MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

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Sarcopenia: a narrative review on definition, diagnosis, and management

ARTIGO DE REVISÃO

ÁREA CIENTÍFICA DE MEDICINA

Trabalho realizado sob a orientação de:
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ABRIL/2022

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SUMMARY

ABBREVIATIONS LIST

1RM – One repetition maximum

ASM – Appendicular skeletal muscle mass

BIA – Bioelectrical Impedance Analysis

BMI – body mass index

BSGG – Belgian Society of Gerontology and Geriatrics

CT – Computed Tomography

DXA – Dual-energy X-ray Absorptiometry

EAA – Essential amino acids

EWGSOP – European Working Group on Sarcopenia in Older People

EWGSOP2 – European Working Group on Sarcopenia in Older People, revision

F-A-C-S – Find-Assess-Confirm-Severity algorithm

HBM – β-hydroxy-β-methylbutyrate

ICSFR – International Conference on Sarcopenia and Frailty Research

IGF-1 – Insulin-like growth factor-I

MRI – Magnetic Resonance Imaging

PS – Protein supplementation

QoE – Quality of evidence

QoL – Quality of life

RT – Resistance training

SARMs – Selective androgen receptor blockers

SCWD – Society of Sarcopenia, Cachexia and Wasting Disorders

SMM – Skeletal muscle mass

SNPs – Single nucleotide polymorphisms

SPPB – Short Physical Performance Battery Protocol

TNF-α – tumor necrosis factor-α

TUG – Timed-Up and Go test

ABSTRACT

Sarcopenia is a common age-related condition with progressive and adverse muscle changes resulting in declines in strength, muscle mass, and physical performance. It has been associated with functional decline, higher rates of falls, higher hospitalization rates, higher hospital costs, and higher mortality rates. Because of the serious public health issue that sarcopenia represents, it is imperative that we understand this condition and its consequences. The etiology of this condition is complex and multifactorial, encompassing decreased physical activity and poor nutritional habits, but also different mechanisms related to muscle anabolism.

For a long time, there was no consensus on the definition or diagnostic criteria for sarcopenia which makes research on management and treatment difficult. In recent years, there has been an effort to change this, resulting in an operational definition of sarcopenia intended to increase the consistency of research and promote better care for sarcopenic patients. The new definition focuses on low muscle strength as a key characteristic and gives detailed diagnostic criteria that are intended to be easy to use in clinical practice.

Sarcopenia treatment, through the years, consisted of exercise and nutrition interventions. In this study, we found these interventions, and specifically their association, to be the most important tools for the management of this condition. Despite this, the quality of evidence is low due to shortfalls in research that need to be fixed in future studies. Pharmacological treatments still do not show a strong positive effect and as such are not recommended.

The aim of this study is to compile the best current evidence about sarcopenia that is available, addressing epidemiology, pathophysiology, diagnosis, treatment, prevention, and recommendations for further research.

KEYWORDS

Sarcopenia; Aging; Muscle strength; Exercise; Nutrition therapy.

RESUMO

Sarcopenia é uma condição relacionada com o envelhecimento em que ocorrem mudanças musculares prejudiciais que resultam em decréscimos de força, massa muscular e desempenho físico. Foi associada com declínio funcional, maior incidência de quedas, maior taxa de hospitalização, maiores custos hospitalares, e maior taxa de mortalidade. Devido ao facto da sarcopenia representar um grave problema de saúde pública, é imperativo que compreendamos esta condição e as suas consequências. A etiologia desta condição é complexa e multifatorial, envolvendo diminuição da atividade física e maus hábitos nutricionais, como também vários mecanismos diferentes envolvidos no anabolismo muscular.

Durante bastante tempo não existiu consenso na definição ou nos critérios de diagnóstico da sarcopenia o que dificultou a investigação da abordagem e tratamento da mesma. Mais recentemente, tem-se trabalhado para mudar isto, sendo que agora temos uma definição operacional de sarcopenia que pretende aumentar a consistência na área da investigação e promover melhores cuidados para doentes sarcopénicos. Esta nova definição foca-se na baixa força muscular como característica fundamental da sarcopenia e fornece critérios de diagnóstico detalhados com a intenção de que o seu uso na prática clínica seja fácil.

O tratamento da sarcopenia, ao longo do tempo, consistiu em intervenções de exercício e nutrição. Neste estudo concluímos que estas intervenções, e especialmente a sua associação, são a melhor opção na gestão desta condição. Apesar disto, a qualidade da evidência é baixa devido a deficiências na literatura que serão abordadas neste trabalho. Tratamentos farmacológicos continuam sem mostrar um efeito positivo significativo e, por isso, não são recomendados.

