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REVIEW

Sarcopenia: an overview

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Abstract Sarcopenia, the age-dependent loss of muscle mass and function, is a common condition among older adults, and is associated with several adverse health outcomes. Owing to the impact of sarcopenia on quality of life, disability and mortality, a greater awareness is necessary in order to correctly identify the condition both in community and geriatric settings. Research on sarcopenia prevention and treatment is developing quickly, but many questions are still unanswered. The core of the sarcopenia condition involves quantitative and qualitative losses of skeletal muscle. These two dimensions should therefore be considered when designing and testing preventive and therapeutic interventions. The recently released operationalization of sarcopenia by the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project allows for the framing of an objective, standardized, and clinically relevant condition, which should facilitate its translation into the clinical arena as well as its adoption by public health and regulatory agencies. Such a conceptualization might eventually encourage key stakeholders to combine their efforts in approaching the sarcopenia condition. Bearing these considerations in mind, the "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" project has operationalized a specific condition, named physical frailty and sarcopenia (PF&S), characterized by the combination of low physical performance (based on the Short Physical Performance Battery) and low muscle mass (according to the FNIH cut-points). A randomized controlled trial will be conducted to evaluate the efficacy of a multi-component intervention for preventing mobility disability and other adverse health outcomes in older adults with PF&S.

Keywords Muscle mass · Muscle strength · Physical function · Disability · Prevention · Treatment

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Introduction

Sarcopenia is the age-related decline in skeletal muscle mass concomitant with decreased strength and/or function [1]. The concept of sarcopenia is being encountered with increasing frequency in clinical practice and research not only in geriatric medicine, but also in a wide range of other medical specialties [2]. While sarcopenia is a highly prevalent condition with enormous personal and societal costs, a unique operational definition has not yet been achieved. As a consequence, no definite treatment guidelines are presently available [3].

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In 1989, Irwin Rosenberg [1] coined the term 'sarcopenia' (Greek "sarx" or flesh + "penia" or paucity) to describe the age-related decrease of muscle mass. Subsequently, the term has been used to indicate the co-occurrence of loss of skeletal muscle mass and strength in advanced age [4]. From a pathophysiologic perspective, sarcopenia can be considered an organ failure (i.e., "muscle insufficiency") which can develop chronically (more often) or acutely (e.g., during hospital stay and prolonged bed rest).

Past the age of 40, healthy adults lose approximately 8% of their muscle mass every 10 years. Hence, between 40 and 70 years, healthy adults lose an average of 24% of muscle, which accelerates to 15% per decade past the age of 70 [5]. A recent systematic review found that the prevalence of sarcopenia, operationalized according to the European Working Group on Sarcopenia in Older People (EWGSOP) criteria [6], was 1–29% in the community, 14–33% in long-term care setting, and 10% in acute hospital care, with substantial variations depending on age and geographic area [7].

What is sarcopenia?

Despite the high prevalence and detrimental consequences of sarcopenia, the condition is still orphan of an univocal operational definition. A practical clinical definition of sarcopenia was developed by the EWGSOP [6]. Accordingly, sarcopenia is described as "a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death" [6]. As recommended by the EWGSOP [6], the identification of sarcopenia should be based on the co-occurrence of low muscle mass and low muscle function (strength or performance).

The rationale for using two defining parameters resides in the fact that, although muscle mass and strength are related to one another, their trajectories of decline during aging do not overlap. Indeed, the decline in muscle strength is much greater than that predicted by the decrease in mass [8]. Furthermore, muscle strength is a stronger predictor of adverse outcomes than muscle mass [9, 10]. Hence, defining sarcopenia only in terms of muscle mass would be of limited clinical value. Some authors have argued that the term dynapenia is better suited to describe age-associated loss of muscle strength and function [11]. Nevertheless, muscle mass per se has shown to predict survival in older adults [12, 13]. It may therefore be expected that the co-existence of low muscle mass and reduced muscle strength/function would identify a population of older persons at especially high risk of adverse health outcomes.

