comparison studies, assessing body composition with DXA pencil-beam and fan-beam have found that the latter measurement overestimates lean mass with, on the counterpart, an underestimation of fat mass with differences between various hardware and software between 1% and 5% for different tissues.^{52,53}

DXA has the advantage, as compared with BIA, that allows, not only total body, but also regional body composition assessment and in particular appendicular lean mass measurement.

Potential interference of fluid accumulation in the body should be considered even when using DXA, but to a lesser extent as compared with BIA.

Hydration status alterations, for example consumption of 1 to 2.4 L of water 1 hour before DXA scan could determine an increase of FFM, because of alteration of extracellular fluid volume, whilst the ingestion of small amount of water did not affect body composition measurement.

DXA is considered a reasonable alternative for

muscle mass assessment compared to much more sophisticated, time-consuming and expensive techniques such as magnetic resonance imaging (MRI) and CT. DXA likely represents the most accessible technique for high quality and precise body composition assessment. The radiation exposure associated with DXA is low and highly acceptable (*i.e.*, about 1 mrem; similar to that of a 3-day background). Nevertheless, even this low dose radiation needs to be considered as a limiting factor for routine assessment of body composition.

The main limitations of DXA reside in the instrument cost⁴⁴ and by the dimensions of the table of the densitometer, which is limited in size and weight and therefore may not be suitable for the evaluation of subjects with high-grade obesity.

CT scan is based on X-rays that pass through the different body tissues and are attenuated in relation to the physical density of the tissues examined. The CT method offers high quality images with clear distinction between fat and other soft tissues.

CT and MRI are considered gold standards for clinical research, although they are expensive and difficult to adopt on a large scale.⁴⁴

This allows a clinician to visually and mathematically distinguish the different tissues with dedicated software and in particular at the muscle level to separate intermuscular adipose tissue from mean skeletal muscle based on the differences in attenuation characteristics.⁵⁴

CT has high precision with <1% of error and is considered the best method to measure body composition changes and the effect of life style interventions in humans.

The most important limitation for the routine use of CT exposes individuals to ionizing radiation (*i.e.*, about 15 mrem, much higher than DXA) and provide a marker of muscle fat content but not a quantitative determination of fat content.⁴⁴ Advantages are the reliability and the relative simplicity.

Several studies support the validity of MRI estimates to quantify skeletal muscle by comparison with the dissection in human cadavers. Mitsiopoulos *et al.*⁵⁵ compared the cross-sectional area measurements of skeletal muscle and subcutaneous adipose tissue determined from the entire arm and leg regions of cadavers with corresponding MRI-measured cross-sectional areas and reported the correlation coefficient between the two approached units.

Limitations for the use of MRI in body composition studies are attributed to limited access of instrumentation, the higher technical complexity and costs, time required for scan acquisition (about 45 min), and the inability to evaluate subjects with older models of implanted metal devices (*e.g.*, joints, pace-makers, metallic particles in the eye, *etc.*). On

the other hand, MRI shows a high agreement with the CT and provides similar measures. It does not involve radiation exposure and, furthermore, it also has the additional capacity of multiple slice acquisition (thus, rendering 3D volumetric estimates for muscle mass).

Methods for muscle strength evaluation

Different assessments have been proposed to measure muscle strength in the geriatric population.

To date, the most widely used method in clinical practice appears to be the handgrip strength dynamometry because of its simplicity, time-efficiency, affordability, and reliability. This method has been shown to reflect the overall strength status of an old subject and to be a good predictor of morbidity, hospitalization and mortality.⁵⁶ Standardized conditions for the test⁵⁷ include seating the subject in a standard chair with their forearms resting flat on the armchairs; six measures should be taken, three with each arm; the highest reading of the 6 measurements is reported as the final result. According to guideline for European working group on sarcopenia in older people (EWGSOP, the Sarcopenia Working Group), low muscle strength, using cut-off point for handgrip strength at two standard deviations below the mean reference value, is defined as <30 kg in men and <20 kg in women.¹⁸

Since lower extremity strength and in particular muscle extensor appear to be crucial in a variety of functional tasks, knee extension strength measured by isokinetic and/or isometric dynamometry has also been proposed as tool for quantification of muscle strength in elderly. However, although the measurement is feasible in frail older people,^{58,59} its practical applicability seems to be limited because it is more complex and time-consuming, and so far, there are limited data in older population.