O objetivo deste estudo é reunir a melhor e mais recente evidência sobre sarcopenia que está disponível, abordando temas como epidemiologia, fisiopatologia, diagnóstico, tratamento, prevenção, e recomendações para futuros estudos.

PALAVRAS CHAVE

Sarcopenia; Envelhecimento; Força Muscular; Exercício Físico; Terapia Nutricional.

1. INTRODUCTION

Sarcopenia, from the Greek *sarx* (flesh) and *penia* (loss), was defined in 1988 by Rosenberg as loss of muscle mass related to aging.[1] In 2010 the European Working Group on Sarcopenia in Older People (EWGSOP)[2] published a new definition of sarcopenia that they revised in 2018[3] (EWGSOP2). This new definition of sarcopenia focuses on more than just loss of muscle mass including muscle quality, physical performance, and muscle strength, the latter being a key component; it also recognizes that although sarcopenia is recognized as a condition of old age, it begins developing early in life.[3] In this revised definition, sarcopenia is likely when we detect low muscle strength and is confirmed when there is established low muscle quantity or quality; when there is low muscle quality/quantity, low muscle strength, and low physical performance occurring at the same time we call it severe sarcopenia.[3] The EWGSOP2 further categorizes sarcopenia into primary or secondary and acute or chronic sarcopenia; it also mentions other conditions related to sarcopenia that sometimes are thought to be interchangeable but are distinct such as sarcopenic obesity, frailty, and malnutrition.[3]

The pathophysiology of sarcopenia is complex and multifactorial. One of the biggest risk factors for sarcopenia is low physical activity which is prevalent in old age; low physical activity contributes to and worsens the decline of muscle mass that already happens with aging. Besides this, aging is usually accompanied by processes that are linked to sarcopenia such as hormonal changes, increased inflammation, neuromuscular junction degeneration, decreased caloric intake, and decreased protein synthesis.[4]

Definition and diagnostic criteria for sarcopenia vary widely so it is difficult to talk about prevalence. A 2021 meta-analysis[5] of studies that followed the most used definitions of sarcopenia found the overall prevalence to vary between 10% and 27%; as expected the studies included had a lot of heterogeneity. Another meta-analysis[6] that focused on the prevalence of sarcopenia in different settings found that hospitalized people and residents of nursing homes had increased rates when compared to community-dwelling men and women – 31% and 51% in women and men in nursing homes, respectively; 24% and 23% in hospitalized women and men, respectively; and 9% and 11% in community-dwelling women and men, respectively.

It is important to understand sarcopenia because this condition represents a big burden to the healthcare system and comes with many negative impacts on quality of life (QoL).[7,8] Several studies show increased healthcare costs related to sarcopenia, with increased rates of hospitalization and increased costs of those hospitalizations.[7,9,10] Sarcopenia is associated with many adverse outcomes such as a higher rate of falls, functional decline with a decrease of mobility, and a higher rate of mortality making it a serious public health issue.[11] Sarcopenia

is also associated with a worse prognosis of various types of cancer, worse surgery outcomes with more complications, risk of cognitive impairment, and several metabolic diseases.[12]

As life expectancy continues to increase worldwide, the prevalence and burden of sarcopenia will also increase, so we must be informed and updated about this condition. This study aims to gather the most updated and clinically relevant information about sarcopenia regarding its definition, diagnosis, and treatment so that this complex and current issue can be approached in an evidence-based way.

2. MATERIALS AND METHODS

For the elaboration of this study, a literature search was conducted using the PubMed database. A structured search was done using the term “Sarcopenia” in combination with other relevant terms such as “prevalence”, “epidemiology”, “definition”, “costs”, “risk factors”, “diagnosis”, “pathophysiology”, “exercise”, “nutrition”, “approach”, and “treatment”.

The search was restricted to English and umbrella reviews, meta-analysis, and systematic reviews were preferred. Regarding publication date, it was essentially restricted to studies published after 2010 as that was when the definition of sarcopenia was updated; a few older studies were also consulted for biological models or context reasons.

The selection was refined after the exclusion of some studies firstly by the title, then abstract, and then after complete reading, as they were found to not be of use. A few studies were also found and selected based on cross-referencing.

3. PATHOPHYSIOLOGY

The pathophysiology of sarcopenia is complex and multifactorial with countless contributing factors identified or proposed (Fig. 1). Aging disrupts the normal pathways and mechanisms related to skeletal muscle; some of these changes are better understood than others and will be explained here.