Risk factors for sarcopenia

Several risks factors may contribute to the development of sarcopenia (Fig. 1). All conditions related to reduced muscle activity predispose to sarcopenia (e.g., sedentary lifestyle, hospitalization, immobilization, prolonged bed rest). Certain diseases can also promote the development of sarcopenia through chronic inflammation and metabolic derangements, such as endocrine disorders, malignancies, chronic inflammatory diseases, and advanced organ failure

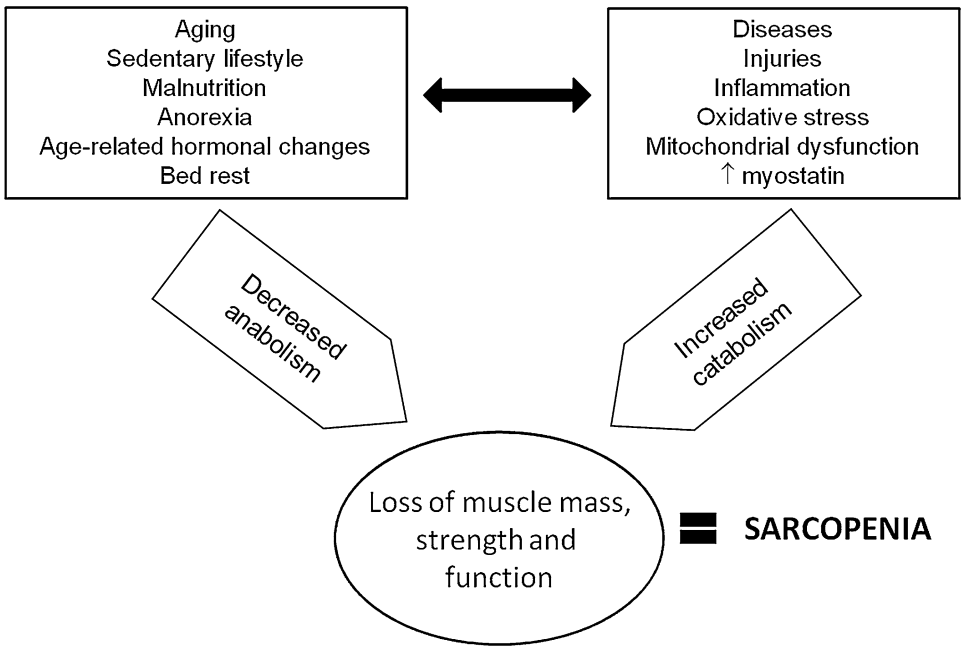

Fig. 1 Major risk factors for sarcopenia

(heart, lung, liver, kidney or brain) [14]. Finally, nutrition has a great impact on muscle health by influencing myocyte homeostasis and energy metabolism. In particular, inadequate intake of energy and/or proteins due to malabsorption, gastrointestinal disorders or the use of anorexigenic drugs has been linked to sarcopenia [15].

Simplifying, the risk factors for the development of sarcopenia can be grouped into different categories:

A. *Personal factors* It is well established that age per se and gender impact the prevalence of sarcopenia [2]. Furthermore, early-life events, including low birth weight, increase the risk of sarcopenia in later life, and various genetic characteristics influence muscle metabolism and turnover over the course of life [16].
B. *Hormonal factors and inflammation* Derangements of several hormonal pathways (e.g., testosterone, estrogens, growth hormone, insulin-like growth factor-1) have been described with aging and are associated with declining muscle mass [17]. Chronic low-grade (subclinical) inflammation, a hallmark of the aging process, is also involved in the pathogenesis of sarcopenia [18, 19]. Finally, mitochondrial dysfunction in myocytes is thought to be a major contributor to muscle loss with aging [20].
C. *Lifestyle habits* Lifestyle choices, including decreases in food intake and particularly protein intake [21], sedentary behavior or reduced physical activity over the life course, alcohol abuse, and tobacco use, have all been associated with a high risk of sarcopenia [2]. Furthermore, protracted bed rest and immobility cause weightlessness and are responsible for dramatic muscle loss in older adults [22].
D. *Chronic health conditions* Many long-lasting health conditions (including cognitive impairment, mood disturbances, diabetes, and end-stage organ diseases) are associated with accelerated loss of muscle mass and strength [2].

