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REVIEW

Sarcopenia: a predictor of mortality and the need for early diagnosis and intervention

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Abstract The term sarcopenia refers to the loss of muscle mass that occurs with aging. Sarcopenia is defined by the European Working Group on Sarcopenia in Older People (EWGSOP) as low muscle mass and low muscle function (strength and performance). Its prevalence varies depending on the definition used for it, but estimates propose a loss of approximately 8 % per decade until the age of 70 years; afterwards, the loss increases and ranges from 13 to 24 % per decade. Irrespective of how sarcopenia is defined, both low muscle mass and poor muscle strength are highly prevalent and important risk factors for disability and increased mortality in individuals as they age. In this review, we address age-related muscle loss and the risk factors of mortality, emphasizing the need for early diagnosis and intervention.

Keywords Sarcopenia · Mortality · Disability · Aging

Introduction

Sarcopenia is a condition that is characterized by progressive and generalized loss of muscle mass and strength with a high risk of adverse outcomes, such as decreased physical performance, poor quality of life and death [1–4]. From a histological point of view, sarcopenia is characterized by a decrease in the number and size of the muscle fibers [5]. The term "sarcopenia", coined by [6], originates from the Greek words *sarx* (flesh) and *penia* (loss) [7]. Nevertheless, clinicians and researchers are largely unaware of the term "sarcopenia". Often, this term is mistakenly confused with other definitions, such as cachexia (loss of skeletal muscle mass due to disease) or atrophy (loss of skeletal muscle mass due to inactivity) [8]. The term 'sarcopenia' was originally defined as a decrease in muscle mass related to aging [9]. However, it has since become a general term to define loss of muscle mass and muscle strength related to aging [10]. Recently, studies have shown that decreased muscle strength is more pronounced than the reduction in muscle mass among the elderly [3, 11–14], and muscle strength is a better predictor of disability [15]. Newman et al. [3] demonstrated that low muscle mass did not explain the strong association of strength with mortality, demonstrating that muscle strength is more important than quantity as a marker of muscle quality in estimating mortality risk. For this reason, the European Working Group on Sarcopenia in Older People (EWGSOP) developed an algorithm to diagnose sarcopenia based on three criteria: decrease of muscle strength, reduced muscle mass and impaired physical performance [16].

The causes of sarcopenia are multifactorial and can include many factors, such as physical inactivity, decreased mobility, slow gait, and poor physical endurance. These factors are linked with motor unit loss, declines in mitochondrial biogenesis and chronic inflammatory processes [1, 17, 18], and they are thought to perpetuate the loss of muscle throughout the aging process through mechanisms that are not fully understood [18, 19]. Furthermore, aging

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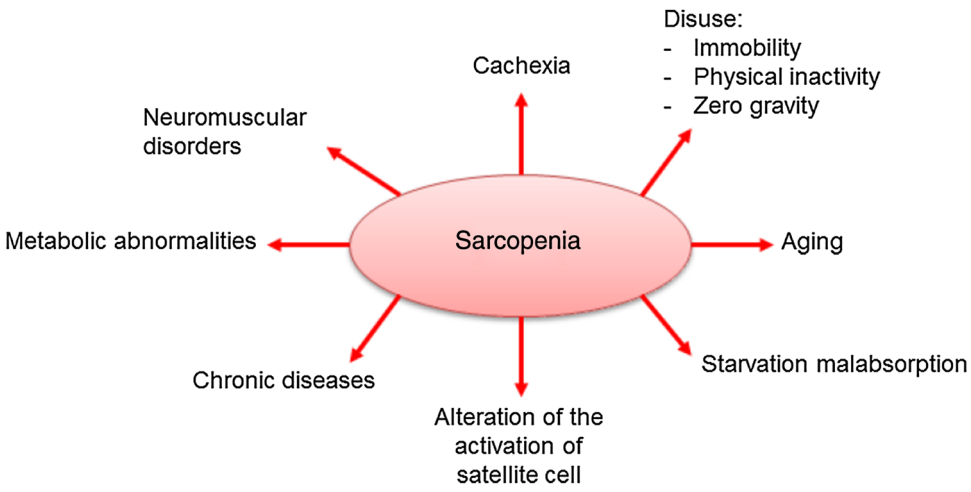

Fig. 1 Conditions potentially leading to sarcopenia. Sarcopenia can be observed at any age and can result from inflammatory diseases, malnutrition, disuse or endocrine disorders. These conditions may act as accelerants of the underlying causes of age-related sarcopenia

and physical disability are related to an increase in fat mass, particularly visceral fat [20], which is correlated with the development of metabolic syndrome and cardiovascular disease [21], which consequently increase mortality [22].