Sarcopenia is not confined to only upper or lower limb muscles but rather involves a more generalized loss of skeletal muscle mass and strength, including a decline in mass and strength of the respiratory chest muscles.^{60,61} The EWGSOP used peak expiratory flow (PEF) value to measure respiratory muscle strength in people without lung disorders.¹⁸ However, studies on respiratory function and sarcopenia are limited and PEF values cannot currently be recommended for use as a single parameter of muscle strength.

Methods for physical performance evaluation

Gait speed, sit-to-stand time and standing balance are the most widely used tools for the assessment of functional performance. They can be evaluated as

single items, but, in clinical practice, they are more often measured within the context of the short physical performance battery (SPPB).⁶² The SPPB is really the most commonly employed method of assessing the ability to perform the activities of daily living in mobility-limited older adults;⁶³ it focuses primarily on lower extremity function and includes a 4 meter walk to measure gait speed, one chair stand (followed by 5-time chair stands, if the first is successfully completed), and balance stands with the feet held in different positions for 10 sec each. The test is easily administered in a variety of contexts or settings, and a score between 0 and 4 is assigned to each component (with a maximum of 12 points). Participants presenting a score ≤ 8 points have been described as having a poor physical performance.¹⁸

Although the usual gait speed test measured as the pace on a 4- or 6-m course is the most popular physical function and performance test in clinical practice, and sarcopenia research and is often referred to as the *new vital sign* because it is a sensitive predictor of physical disability, fall risk, chronic illness and premature death and has been strongly associated with independent functioning in older adults,^{64,65} other independent tests used to assess physical performance include the 6-min walk distance (6MWT) or 400 m walk test, the stair climb power test, the timed up and go (TUG) test.¹⁸

In the TUG test subjects are asked to stand up from a standard chair (seat height between 44 and 47 cm), walk a distance of 3 m (marked on the floor) at a comfortable pace, turn, walk back and sit down. The TUG is an easy-to-apply, fast and inexpensive test; it serves as an assessment of dynamic balance, and it has been shown to be a good predictor of sarcopenia in elderly hospitalized patients⁶⁶ as well as in home-dwelling elderly persons.⁶⁷

Longer distance walking tests are also used as valid alternative tools to evaluate the exercise capacity at levels corresponding to efforts commonly performed by elderly during daily activities. Some versions of these tests measure either distance traveled in a set amount of time, as for the 6MWT that measures the distance an individual is able to walk in 6 minutes on a hard, flat, indoor surface, or the time to walk a set distance, such as the usual-pace 400 m walk.⁶⁸ These tests have been shown to be good indicators of functional performance in older adults,^{68,69} and have been used as an outcome in clinical trials, however they only include walking ability.

The stair climb power test assesses the ability to ascend and descend a flight of stairs, as well as lower extremity strength, power, and balance.⁶⁹ It may be of some use in research settings.¹⁸

Finally, jumping mechanography, a procedure that uses maximal countermovement jumps to assess

muscular power, has been proposed as new tool to assess muscular function in older adults.⁷⁰ The test is a strength measurement of muscle that incorporates the functional components assessed in traditional chair rise and gait speed testing. It has been shown that jump test variables are positively correlated with lean tissue and lower body muscle strength⁷⁰ and that in older adults has excellent retest reliability that was comparable to grip strength and possibly better than SPPB and gait speed, is stable over time, and can be performed safely.^{70,71} However, more studies in older populations and comparison of this approach with traditional assessment tools in longitudinal interventional studies are needed.

Questionnaires for sarcopenia screening

As previously reported, the EWGSOP, as well as the International Working Group on Sarcopenia (IWGS), established three criteria necessary for the diagnosis of sarcopenia, namely decreased muscle mass, reduction of muscle strength and/or decreased physical performance. Besides the EWGSOP consensus statement on sarcopenia, a number of other definitions have been published.^{72,73} Therefore, the diagnostic criteria include muscle mass, gait speed and/or handgrip measurements that must be performed by trained operators and preferably in a laboratory assessment.