Sarcopenia and negative outcomes

A growing body of evidence supports the relationship between sarcopenia and several negative health outcomes. In particular, sarcopenia has been linked to falls, physical frailty and disability. Sarcopenia has also been linked to mortality in different care settings. An observational study carried out in a population of elderly persons aged 70 years and older in Italy showed that sarcopenia was highly prevalent among nursing home residents, and associated with a significantly increased risk of all-cause mortality [23]. A later study from the same group showed that older community-dwellers with sarcopenia had a significantly higher risk of death for all causes compared with non-sarcopenic peers over 7 years of follow-up [24]. Sarcopenia was also associated with increased in-hospital and 1-year mortality in older adults admitted to acute care wards [25]. These results are consistent with those obtained by the CRIteria to assess appropriate Medication use among Elderly complex patients (CRIME) study [26], a multicenter observational study involving 770 in-hospital patients. In another study, sarcopenia was shown to be independently predictive of higher complication rates, discharge disposition, and in-hospital mortality in older emergency surgery patients [27].

Recently, the National Health and Nutrition Examination Survey (NHANES) III [28] showed that women with sarcopenia and sarcopenic obesity had a higher mortality risk than those with normal body composition. The risk of death associated with sarcopenia and sarcopenic obesity was not significant in men.

Sarcopenia has also been linked to falls. In a study conducted in a community population, sarcopenic participants were over three times more likely to fall during a follow-up of 2 years than those without sarcopenia, regardless of age, gender and other possible confounding factors [29]. Finally, sarcopenia and osteoporosis, which are believed to share common pathogenic pathways, have also been linked [30–32]. A study demonstrated a higher prevalence of osteoporosis in sarcopenic hip-fractured women [33].

Identification of sarcopenia

Identifying older adults with sarcopenia in clinical practice is an important task, because it may allow for implementing therapeutic strategies to impede the progression toward disability and other adverse health outcomes. As previously argued, regardless of the operational definition, the diagnosis of sarcopenia requires documentation of low muscle mass plus reduced muscle function (strength or performance) [6].

Quantification of muscle mass

A wide range of techniques can be used to quantify muscle mass [7]. Cost, availability and ease-of-use should determine which technique is better suited to the specific setting.

Imaging techniques and bioelectric impedance analysis (BIA) are among the most popular approaches [34]. With regard to imaging, computed tomography (CT) and magnetic resonance imaging (MRI) are considered to be the gold standard methods for quantifying muscle mass, owing to their abilities to separate fat from other soft tissues. High cost, technical complexity, limited access to the equipment at some sites and concerns about radiation exposure (for CT) limit the use of these whole-body imaging methods for

routine clinical practice. Dual energy X-ray absorptiometry (DXA) is an attractive alternative approach to differentiate fat, bone mineral and lean tissues. This whole-body scan exposes the person to minimal radiation. The main disadvantage is that the equipment is not portable, which may preclude its use in large-scale epidemiological studies [6, 34].

BIA provides an estimate of fat and lean body mass. The test is inexpensive, easy to perform, readily reproducible and appropriate for ambulatory and bedridden patients. BIA measurement techniques, conducted under standard conditions, have been studied for over 10 years, and results found to correlate nicely with MRI scans. Prediction equations have been validated for multiethnic adults and reference values established for adult white men and women, as well as older persons. Thus, BIA may be a valid portable alternative to DXA [6, 34].

On the other hand, BIA and especially DXA may not be available in primary care settings [35]. In such a situation, anthropometric measurements could be very practical for the initial assessment of sarcopenia [36, 37]. Anthropometry offers the most portable, commonly applicable, inexpensive and non-invasive technique for assessing the size, proportions and composition of the human body. For these reasons, anthropometric measures are utilized in many contexts to screen for or monitor diseases among children and young people. Conversely, anthropometry is relatively less used and thus less standardized among older adults. Nevertheless, mid-arm muscle circumference and calf circumference have shown to reflects both health and nutritional status and predicts performance, health and survival in older people [36, 37]. However, age-related changes in fat deposits and loss of skin elasticity contribute to errors in body composition estimation in old age. For this reason, anthropometric measures are not recommended to diagnose sarcopenia in older and obese people [6].

