

Emerging research on importance of muscle mass and function

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Sarcopenia, the age-related loss of muscle mass and strength with impaired function, is progressively documented as a major issue in geriatric medicine. It is remarkable that the study of this condition has recently extended beyond the borders of geriatrics, highlighting the importance of muscle physiology to the overall health status. Definitely, the assessment of sarcopenia is increasingly raised as an important tool for the risk stratification of patients suffering from different medical conditions, such as cardiovascular and pulmonary diseases, chronic kidney failure, among others. The wide range of negative health-related events to which sarcopenia contributes has activated rigorous research efforts in the attempt to untangle its multifaceted pathophysiology and develop effective specific treatments.

Key words: Sarcopenia, Physical performance, Negative outcomes

Sarcopenia, the age-related loss of muscle mass and strength with impaired function, is progressively documented as a major issue in geriatric medicine. It is remarkable that the study of this condition has recently extended beyond the borders of geriatrics, highlighting the importance of muscle physiology to the overall health status. Definitely, the assessment of sarcopenia is increasingly raised as an important tool for the risk stratification of patients suffering from different medical conditions, such as cardiovascular and pulmonary diseases, chronic kidney failure, among others. The wide range of negative health-related events to which sarcopenia contributes has activated rigorous research efforts in the attempt to untangle its multifaceted pathophysiology and develop effective specific treatments (Fig. 1).

older subjects may hints to functional impairment (e.g., poor endurance, slow gait speed and decreased mobility). Such condition is highly predictive of incident disability, poor quality of life and all-cause mortality in older people ². The loss of muscle mass, pooled with the significance lack of strength as an central determinant of aging process, may encourage to the operationalization of a muscle quality definition based on the strength production capacity per unit of muscle mass ³. Accordingly, an understanding of the influence of aging per se on the skeletal muscle needs particular consideration to modifications in muscle volume but at the same time in muscle quality. This is principally important when pondering the potential effects of treatments, in terms of enhancements not only in muscle mass but also in function and physical performance ⁴.

INTRODUCTION

One of the most thoughtful consequences of aging is the onset of sarcopenia, which consists in a progressive decline in skeletal muscle mass and strength ¹. This deterioration accelerates after the age of 50 and in

SARCOPENIA DEFINITION

In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) published the first sarcopenia definition with the specific aims to promote

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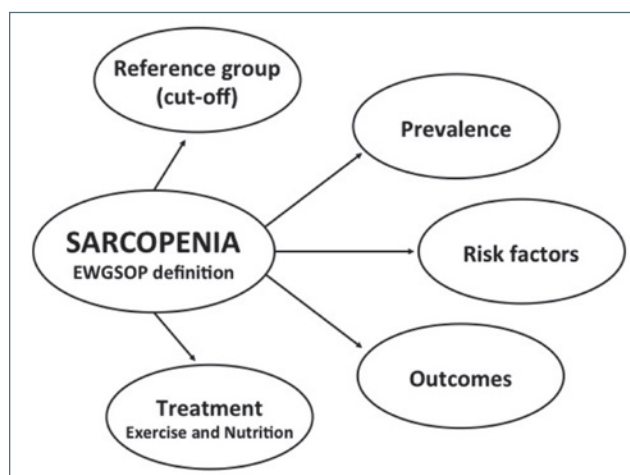


Figure 1. Sarcopenia overview: from definition to treatment.

improvements in identifying and treating for subjects with sarcopenia ⁵. In 2018, the same Working Group met again (EWGSOP2) to update the original definition in order to reflect scientific and clinical evidences that have emerged over the last ten years ⁶.

In this revised and updated consensus paper on sarcopenia, EWGSOP2 “*focuses on low muscle strength as a key characteristic of sarcopenia, uses detection of low muscle quantity and quality to confirm the sarcopenia diagnosis, and identifies poor physical performance as indicative of severe sarcopenia*” ⁶. Accordingly, the European group delineated the new clinical algorithm to be used for sarcopenia case-finding, diagnosis and confirmation, and severity determination. Finally, the EWGSOP2 provided the updated cut-off points for measurements of variables that identify and characterize sarcopenia ⁶.

In this respect, it is important to highlight that methods to assess muscle quantity are available in many but not all clinical settings. As equipment and methods to estimate muscle quality are developed and refined in the future, this factor is estimated to rise in meaning as a defining feature of sarcopenia. Physical performance was previously contemplated as part of the definition of sarcopenia, but sometime this domain has been used as an outcome measure. In the new definition physical performance is considered to categorize the severity of sarcopenia. To use this definition in clinical practice, the EWGSOP2 consensus paper reviewed tests and tools for assessing muscle mass, strength and physical performance, addressing the updated version of a practical algorithm for sarcopenia case-finding, diagnosis and severity determination ⁶.