Since these measurements are not always available and easily performed in general practitioner, acute-care and long-term care settings, there is need for an easy-to-use and widely available pre-screening tool to identify the risk of sarcopenia. Moreover, it has been shown that the gait speed test, the first step for EWGSOP diagnosis criteria, cannot be performed in nearly half of the elderly population within previously described settings.^{74,75}

Moreover, the prevalence of sarcopenia among the different study populations varies depending on whether IWGS or EWGSOP criteria were used,⁷⁶ the variations widely explained by the use of different muscle indices. As a consequence, also in order to reduce the costs related to diagnosis, recent emphasis has been placed on the diagnosis of clinically important sarcopenia, developing tools able to identify clinical risk parameters of sarcopenia.

Malmstrom and Morley developed a 5-item questionnaire, the SARC-F, based on principal features and health consequences of sarcopenia, as described in literature.⁷⁷⁻⁷⁹

The SARC-F scale includes questions that investigate strength, assistance walking, rise from a chair, climb stairs and falls. Strength was measured by asking subjects how much difficulty they had lifting or carrying 10 lbs (0=no difficulty, 1=some, and 2=a lot or unable to do). Assistance walking was

investigated by asking participants how much difficulty they had walking across a room and whether they used aids or needed help to do this (0=no difficulty, 1=some, and 2=a lot of difficulty, use aids, or unable to do without help). Rise from a chair was measured by asking respondents how much difficulty they had transferring from a chair or bed and whether they used aids or needed help to do this (0=no difficulty, 1=some, and 2=a lot of difficulty, use aids, or unable to do without help). Climb stairs was measured by asking respondents how much difficulty they had climbing a flight of 10 steps (0=no difficulty, 1=some, and 2=a lot or unable to do). Falls were scored a 2 for respondents who reported falling four or more times in the past year, 1 for respondents who reported falling 1-3 times in the past year, and 0 for those reporting no falls in the past year. The score range obtained with the SARC-F questionnaire ranges from 0 to 10 (0-2 points for each item, 0=best score, 10=worst), dichotomized to represent symptomatic subjects (score ≥ 4) compared to the healthy ones (score 0-3).

Malmstrom *et al.* investigated the utility of SARC-F in the African American Health (AAH) study, Baltimore Longitudinal Study of Aging (BLSA) and National Health and Nutrition Examination Survey (NHANES).

The AAH study includes community-dwelling, late middle-aged African Americans aged between 49-65 years old at initiation in 2000-2001 and had high level of disability.^{80,81} The BLSA is an ongoing survey started in 1958 on normal human aging; subjects included were healthy adults at the time of enrolment. The NHANES is a nationally representative study of approximately 5000 community-dwelling individuals.

In the AAH cohort, subjects with SARC-F score ≥ 4 showed more deficits in the instrumental activities of daily living (IADL) than those who scored 3 or less, longer standing-time from the chair, lower grip strength, lower SPPB scores with poorer physical performance, higher probability of hospitalization and of having a gait speed < 0.8 m/s.⁸² SARC-F score ≥ 4 in BLSA was associated with higher IADL deficits, worse grip strength (at both right and left hands) and mortality in follow-up (39.4% for SARC-F ≥ 4 vs 8.0% in SARC-F < 4). NHANES participants with SARC-F scores ≥ 4 had lower walking speeds (slower time to walk 20 ft), lower strength (knee extension) and were more likely to have been hospitalized recently in cross-sectional analysis.

Cao *et al.* showed that SARC-F was associated with poor physical performance, grip strength and hospitalization in the previous 2 years.⁸³ In this study, two hundred and thirty Chinese people over 65 years of age were assessed by the SARC-F scale, physical self-maintenance scale (PSMS),⁸⁴ IADL, and the

shortened version of the falls efficacy scale-international (the short FES-I).⁸⁵ Physical performance and strength were measured respectively with the SPPB and handgrip test; hospitalization was also investigated. Poor physical performance and grip strength were independently associated with a SARC-F score ≥ 4 . The short FES-I was correlated to SARC-F, poor PSMS and IADL scores were associated with SARC-F ≥ 4 and SARC-F ≥ 4 was associated with hospitalization in the past 2 years.