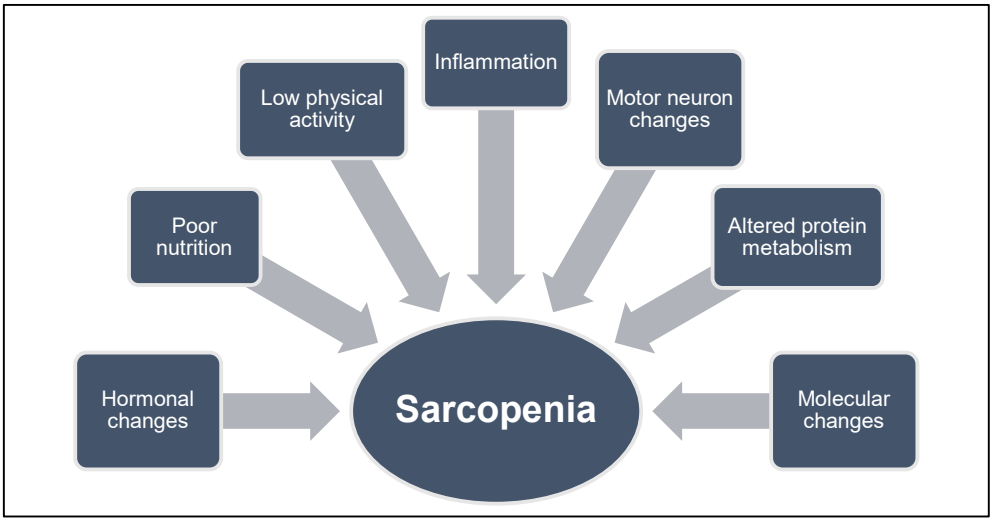

Figure 1. Multifactorial etiology of sarcopenia

There are external and internal contributions to the decline of skeletal muscle that work together and in a cumulative fashion to the development of sarcopenia.[13] As an external factor, we have decreased physical activity that usually occurs with aging and is one of the main risk factors for this condition.[14–16] The other external contributor and main risk factor for sarcopenia is poor nutrition. Poor nutrition, in this case, refers to decreased caloric intake or the exact opposite in sarcopenic obesity; decreased nutritional value with old people eating less protein; low vitamin D levels, although the latter is more controversial when we look at vitamin D intake.[17–20]

With aging, there is a gradual loss of muscle fibers that starts around the 50 years mark and by the age of 80 approximately 50% of the fibers were lost; this reduction also happens to a degree in athletes indicating that there are intrinsic factors at play.[21] One of these intrinsic changes is the preferred atrophy of type II muscle fibers (fast-twitch) versus type I (slow-twitch), meaning that the reduced muscle mass present in sarcopenia can be attributed, mainly, to the decrease in size of type II muscle fibers.[22] Since type II fibers are responsible for fast muscle force production, this imbalance impairs activities such as rising from a chair or climbing steps and can also explain the big reduction in strength that occurs with aging.[23] There is also mitochondrial dysfunction in myocytes; myosteatosis that consists of fat infiltration in skeletal

muscle and negatively correlates with muscle mass and strength; neuromuscular junction degeneration; tendon changes that interfere with muscle force production.[24,25]

Hormonal changes are another influential factor in the development of sarcopenia. Aging comes with declines in anabolic hormones, such as testosterone and its precursors, growth hormone, and insulin-like growth factor-I (IGF-1).[17] The decline of these hormones with aging contributes to sarcopenia since they are an essential part of muscle-building and maintenance pathways.[17]

Chronic low-level inflammation caused by increased oxidative stress that comes with aging leads to increased inflammatory markers in sarcopenic patients (mainly tumor necrosis factor-α (TNF-α) and interleukin-6). This inflammatory state contributes to tissue degradation and to a process called anabolic resistance. Anabolic resistance is a process where the protein metabolism is altered and we simultaneously have decreased protein synthesis and increased muscle breakdown; it is caused by the increased inflammation factors and the hormonal changes described above.[4,17,23]

Other cellular and molecular mechanisms with increased complexity are being studied for their importance in sarcopenia, such as reactive oxygen species imbalance that can lead to decreased proliferation and differentiation of stem cells responsible for skeletal muscle.[26] There is also increased myostatin, a protein produced in myocytes – myokine, that stimulates muscle atrophy and inhibits myogenesis; increased myostatin correlates with reduced muscle mass in humans.[17,27]

As it is with most conditions there may be a genetic component to sarcopenia. Single nucleotide polymorphisms (SNPs) have been found in large-scale genome-wide association studies to be linked to muscle metabolism, structure, and function of skeletal muscle fibers. These studies focused mainly on variations of gait speed, grip strength, and lean body mass.[17]

To summarize, the pathophysiology of sarcopenia encompasses many complex mechanisms that work together. It is important to understand these mechanisms as they can represent targets for interventions and treatments or can highlight preventable causes of this condition.