Measurement of muscle strength

The best validated techniques to measure muscle strength are handgrip strength and knee flexion/extension testing. Grip strength is a good, simple and inexpensive measure of muscle strength. A well-studied model of handheld dynamometer with reference populations can be a reliable surrogate of more sophisticated measures of muscle strength of either upper or lower extremities. Indeed, handgrip strength is strongly related with lower extremity muscle power and knee extension torque as well as with calf cross-sectional muscle area [38]. The technique has received validation in older populations and is related to relevant outcomes, such as incident disability in the activities of daily living (ADL) [6].

Strength of the lower limbs can be measured isometrically or isokinetically. Isometric strength tests the maximum number of voluntary contractions and is usually measured as the force applied to the ankle, with the subject seated on an adjustable straight-back chair, the lower leg unsupported and the knee flexed at 90° [6]. Measurement of knee flexion/extension can easily be conducted in frail older people and some data are available for older populations [6], but more information is needed from a wider range of ages and ethnicities. These techniques are mostly applied in research studies and their use in clinical practice is limited by the need for special training and equipment.

Assessment of physical performance

A diverse selection of tests of physical performance are available, including gait speed, the Short Physical Performance Battery (SPPB), the 6-min walk test and the stair climb power test.

The SPPB is a composite of three separate tests that assess balance, gait, and strength by examining an individual's ability to stand with the feet in side-by-side, semi-tandem and tandem positions, time to walk 4 m, and time to rise from a chair and return to the seated position five times [39]. An international working group has recommended that the test be used as a measure of functional outcomes in clinical trials for frail older persons [40]. The SPPB can also be used as an effective standard measure of physical performance in clinical practice.

Usual gait speed is part of the SPPB, but it can also be used as a single parameter for clinical practice and research [41]. A non-linear relationship between leg strength and usual gait speed has been found, explaining how small changes in physiological capacity may have substantial effects on performance in frail adults, while large changes in capacity have little or no effect in healthy adults [41].

Timed get-up-and-go test (TGUG) can also serve as a performance measurement. It measures the time needed to complete a sequence of actions (stand up from a chair, walk a short distance, turn around, return and sit down again). It thus serves as an assessment of dynamic balance and is scored on a five-point scale [6].

Stair climb power test may be of some use in research settings. The test has been proposed as a clinically relevant measure of leg power [6].

Interventions against sarcopenia

Nutrition and physical exercise are the two most important components of any intervention for sarcopenia [6]. The many advantages of physical exercise have been repeatedly demonstrated in different fields of medicine and in

the prevention and outcomes of metabolic, cardiovascular and oncologic diseases [22]. Resistance exercise training increases muscle strength and mass and improves protein accretion in skeletal muscles. Aerobic exercise training is thought to also improve insulin sensitivity [42].

A recent review examined the effect of physical exercise in several studies focused on sarcopenia [7]. Most exercise trials had evidence of improved muscle strength and physical performance, but only three of the seven studies found increases in muscle mass. The results suggest that combining various types of exercise into a program may improve muscle strength and physical performance more than a single exercise regimen. All the trials considered were carried out in frail, sedentary, community-dwelling older individuals. Investigations involving other populations are still anecdotal and were thus not considered. No trials existed that recruited individuals based on their sarcopenic status. Most of the exercise studies had a limited number of participants and were generally conducted within a single country [7].

The correction of nutritional deficits represents another major objective when dealing with sarcopenia [43]. The recommended daily protein intake in sarcopenic older adults is >1.2 g per kg of body weight, with an exception for persons with significant kidney dysfunction [7, 44]. Although nutritional intervention is considered to be one of the standard approaches in the management of sarcopenia, large clinical trials using standardized approaches with single or complex nutritional interventions are still lacking. Five studies failed to demonstrate a consistent effect of protein supplementation on muscle mass and function [7]. The same occurred for essential amino acid supplementation (in particular leucine), which showed only a small effect on muscle mass and function [7]. There is some evidence to suggest that β-hydroxy β-methylbutyrate (HMB), creatine and some milk-based proteins may have beneficial effects on protein balance in skeletal muscle [7]. The correction of vitamin D deficiency is also needed for proper muscle function and is generally recommended, but the efficacy of supplementation in the presence of normal blood levels is debated and so are its effects in sarcopenia [7].