The prevalence of sarcopenia varies depending on the definition used, but estimates propose a loss of approximately 8 % per decade until the age of 70 years, and after that age, the loss increases and ranges from 13 to 24 % per decade [23, 24]. Using data from China, Lau et al. [25] found a 12.3 % prevalence of sarcopenia in men and 7.6 % in women. Additionally, Wu et al. [26] used data from a Taiwanese population and Silva et al. [13] used data from a Brazilian population to find rates of 6.5 and 16.1 % in women and 8.2 and 14.4 % in men, respectively.

Although many studies have looked at the prevalence of sarcopenia, the actual costs caused by this disability are much more difficult to identify. The estimated direct healthcare costs attributable to sarcopenia in the USA in 2000 were $18.5 billion ($10.8 billion for men and $7.7 billion for women), which represented approximately 1.5 % of the total healthcare expenditures for that year. A 10 % reduction in the prevalence of sarcopenia would result in savings of $1.1 billion (dollars adjusted to 2000 rate) per year in US healthcare costs [27]. Few studies have estimated the prevalence and cost attributable to sarcopenia in Latin America.

The observed cost of this disability is reflected in the growing number of clinical trials seeking to improve the lives of people with sarcopenia. Currently, 62 trials have been described on www.clinicaltrails.gov for sarcopenia in the USA and two trials in Brazil. These trials have tested different types of nutrition, training resistance, insulin, testosterone, dietary supplements, electrostimulation, and an experimental drug. Given the increasing search for therapy for sarcopenia, the cost-effectiveness on screening strategies will be important.

Methods

In this review, the selection of articles was performed using the following criteria: published during the last 10 years; available in the websites Pubmed, Scielo, Lilacs and Medline; written in English, Spanish or Portuguese; and reporting cohort or cross-sectional studies. The key words used for the search were “aging sarcopenia” and “mortality”.

Assessment methods and prevalence of sarcopenia

Sarcopenia is a syndrome characterized by progressive, generalized loss of skeletal mass and strength with a risk of adverse outcomes, such as physical disability, poor quality of life and death [16].

Different mechanisms may be involved in the onset and progression of sarcopenia, such as aging, physical activity reduction, metabolic abnormalities (especially in proteins, carbohydrates, and lipids), neuromuscular disorders, impaired cognition, chronic diseases, and changes in the activation of satellite cells [22, 28, 29] (Fig. 1).

Early definitions of sarcopenia are based exclusively on muscle mass in relation to the range of muscle mass within a reference population [1, 28]. Currently, there is no widely accepted operational definition for sarcopenia nor is there a group of instruments for evaluating sarcopenia. Recently, the EWGSOP, via an algorithm of sarcopenia diagnosis, recommends the use of both low muscle mass and low muscle function (strength and performance) [16] for diagnosing sarcopenia. The algorithm is based on the preliminary screening of low gait speed (threshold established at ≤ 0.8 ms^{-1}) and low handgrip strength (lowest quartile of the sample distribution). The rationale for the use of two criteria is that the muscle strength does not depend solely on the muscle mass and the relationship between strength and mass is not linear [1].

Table 1 Prevalence and assessment methods for the diagnosis of sarcopenia

	Design	Subjects	Definition	Assessment method	Prevalence of sarcopenia	Reference
NMEHS (USA)	Population-based survey	>60 years	ASM/height^2 <2SD mean of a young reference population	Anthropometric equation for predicting ASM (sub study: DEXA-$R^2 = 0.82$)	70 years: 13–24 % ≥80 years: >50 %	[42]
NHANES III (USA)	Cross-sectional survey	≥60 years	SMI (%; total SMI [kg]/weight [kg] ×100) *Sarcopenia class I:* <1–2 SD *Sarcopenia class II:* >2 SD below the mean of young subjects	BIA	*Sarcopenia class I:* men: 45 % women: 59 % *Sarcopenia class II:* men: 7 % women: 10 %	[1]
ilSIRENTE study (Italy)	Prospective cohort study (7-year)	80–85 years	EWGSOP criteria: ↓ muscle function (strength or performance) and ↓ muscle mass	Muscle mass: MAMC; Physical performance: 4-m walking test; Muscle strength: hand grip strength	Men: 25.7 % women: 19.8 %	[33]
AAH Study	Cross-sectional survey plus Prospective cohort study (6-year)	52–68 years	SCWD criteria: limited mobility (with ↓ ASM) and gait speed walk ≤1 m/s or with a 6-min walk distance less than 400 m	Muscle mass: DEXA	Sarcopenia: 4 % Sarcopenia with limited mobility: 1.3 %	[37]
Sabe Study (Brazil)	Cross-sectional survey	60–64 years	EWGSOP criteria: ↓ muscle function (strength or performance) and ↓ muscle mass	Muscle mass: estimated by ASM Physical performance: gait speed (in m/s) Muscle strength: hand grip strength	Men: 14.4 % women: 16.1 %	[20]