4. DEFINITION AND DIAGNOSIS

The definition of sarcopenia evolved since it was coined by Rosenberg in 1988[1] and for many years there was little consensus about this condition. This led to the formation of the European Working Group on Sarcopenia in Older People (EWGSOP) in 2010 and further revision in 2018 as EWGSOP2.[2,3] The definition now brings muscle strength to the forefront as a predictor of sarcopenia instead of low muscle mass as a principal parameter.

4.1. Sarcopenia algorithm

EWGSOP2 created a new algorithm (Fig. 2) for case finding, diagnosis, and severity classification. The goal was to make it straightforward for clinicians to diagnose and treat sarcopenia, as it has been difficult to do so because of the complexity of the assessment.[3]

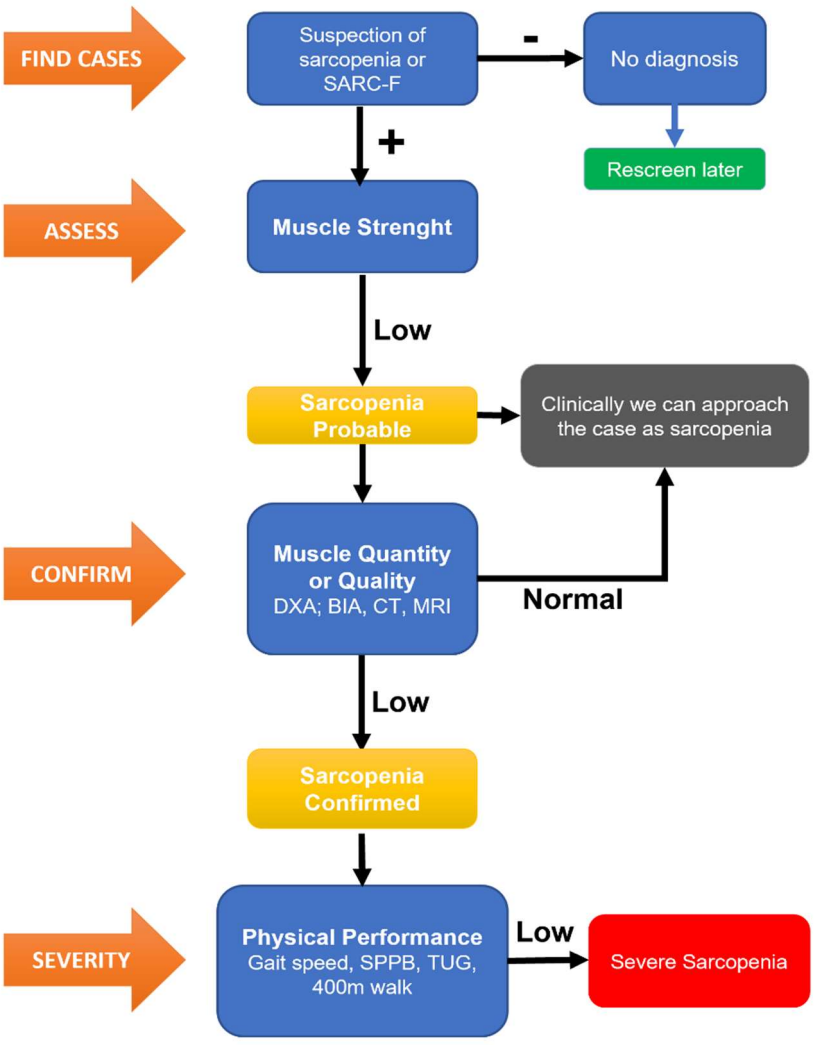

Figure 2. EWGSOP2 algorithm, F-A-C-S, to approach sarcopenia. (Adapted from Cruz-Jentoft et al., 2019.[3] DXA, Dual-energy X-ray Absorptiometry; BIA, Bioelectrical Impedance Analysis; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; SPPB, Short Physical Performance Battery Protocol; TUG, Timed-Up and Go test).