REFERENCE GROUP AND CUT-OFF POINTS

The of age-related deterioration, and the age at which declines in muscle mass, muscle strength, and physical performance can first be recognized, have not been widely studied. Recently, we investigated the modification of muscle mass, strength, and physical performance across age in a large and unselected sample of community-dwelling individuals ⁷. These findings clearly display that different patterns of muscle mass and physical decline with age are reported for different ages. In particular, muscle mass (measured by calf circumference) slightly decreases with advancing age. Interestingly, for muscle strength (measured by hand grip test) and physical performance (measured by chair stand test) there is stability in the first decades of adulthood, and decrement in the middle years (45 +) and late adulthood. Subjects older than 75 years lose around 60% of their muscle strength and 30% of their physical function. In this study a linear pattern of age-decline has been observed and this pattern is similar in men and women across the entire course of life ⁷.

In a similar study, we investigated the modifications of muscle mass and strength across ages in a large and unselected sample of Italian and Taiwanese community-dwelling people ⁸. As expected, muscle mass and strength decline with advancing age in both ethnic groups. In particular, compared with younger individuals, those aged 80 + show about 10% lower skeletal muscle mass and 20% lower muscle strength. The pattern of age-related decline in both muscle measures is interestingly analogous in men and women across the age groups studied. The overall shape of the curves is similar between the two samples. Nevertheless, muscle mass and muscle strength are significantly greater in Italian participants relative to Taiwanese individuals in all age groups ⁸.

In light of what has been observed in these population studies, internationally recognized cut-offs have to be found to identify individuals with sarcopenia. These reference values must be specific for age, gender and race.

PREVALENCE OF SARCOPENIA IN DIFFERENT SETTINGS

The prevalence of sarcopenia varies in different studies based on the population studied and the diagnostic criteria adopted. In general, the prevalence and incidence of sarcopenia are very high in older subjects, particularly in institutionalized or hospitalized ones. As expected, sarcopenia is highly prevalent among the population over the age of 65 years and more. However, the prevalence of sarcopenia varies across diverse populations and according to age, gender, and living

setting⁹. Based on results from previous studies, the prevalence of sarcopenia ranges between 5% and 13% among 60- to 70-year-old subjects and between 11% and 50% in those aged 80 years or older¹⁰, depending on the used definition for such condition.

Using the algorithm proposed by the EWGSOP, of 730 participants enrolled into the InCHIANTI study¹¹, 122 (16.7%) subjects living in community were identified as affected by pre-sarcopenia and 55 (7.5%) by sarcopenia. Among them, 39 (5.3%) were sarcopenic because of low gait speed ($n = 19$, 2.6%) or poor grip strength ($n = 20$, 2.3%), whereas 16 (2.2%) had the concomitant presence of reduced muscle strength and slow gait speed. Prevalence of sarcopenia improved with age, from 2.6 and 1.2% respectively in women and men aged 70-74 years, to 31.6 and 17.4% in women and men older than 80 years¹¹.

The prevalence of sarcopenia and the association of such condition with functional and clinical status in older people aged 70 years and older living in nursing homes have been estimated¹². These findings show that sarcopenia-assessed using the EWGSOP algorithm - is highly prevalent in institutionalized older persons (68% among male residents and 21% among female residents)¹².

Among the 770 study participants enrolled in the CRIME study¹³ (mean age: 80.8 ± 7 years; 56% women), 214 (28%) met the EWGSOP criteria for the diagnosis of sarcopenia and 556 (72%) did not at the time of admission in the acute care hospital.

In the sample of 655 older hospitalized patients enrolled in the GLISTEN study¹⁴ (mean age 81.0 ± 6.8 years, 51.9% women), mean skeletal muscle index (SMI), evaluated at admission, was 8.16 ± 2.10 kg/m². The SMI was greater in men ($p < .0001$), was inversely correlated with age ($p < 0.0001$), and related with handgrip strength ($p < 0.0001$) and walking speed ($p = 0.005$). Adopting the EWGSOP algorithm, 227 (34.7%) patients were diagnosed as affected by sarcopenia; of them, 101 (44.5%) were sarcopenic because of low gait speed ($n = 43$, 18.9%) or poor grip strength ($n = 58$, 25.6%), whereas 126 (55.5%) had the concomitant presence of reduced muscle strength and slow gait speed. Of the 169 subjects with walking speed lower than 0.8 m/s at hospital admission, 90 (53.3%) had walking disability and 116 (68.6%) had basic ADL disability in the 2 weeks preceding hospitalization. Finally, prevalence of sarcopenia at the time of hospital admission increased sharply with age, from 11.1% and 30.2% in women and men aged 65-74 years, to 46.7% and 50.7% in women and men older than 85 years, respectively¹⁴.