Woo *et al.* conducted a validation study of SARC-F on a cohort of 4000 Chinese community residents aged 65 and over.⁸⁶ SARC-F has been validated and compared with the three definitions of sarcopenia for the European consensus groups (EWGSOP), Asian (AWGS) and the international group (IWGS); the ability of all four diagnostic tools to predict physical limitation at four years of follow-up, walking speed and ability to stand up from a chair was compared. Sarcopenic subjects according to SARC-F, EWGSOP, IWGS and AWGS all showed increased risk of physical limitations and poor physical performance at follow-up, both men and women. The SARC-F questionnaire showed a high specificity (94-99%) and high negative predictive value, but low sensitivity (4.2% men and 9.9% women) for sarcopenia by using the EWGSOP criteria.

More recently Rossi *et al.* developed the Mini Sarcopenia Risk Assessment (MSRA) questionnaire as a prescreening tool for assessing the risk of sarcopenia.⁸⁷

The questionnaire is composed of seven items and investigates anamnestic and nutritional characteristics related to the risk of occurrence of sarcopenia; four questions about general assessment (age ≥ 70 or < 70 years, physical activity level as walking more or less than 1000 meters, number of hospitalizations in the previous year and weight loss), and three about nutritional status (consumption of proteins and dairy products, number of meals per day). These questions reflect risk factors of muscle mass and strength loss as shown in literature.

MSRA was used in a post-hoc observational study of a community-aged population of 274 subjects, 177 women and 97 men, aged 66-78 years. According to the EWGSOP diagnostic criteria, the subjects of the study were classified as sarcopenic and not sarcopenic.

The results showed that 33.5% of the study population was classified as sarcopenic. Using the form of MSRA extended to 7-item, subjects with a score equal to or less than 30 had a 4-fold higher risk of being sarcopenic than subjects with a score greater than 30, taken as a cut-off value [odds ratio (OR): 4.20; 95% confidence interval (CI): 2.26-8.06]; the area under the ROC curve was 0.786 (95% CI: 0.725-0.847).

In a logistic regression, considering the probability

of being sarcopenic as the dependent variable and the variables corresponding to the 7 items of the questionnaire as independent, two items (number of meals and consumption of milk and dairy products) showed not significant diagnostic power. A cut-off score for the 5-item questionnaire was then obtained, where the area under the ROC curve was 0.789 (95% CI: 0.728 to 0.851).

Taking into account the cost of false positives and false negatives and the prevalence of sarcopenia, the *optimal* threshold of the original MSRA score based on 7 items is therefore 30, with a sensitivity of 0.804 and a specificity of 0.505, while the threshold *optimal* of the MSRA score based on 5 items is 45, with a sensitivity of 0.804 and a specificity of 0.604.

In this preliminary study, the MSRA questionnaire was predictive of sarcopenia and may be suggested as a pre-screening tool to detect this condition. In particular, the use of the short form of the MSRA questionnaire improves the ability to identify sarcopenic subjects, for sensitivity and specificity values (Tables 2⁷⁷ and 3⁸⁷).

Conclusions and perspectives

The research in the field of sarcopenia has progressed significantly over the past decade, but yet it continues to lag behind the clinical assessment, treatment, and outcomes that have been well-established in the field of osteoporosis. With the EWGSOP and IWG consensus and the ongoing FNIH activities in the Biomarkers Consortium, further refinements of sarcopenia criteria are expected.

The validation of the MSRA and SARC-F questionnaires should be part of further prospective or retrospective studies in wider populations. The MSRA and SARC-F questionnaires are designed to provide an inexpensive and easy-to-use tool capable of capturing the key features of sarcopenia and rules out subjects unlikely to be sarcopenic. They have the advantage that can be compiled also by the patient or by the caregiver and are applicable in postal screening, phone calls or general practitioners settings as well, thus allowing the screening for sarcopenia in outpatients.

While further studies are needed to provide a full evidence-based guidance, the management and assessment of sarcopenia is very important in the mainstream of clinical care to ensure a reduction in age-related falls, fractures, and disability and to guarantee a better quality of life with aging.

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