This algorithm is called Find-Assess-Confirm-Severity (F-A-C-S). It recommends starting by finding cases of people at risk of sarcopenia; then assessing for evidence of sarcopenia by testing muscle strength. The third step is confirming the diagnosis of sarcopenia, which is based on muscle quantity and/or quality. At last, the algorithm recommends using performance tests to determine the severity of sarcopenia.[3]

4.1.1. Finding Cases

When we are in the presence of symptoms or signs of sarcopenia we should start to suspect this condition and additional testing is advised; these signs and symptoms can be as simple as feeling weaker or slower.[3]

The EWGSOP2 recommends the SARC-F questionnaire (Table 1) for assessing the risk of sarcopenia.[3] This simple five-question questionnaire is based on questions targeting five components of sarcopenia to predict poor functional outcomes.[28,29]

Table 1. SARC-F questionnaire for sarcopenia screening. (Adapted from Malmstrom et al., 2013[28] and Malmstrom et al., 2016[29]).

Component	Question	Score
Strength	How much difficulty do you have in lifting and carrying 10 pounds?	None = 0 Some = 1 A lot or unable = 2
Assistance walking	How much difficulty do you have walking across a room? Any aids or help?	None = 0 Some = 1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed? Any aids or help?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1-3 falls = 1 4 or more falls = 2
The score can range from 0 to 10; a score equal to or greater than 4 is predictive of sarcopenia		

The SARC-F was validated for identifying subjects with an increased risk of poor outcomes related to sarcopenia, it has good specificity but a low to moderate sensibility.[29,30] EWGSOP2 recommends the use of SARC-F despite its sensibility because it is an inexpensive tool, is easy to use as a screening method, and does not take too much time.[3] For clinicians who prefer a screening tool with better mathematical properties, despite being more complex and time-consuming, there is the one by Ishii et al.[31] that fared better in a comparison of performance of different sarcopenia screening tools.[3,32]

If there are no signs of sarcopenia and the SARC-F is negative, we assume that the diagnosis of sarcopenia is not likely, and the algorithm ends there; sarcopenia may develop later so rescreening regularly is indicated. In the case of a positive SARC-F questionnaire or clinical suspicion of sarcopenia, we advance to the next step of the algorithm – assess.[3]

4.1.2. Assess for evidence of sarcopenia

In the second step of the F-A-C-S algorithm, we assess patients for evidence of sarcopenia. EWGSOP2 recommends using low muscle strength as evidence of sarcopenia as strength has been found to be a better predictor of worse outcomes when compared to muscle mass.[3,33–35] Another important factor for preferring strength is that other parameters such as muscle quality and quantity are harder to assess, define, and the tests used are more expensive or have less availability.[3,36,37]

Two tests are preferred for testing muscle strength: grip strength test and chair stand test.[3] Low grip strength is important by itself because it has been associated with longer hospitalization times, increased functional limitations, and more importantly, higher all-cause mortality.[34,35] Grip strength can be easily evaluated using a handheld dynamometer and its result can be reliably used as a surrogate for strength in other body parts.[3] The chair stand test (or chair rise test) is used to assess strength in the lower limb musculature, it measures the time someone takes to raise five times from a seating position without using their arms; there is a timed variation that counts the number of chair rises in a thirty-second interval.[3] The chair stand test is useful in a primary care setting or in a context where there is no dynamometer available.[38] The EWGSOP2 gives specific cut-off points for these tests based on current literature while trying to simplify the specific values for ease of use in clinical practice.[3]

If muscle strength is found to be low, we say that sarcopenia is probable and clinically we can start treating it as such.[3]

4.1.3. Confirm Sarcopenia

In the third step of the F-A-C-S algorithm, the goal is to confirm sarcopenia. We do this by confirming the presence of low muscle quantity and/or quality.[3] This step is less important than the first two because it is used more for research purposes and doesn't drastically change how we deal with sarcopenic patients.[3] As explained in the previous step, the detection of low muscle strength means that we treat the patient as sarcopenic and that remains true even if muscle quantity/quality is found to be normal.[3]

4.1.3.1. Muscle Quantity

Of the two parameters, quality and quantity, quantity has been more researched and is easier to check. The first thing to understand is that there is no perfect test since most of the techniques used have some type of limitation.[24] Muscle quantity, also called muscle mass, is reported as total body skeletal muscle mass (SMM), appendicular skeletal muscle mass (ASM), or cross-section area of different muscles; these results can be further adjusted for body size using height, height squared, weight or body mass index (BMI).[39]