Among patients without sarcopenia at hospital admission ($n = 394$), 58 participants (14.7%) met the EWGSOP sarcopenia diagnostic criteria at hospital

discharge¹⁵. More than 50% of those who developed sarcopenia during hospital stay showed over 10% muscle mass loss compared with baseline values. Patients who developed sarcopenia were significantly older than those who did not (82.0 ± 7.2 vs 79.2 ± 6.2 years, respectively; $p < 0.01$). Subjects with incident sarcopenia during hospital stay presented significantly lower baseline body mass index compared with participants who did not develop sarcopenia (25.0 ± 3.8 kg/m² vs 27.6 ± 4.9 kg/m², respectively; $p < 0.001$). Likewise, SMI at hospital admission was significantly lower among subjects who developed sarcopenia during hospital stay (8.4 ± 1.5 kg/m² vs 9.0 ± 1.8 kg/m², respectively; $p = 0.01$)¹⁵.

SARCOPENIA RISK FACTORS

The number of risk factors of sarcopenia is high and appears to be rising with recent researches¹⁶. It is well documented that age and sex vary the prevalence of sarcopenia. The ageing process itself changes muscle turnover, with amplified catabolic stimuli and reduced anabolic stimuli¹⁷. Subclinical inflammation can play an important role in these modifications¹⁸. Numerous hormonal deregulations, such as testosterone and the growth hormone, insulin-like growth factor-1 pathways, have been observed during ageing process, as well as changes in neural input. Overall, these modifications have been correlated with the skeletal muscle mass decline and muscle quality changes. Moreover, mitochondrial dysfunction has also been related with muscle mass and ageing¹⁸. Life style habits, including a decrease of food intake and specifically protein intakes, together with sedentary pattern and/or reduced physical exercise during life course, have all been associated with a higher risk of sarcopenia¹⁸. Variations in specific living conditions, such as protracted bed rest, immobility and deconditioning, have documented to increase the incident sarcopenia. Finally, a long list of chronic health conditions (comprising cognitive impairment, mood disorders, diabetes and end-stage organ diseases) has also been related with a loss of muscle mass and strength¹⁸.

Even though sarcopenia is related to many potential risk factors, less food intake and/or loss of appetite (defined as anorexia of aging) are the most common risk factor in older subjects. Recently, the association of anorexia with sarcopenia has been extensively studied¹⁹. These findings show that, in older persons, sarcopenia is correlated with the presence of anorexia, independently of clinical evidence of malnutrition (i.e., weight loss and BMI lower than 20 kg/m²)²⁰. Overall, the results showed that the anorexia is common among

community-dwelling older subjects and suggest that among old-old subjects, the presence of anorexia is associated with sarcopenia, as assessed by means of European Consensus²⁰. Scientific evidence indicates that a significant number of elderly fail to get proper amount and specific types of food necessary to meet essential energy and nutrient needs. Finally, the identification of particular biomarkers that may help in the development of noninvasive tools for the evaluation and monitoring of the relationship between inflammation and muscle wasting situations has been required for a long time²¹. Recent research efforts on definite “danger molecules” that stimulate inflammation and connect this process with muscular mitochondrial dysfunction could improve the comprehension of muscle pathophysiology. Results from numerous studies show the significant contribution of microbial variations and activity in the gut to the repertoire of inflammatory molecules involved in the milieu describing muscle aging. This is an important matter to be addressed by future studies to untangle the signaling pathways that may act as targets for specific interventions²¹.

SARCOPENIA AND NEGATIVE OUTCOMES

Sarcopenia, like all geriatric syndromes, is related to numerous negative outcomes, including increased risk of falling, disability, and mortality²².

The effect of sarcopenia on the risk of falling during a period of 2 years has been studied in a population of older persons aged 80 years and older living in community²². According to these findings, sarcopenia – evaluated using the EWGSOP algorithm – is greatly prevalent among older persons. Also, the rate of such condition does not change across gender. Individuals with sarcopenia are at increased risk of falling regardless of age, gender and other confounding factors²². At the population level, sarcopenia seems to be a risk factor for falls. The assessment of muscle mass, muscle strength and physical performance may provide an important benefit for the risk stratification process for primary prevention of falls. A better understanding of the mechanisms underlying the association between sarcopenia and falls may also help the elaboration of valuable interventions across the life course to preserve muscle function and prevent falls²³.