No drug is currently approved for the treatment of sarcopenia and studies with anabolic hormones failed to find any clinically meaningful effect [45].

Why SPRINTT?

The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) is a project being conducted under the auspices of Innovative Medicine's Initiative (IMI) [46]. SPRINTT focuses on the newly operationalized physical frailty and sarcopenia (PF&S) condition [47]. This project aims at addressing academic, regulatory, and operational challenges associated with the study of older adults with PF&S in order to develop new treatment approaches addressing this unmet medical need. Amongst other important elements, the SPRINTT project intends to reach a clinical consensus over PF&S, develop a regulatory work-stream, and sponsor a randomized controlled trial comparing the effects of a multi-component intervention (based on physical exercise, nutritional counseling, and information and communication technology) in community-dwelling older persons with PF&S. The trial should allow clear characterization of the condition and support the identification of those individuals who may most benefit from therapeutic interventions [46].

Although physical frailty encompasses only a part of the wide spectrum of frailty, the identification of a definite pathophysiological basis (i.e., decline in skeletal muscle mass and function) opens new venues for the development of interventions to slow or reverse the progression of this condition [48]. In other words, sarcopenia might be considered both the biological substrate for the development of physical frailty and the pathway through which the negative health-related outcomes of frailty ensue [49].

To date, no large-scale intervention study specifically targeting frail European older persons has been conducted [6]. In this scenario, the SPRINTT project represents the first attempt to (1) identify a precise subset of frail elderly with unmet medical needs, and (2) implement a multi-component intervention aimed at preventing incident disability and other major negative health-related events. The main feature of the SPRINTT target population is represented by the PF&S syndrome [48, 49], defined by poor physical performance according to the SPPB and low muscle mass [based on the cutoffs recommended by the the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project] [50].

The recent reports by the FNIH initiative have caused a re-evaluation of previously existing operational definitions of sarcopenia (including the one proposed by the EWGSOP) that were largely based on experts' consensuses. Indeed, findings of the FNIH were generated through ad hoc analyses of multiple cohort studies of older persons. More specifically, the FNIH project recommended two alternative gender-specific measures used to define low muscle mass [51]. The first criterion [i.e., appendicular lean mass (ALM)-to-body mass index (BMI) ratio, ALM_{BMI}] is the one recommended by the FNIH project, while the second (i.e., crude ALM) is proposed as an alternative. Given the relevance of the FNIH initiative and the adopted approach, these definitions might be easily considered the current "best practice" for defining low muscle mass in the elderly. In SPRINTT, it was therefore decided to follow the FNIH recommendations. Thus, each potential participant is

considered to be "eligible" only if presenting an ALM_{BMI} below the gender-specific cut-points indicated in the FNIH reports [51]. When this first recommended criterion is not fulfilled, the individual is then tested with the alternative criterion (based on the crude ALM) to verify the true absence of a sarcopenic phenotype. This approach does not only render feasible the recruitment of participants in the clinical trial, but will also allow the conduction of pre-planned and post-hoc analyses aimed at refining the PF&S operational definition at the end of the SPRINTT project on the basis of the collected data. In fact, the combination of the two criteria will lead to the recruitment of participants with a sufficiently wide spectrum of body composition profiles. Within this wider range, it will then be possible to identify which characteristics impact the response to the interventions.

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Compliance with ethical standards

Conflict of interest The authors of the present work are partners of the SPRINTT Consortium, which is partly funded by the European Federation of Pharmaceutical Industries and Associations (EFPIA). E.M. served as a consultant for Huron Consulting Group, Genactis, and Novartis. M.C. served as a consultant for and/or received honoraria for scientific presentations from Nestlé.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, informed consent is not required.

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