Computed tomography (CT) and magnetic resonance imaging (MRI) are the gold standards for non-invasive assessment of muscle mass, but their use is not recommended outside of research; this is explained by the high cost, lack of accessibility and practicality, and in the case of CT the radiation exposure.[40]

Dual-energy X-ray absorptiometry (DXA) is considered the reference standard to measure muscle mass because of its accuracy, ease of use, low cost, and low radiation exposure.[36] One disadvantage of DXA is that it is not portable which makes it harder to use in primary care settings and larger studies, and this is where bioelectrical impedance analysis (BIA) can be an important tool.[3] BIA is an indirect way to measure muscle mass, deriving its result from body conductivity; this means that its accuracy on an individual level is not as good, as it uses equations to estimate muscle mass instead of measuring it, with some studies finding a lack of standardization and cross-validation for BIA methods; and that BIA and DXA agreement is low.[36,41,42] Despite this, EWGSOP2 still recommends the use of DXA and BIA in clinical care, as the latter is useful in specific situations.[3]

4.1.3.2. Muscle Quality

Muscle quality is a more ambiguous and recent term than muscle mass, as it can have two meanings: it can refer to muscle function, meaning strength per unit of muscle, and physical changes both microscopic and macroscopic.[43] In research imaging techniques, such as CT and MRI have been used along with BIA phase angle to study muscle quality.[44] Currently, there is no consensus on the assessment of muscle quality and its clinical implications, but in the future, the role of this parameter could increase.[45]

4.1.3.3. Promising tests and tools

Currently, there are several tools and tests to assess muscle mass and diagnose sarcopenia that are being researched and show promise despite not being yet validated to use in clinical practice. One of these tools is ultrasound which has been shown to reliably measure muscle mass in older populations and can even assess muscle quality.[46–48] Ultrasound could

become a simple and accessible way to measure muscle mass, but there is still a need for standardized technique and further validation in specific populations.[49,50] The other promising tool is the D3-creatine dilution method; it consists of the ingestion of deuterated creatine (D3-creatine) and determination of its concentration in urine.[51] Results of this method were found to correlate well with MRI in regards to muscle mass and d3-creatine dilution was better than DXA in regards to physical performance.[51]

4.1.4. Severity

The last step of the F-A-C-S algorithm is to determine severity. This is done by assessing physical performance and if it is low, we can say that sarcopenia is severe.[3] Physical performance is a multidimensional concept that has been described as an objectively measured whole-body function related to mobility; it can be assessed by a variety of tests.[52]

EWGSOP2 recommends several tests to assess physical performance: gait speed, short physical performance battery (SPPB), timed-up and go test (TUG), and the 400-m walk test. Due to its convenience and ability to predict sarcopenia-related outcomes, gait speed is the advised test to use in clinical practice.[3,53,54]

Sarcopenia severity is clinically relevant because several studies have shown that interventions can have different effects on non-severe and severe sarcopenia, and that severity can help predict outcomes.[55–57]

4.2. Sarcopenia categorization and similar conditions

EWGSOP2 further categorizes sarcopenia into primary or secondary, and acute or chronic. Primary sarcopenia is age-related with no other specific causes identified, while with secondary sarcopenia other causes can be identified. Sarcopenia can be secondary to disease, inactivity, and malnutrition. These classifications interact because the secondary sarcopenia factors may work in addition to age-related sarcopenia and many times are impossible to isolate.[3]

We can classify sarcopenia as chronic when it lasts six or more months and as acute when it lasts less. Acute sarcopenia can be the result of acute disease or injury, while chronic sarcopenia is more likely to be age-related and to have worse outcomes.[3]

There are various conditions related to sarcopenia and with similar definitions that sometimes are assumed to mean the same. That is the case of sarcopenic obesity, cachexia, frailty, and malnutrition.

4.2.1. Sarcopenic obesity

This is a condition where we have both low muscle mass and increased adiposity. It may be underdiagnosed because clinicians equate sarcopenia with leanness. Obesity comes with increased inflammation, infiltration of fat into muscle – myosteatosis, and low physical activity; those can worsen sarcopenia and result in increased mortality and disability.[3,17,24]

4.2.2. Cachexia

Cachexia is a syndrome with a lot in common with sarcopenia. It is defined as loss of muscle mass and strength due to an underlying condition such as cancer, AIDS, or organ failure. As such, most cachectic individuals are also sarcopenic but most sarcopenic individuals are not cachectic.[2] Due to the similar definitions distinction between the two is hard; as differences we have weight loss being a bigger part of cachexia while being less important for sarcopenia, and sarcopenia being much more related to aging.[17,24]