In the same sample (il SIRENTE study), the association between muscle mass (as measured by calf circumference) and frailty, physical performance, and functional status has been evaluated²⁴. The results show that in older persons, frailty increases and physical function declines as calf circumference decreases. Specifically, after adjustment for potential confounders, frailty index

and physical performance measures (Short Physical Performance Battery score) were directly associated with calf circumference.

The effect of sarcopenia on functional recovery in a population of older persons admitted to an in-hospital rehabilitation unit following hip fracture repair has been recently evaluated²⁵. According to these findings, sarcopenia – assessed using the FNIH criteria – is highly prevalent. Sarcopenia was significantly associated with worse overall functional status, as evaluated using the Barthel index total score, both at the time of discharge from the rehabilitation unit and after the 3-month follow-up²⁵.

The evaluation of the impact of sarcopenia on survival among frail older subjects is an important and intricate issue. In the il SIRENTE study the association between sarcopenia and 7-year mortality has been assessed²⁶. Sarcopenia, as identified by the EWGSOP criteria (muscle mass, muscle strength and physical performance), is associated with mortality in older adults living in the community, independently of age and other clinical and functional variables²⁶.

In the CRIME study, patients with sarcopenia presented a higher mortality rate when compared with those without sarcopenia during hospital stay ($p = 0.007$). During hospital stay, 10 (6%) deaths occurred among patients with sarcopenia and 12 (2%) among those without sarcopenia. The diagnosis of sarcopenia resulted independently associated to mortality during hospital stay either in the unadjusted model (hazard ratio [HR]: 3.19; 95% CI: 1.38-7.38), age- and gender-adjusted model (HR: 3.00; 95% CI: 1.23-7.28), and fully adjusted model (HR: 3.45; 95% CI: 1.35-8.86). Furthermore, patients with sarcopenia presented a higher mortality rate when compared with those without sarcopenia after 12 months from discharge ($p < 0.001$). The diagnosis of sarcopenia resulted independently associated to 1-year mortality in the unadjusted model (HR: 2.12; 95% CI: 1.45-3.10), age- and gender-adjusted model (HR: 1.56; 95% CI: 1.10-2.30), and fully adjusted model (HR: 1.59; 95% CI: 1.10-2.41).

In a study conducted in nursing home, participants with sarcopenia showed the highest risk of death, regardless of age, gender, and other confounding factors²⁷. A total of 26 deaths (11 men and 15 women) occurred during the 6-month follow-up. Fifteen (37.5%) participants died among subjects with sarcopenia compared with 11 subjects (13.4%) without sarcopenia ($p < 0.001$). In the unadjusted model, there was a direct association between mortality and sarcopenia. Similarly, this association was consistent both in male (HR 8.28, 95% CI: 0.87-78.25) and female (HR 2.23, 95% CI: 0.75-7.62) subjects. After adjusting for potential confounders, including age, gender, cerebrovascular diseases, osteoarthritis, COPD, ADL impairment, and BMI, such

association remained statistically significant although somewhat less strong than that derived from the crude analysis. In the fully adjusted model, participants with sarcopenia had a higher risk of death for all causes compared with non-sarcopenic subjects (HR 2.34, 95% CI: 1.04-5.24) ²⁷.

POTENTIAL TREATMENT FOR SARCOPENIA

Nutrition and physical exercise are the cornerstones of intervention in sarcopenia ²⁷. Resistance exercise training improves muscle strength and mass and increases protein deposit in skeletal muscles ²⁸. Aerobic exercise training may also benefit ageing skeletal muscle and improve insulin sensitivity. Improvement of nutritional deficits is also needed. Caloric intake should be increased to cover increased demands posed by exercise. Protein requirements are also increased, with recommended intakes of proteins in sarcopenic patients of > 1.2 g of protein per kilogram of body weight per day, except in patients with significant renal failure ²⁹. Leucine, β -hydroxy β -methylbutyrate (HMB), creatine and some milk-based proteins may have beneficial effects on protein balance in skeletal muscle ³⁰. Correction of vitamin D deficiencies is needed for proper muscle function, but the role of vitamin D in the presence of normal blood levels is yet to be determined ³¹. No drug is currently approved for the treatment of sarcopenia. Studies with anabolic hormones have been disappointing. The next generation of drugs is directed at exploring inhibition of myostatin and manipulation of the neuromuscular junction ³².

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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