NMEHS New Mexico Elder Health Study, *NHANES III* Third National Health and Nutrition Examination Survey, *ilSIRENTE study* Invecchiamento e Longevità nel Sirente study, *AAH* African American Health, *SABE Study* Saúde, Bem-Estar e Envelhecimento/Health, Wellbeing and ageing Study, *ASM* appendicular skeletal muscle mass, *SMI* skeletal mass index, *EWGSOP* European Working Group on Sarcopenia in Older People, *SCWD* Society on Sarcopenia, Cachexia, and Wasting Disorders, *SD* standard deviation, *BIA* bioelectrical impedance assessment, *DEXA* dual-energy X-ray absorptiometry, *MAMC* mid-arm muscle circumference

However, other sarcopenia criteria have been proposed, including muscle mass, muscle function and physical performance (Table 1). The prevalence of sarcopenia changes depending on the definition used (Table 1), but estimates propose a loss of approximately 8 % per decade until the age of 70 years, and after that age, the loss increases and ranges from 13 to 24 % per decade [23, 24]. Few studies demonstrate data on sarcopenia in the Brazilian population [13, 30, 31], as listed in Table 1.

It is important to emphasize the need for well-established diagnostic criteria that are accepted in international literature. In addition to wide acceptance, it should also be easy to use the criteria in the clinical practice. Therefore, analyzing the presence of sarcopenia would be another early screening test for the elderly, and measures to counteract this disability could be initiated as soon as possible.

Sarcopenia as a marker of mortality

Sarcopenia has been considered a mortality predictor and has been investigated in different settings, such as in communities, nursing homes, and hospitals. The available prospective studies show an association between strength losses or functional measures and mortality rather than muscle mass per se [3]. Newman et al. [3] examined mortality rates in the Health, Aging and Body Composition (Health ABC) Study in African American people. After an average follow-up of 4.9 (standard deviation 0.9) years, the authors concluded that the low muscle mass did not explain the strong association of muscle strength with mortality. Moreover, they demonstrated that grip strength provided a risk estimate that was similar to the estimate using quadriceps strength. Mobility impairment alone is strongly associated with disability and mortality. Afilalo et al. [32] proposed a multicenter prospective cohort study to test the value of gait speed, a clinical marker for frailty, to improve the prediction of mortality and major morbidity in elderly patients undergoing cardiac surgery. The authors concluded that slow gait speed is an independent predictor for a higher risk of mortality and major morbidity after cardiac surgery. In a recent study, Atkins et al. [33] examined the associations between sarcopenia, obesity, and sarcopenic obesity with the risk of cardiovascular disease (CVD) and all-cause mortality in older men. The authors concluded that the sarcopenic obese men had the highest risk of all-cause mortality, but not of cardiovascular disease mortality.

On the other hand, some studies established an association between loss of fat-free muscle mass and high abdominal obesity, which was measured by the waist–hip ratio with mortality among older people [34–37].

In another study, Landi et al. [38] analyzed the impact of sarcopenia on the risk of all-cause death in a population of frail elderly people living in the community as part of a prospective cohort study (7 years). According to the EWGSOP-suggested criteria, 43 subjects with sarcopenia (21.8 %) were identified. During the 7-year follow-up, 29 (67.4 %) participants died among subjects with sarcopenia compared to 63 subjects (41.2 %) without sarcopenia ($p < 0.001$). After adjusting for potential confounders, participants with sarcopenia had a higher risk of death for all causes compared with non-sarcopenic subjects (hazard ratio [HR] 2.32, 95 % confidence interval [CI] 1.01–5.43). Arango-Lopera et al. [39], using EWGSOP in Mexican population, gave a global estimate of the sarcopenia prevalence of 33.8 % in community-dwelling individuals older than 70 years, and they showed an increase in the mortality risk in those subjects identified as sarcopenic. This increased risk was found to be independent of other mortality risk factors.