4.2.3. Frailty

Frailty is a geriatric syndrome that englobes the physical, psychological, and social aspects of aging. It shares physical characteristics with sarcopenia, like low strength and low gait-speed, and weight loss, a characteristic of frailty, can also be an important cause of sarcopenia. The difference between the two is that frailty is a syndrome while sarcopenia is a disease, with the first encompassing much more than the second; we can think of sarcopenia as the physical dimension of frailty.[3,24]

4.2.4. Malnutrition

The new Global Clinical Nutrition Community criteria for the diagnosis of malnutrition[58] has added low muscle mass as one of the phenotypes of malnutrition. This may create some confusion with the differential between sarcopenia and malnutrition, as low muscle mass is also a component of sarcopenia.

The new EWGSOP2 definition of sarcopenia brings muscle strength to the forefront of the diagnosis, so low muscle mass is not enough to establish a diagnosis of sarcopenia.[3] This gives us a way to differentiate between malnutrition and sarcopenia: low muscle mass with normal strength is more likely to be a case of malnutrition. Low fat is also much more characteristic of malnutrition than sarcopenia.[3,24]

5. TREATMENT AND PREVENTION

There are still no universally accepted guidelines for the treatment and management of sarcopenia, although many have been proposed. The difficulty with sarcopenia treatment research is that there is still a lot of heterogeneity between studies: different definitions of sarcopenia are used; the most researched interventions focus on exercise and nutrition, with a high degree of variation between protocols; outcomes measured also vary a lot, both in what the outcome is and how it is measured. These factors can explain the high number of limitations present in most systematic reviews and meta-analyses made in this area, and the low-level evidence of most recommendations.

Despite the limitations of the literature on this subject, there is still a consensus that the interventions to focus on are exercise and nutrition.

5.1. Exercise interventions

From a pathophysiological standpoint, the recommendation of resistance-based physical activity is logical because sarcopenia comes with the transition of type II to type I muscle fibers, decreasing muscle mass and strength. This can be counteracted by resistance training (RT), as RT is associated with the predominant recruitment of type II fibers and, this way, type II muscle fiber hypertrophy.[23]

The Belgian Society of Gerontology and Geriatrics (BSGG) has developed guidelines for the prevention and treatment of sarcopenia and their working group on exercise interventions published their results as an umbrella review.[59] They looked at the efficacy of four exercise categories on sarcopenia: resistance training, resistance training plus nutritional supplementation, multimodal exercise programs, and blood flow restriction training.[59] They found that there is high-quality evidence for a positive and significant effect of resistance training on muscle mass, muscle strength, and physical performance.[59] Furthermore, they found that to maximize strength gains a high-intensity resistance training program (≥ 80% of one-repetition maximum (1RM)) is recommended; low-intensity resistance training (≤50% 1RM) may be sufficient to induce strength gains.[59] This is an important study because they gave specific recommendations for exercise intervention: a total body resistance training program, at a high intensity (≥ 80% of 1RM), for 1–4 sets of 8–15 repetitions, during 2–3 training moments a week.[59]

In 2018 the task force of the International Conference on Sarcopenia and Frailty Research (ICSFR)[60] published a set of guidelines for the management of sarcopenia where they recommend RT for the management of sarcopenia (strong recommendation, moderate certainty of evidence). They report that they got the evidence for this recommendation mostly

from two meta-analyses[61,62] and that it is in agreement with all the international workgroups on sarcopenia. Despite the strong recommendation, they acknowledge that most evidence used came from studies in non-sarcopenic older adults which is a limitation. When looking at the studies that only used sarcopenic patients, they found low certainty of evidence for the beneficial effects of RT.[60]

The Society of Sarcopenia, Cachexia and Wasting Disorders (SCWD) published a position statement in 2019 where they strongly recommend RT for any older person suspected of having sarcopenia, both for secondary prevention and/or treatment.[63] They based this recommendation on two meta-analyses: one from Vlietstra et al.[64] looking at the effects of exercise in sarcopenic individuals and the other from Csapo et al.[65] looking at the effects of RT with heavy vs moderate loads in elderly individuals. The first meta-analyses mixed results from studies with different exercises interventions and the second one did not focus on sarcopenic patients, so there are several limitations to the conclusions.[64,65] Notwithstanding, both found positive effects in muscle strength, which supports RT as a treatment for sarcopenia; besides improved strength, Vlietstra et al. found improved muscle mass, balance, and physical performance.[64,65]