Landi et al. [40], using EWGSOP criteria in elderly persons aged 70 years and older who were living in a nursing home in Italy, reported that the prevalence of sarcopenia was approximately 32.8 %. The authors demonstrated that this condition is more common in men (68 %) than in women (21 %). After adjusting for age, gender, cerebrovascular diseases, osteoarthritis, chronic obstructive pulmonary disease, activity of daily living impairment, and body mass index, residents with sarcopenia were more likely to die compared with those without sarcopenia (adjusted HR 2.34; 95 % CI 1.04–5.24) during the 6 months of follow-up. The authors concluded that sarcopenia is highly prevalent in nursing homes residents, and it can have an independent effect on the survival of these individuals. Volpato et al. [41] used the same criteria as in previous studies (EWGSOP criteria) and found a sarcopenia prevalence of 31.6 % in women and 17.4 % in men. Higher education (odds ratio [OR] 0.85; 95 % CI 0.74–0.98), lower insulin-like growth factor I (lowest vs. highest tertile, OR 3.89; 95 % CI 1.03–14.1), and low bioavailable testosterone (OR 2.67; 95 % CI 1.31–5.44) were independently associated with the likelihood of having sarcopenia.

Malmstrom et al. [42] investigated, in a population-based analysis of African American health, the prevalence of sarcopenia and health outcomes. They concluded that low ASM with limited mobility was associated with poor health outcomes among late middle-aged African Americans. Importantly, this study showed that low ASM with limited mobility is a significant predictor of mortality, and it is associated with activities of daily living disability, instrumental activities of daily living disability, and frailty status at the 6-year follow-up. On the other hand, low ASM alone was only marginally associated with mortality and was not associated with any other study outcomes. Low muscle mass alone does not adequately capture the geriatric syndrome of sarcopenia [43].

Blain et al. [44] showed that poor balance and mobility are significant predictors of 8-year mortality independent of baseline and intermediate events in pre-disabled women aged 75 years and older, suggesting that they may reflect a certain failure to adequately respond in the face of present and future medical and non-medical events. Although different parameters were used, all of these studies concluded that loss of strength and function is associated with increased mortality in these individuals.

Although data exist on the prevalence of sarcopenia in community-dwelling older individuals and nursing home residents, there are few studies on hospitalized older patients according to newly developed criteria. Gariballa et al. [45] evaluated, through EWGSOP criteria, patients with different clinical features within 72 h of admission as well as after 6 weeks and after 6 months. The length of the hospital stay was significantly longer in patients diagnosed with sarcopenia compared to patients without sarcopenia ($p = 0.003$). The risk of non-elective readmission in the 6-month follow-up period was significantly lower in patients without sarcopenia compared with those diagnosed with sarcopenia ($p = 0.013$). Additionally, the death rate was lower in patients without sarcopenia compared with those with sarcopenia ($p = 0.001$). Recently, Smoliner et al. [46] performed a cross-sectional study in an acute geriatric ward of a general hospital. In this study, sarcopenia was defined according to the EWGSOP criteria. The authors reported that 25.3 % of patients had sarcopenia, and 6.6 % were defined as sarcopenic, while 18.7 % were defined as severely sarcopenic. In a group comparison, patients with sarcopenia had a poorer nutritional status. In binary logistic regression analysis, only the body mass index was associated with sarcopenia, whereas gender, age, length of stay, cognitive function, and self-care capacity were not. Although most recent studies on sarcopenia used the EWGSOP criteria, these criteria are not the only diagnosis criteria used. For more accurate comparisons between studies, articles should standardize the diagnosis criteria for sarcopenia. However, it is clear that features of sarcopenia, such as low muscle mass, muscle weakness and decreased mobility, are linked to poor quality of life and higher mortality risks.

Conclusions

Geriatric syndromes are common, complex and costly states of impaired health in older individuals. Geriatric syndromes result from incompletely understood interactions of disease and age in multiple systems, producing a constellation of signs and symptoms. Sarcopenia is considered a geriatric syndrome; it represents a significant change in health status and is associated with adverse outcomes, such as falls, fractures, functional decline, increased mortality, and low quality of life. Therefore, the early diagnosis of sarcopenia is critical for preventing these adverse outcomes, and it is useful for establishing participant selection criteria and outcome measures for trials of pharmaceutical or other interventions. Nevertheless, sarcopenia can be used as a screening tool to identify adults and the elderly who are at risk of developing premature types of disability and medical conditions that may increase the risk of death. More studies are needed to establish the best criteria for diagnosing sarcopenia as well as to develop therapeutic interventions. Focusing on early diagnosis and interventions will in turn decrease the costs associated with this disability.

Conflict of interest The authors have no conflicts of interest to report.

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