Clinical sarcopenia guidelines developed by a collaboration of the Japanese Association on Sarcopenia and Frailty, the Japan Geriatrics Society, and the National Center for Geriatrics and Gerontology found that exercise interventions for three months or longer may help increase skeletal muscle mass, muscle strength, and gait speed, although the evidence level was very low.[66]

In 2020 Sarah et al.[67] published an umbrella review of randomized controlled trials of exercise interventions used to treat sarcopenia that concluded that there was a lack of high-quality research with which to inform the treatment of sarcopenia with exercise as only two studies met the eligibility criteria. The results were that very low to low-quality evidence suggests that exercise interventions may play a role in improving muscle mass, muscle strength, and walking speed after 3 months of intervention.[67]

A 2022 network meta-analysis of randomized controlled trials on the management of sarcopenia by Negm et al.[68] looked at the effect of different interventions on muscle mass (primary outcome), muscle strength, and physical performance. They found that mixed exercise (RT plus aerobic exercise) was the most effective intervention in increasing muscle mass, and one of the three best for increasing muscle strength and physical performance; physical activity with nutritional supplementation was among the most effective interventions on the 3 outcomes.[68] Another similar network meta-analyses found that both exercise alone and the combination of exercise and nutrition have beneficial effects on muscle strength and physical performance in older adults with sarcopenia.[69]

Some patients may not be able to complete an exercise protocol, even an adapted one. In these cases, whole-body vibration therapy may be an option to improve muscle mass, strength, physical performance, and quality of life.[4,17,68,70]

Most of the studies referenced reported limitations such as low sample sizes, differing definitions and outcomes, low duration of the interventions, and high heterogeneity of the exercise protocols used. There is a need for large-scale studies with improved standardization of exercise interventions that use current definitions of sarcopenia.[62,63] This is the hole the SPRINTT randomized trial[71] is trying to fill. This trial is currently testing a multi-component intervention based on long-term structured physical activity, nutritional counseling/dietary intervention, and an information and communication technology intervention; 1500 older adults with physical frailty and sarcopenia will be followed for up to 36 months.[71] The primary outcome of the trial is mobility disability (can be equated with physical performance), with secondary outcomes relevant to sarcopenia including changes in muscle mass and strength.[71]

The SPRINTT trial can also serve as a guide for research in sarcopenia intervention since it has validated methods for eligibility criteria, outcomes, and interventions. Their exercise protocol is based on the one implemented in the LIFE study[72]; it involves walking (goal of 150 min/week), strength, flexibility, and balance training. It gives detailed information about progression schemes, which means it can be followed and replicated.[71,72]

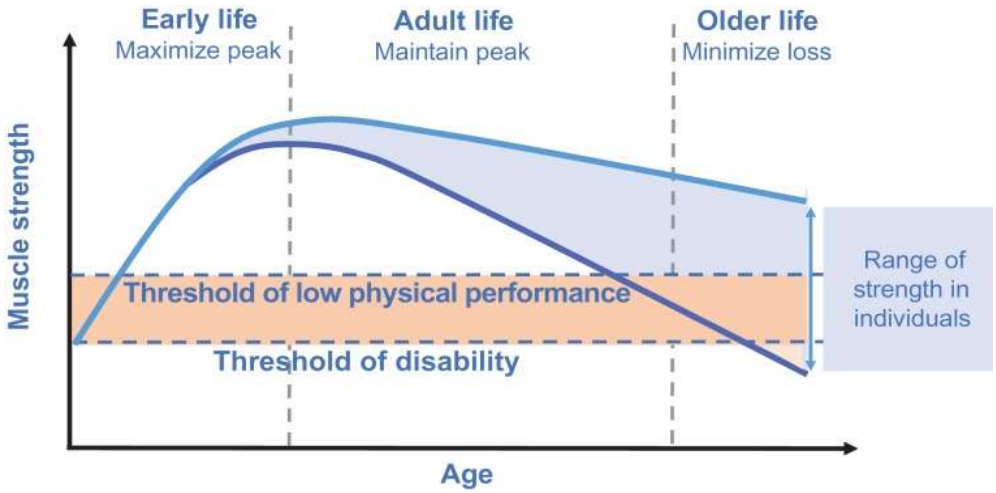

Figure 3. Muscle strength through life. (Cruz-Jentoft et al., 2019[3]).

Regarding prevention, exercise plays a big role as we know that strength and muscle mass later in life are associated with strength and muscle mass obtained earlier in life (Fig. 3).[3,24] There is a gradual loss of muscle mass with aging, and even though this still happens with athletes it does so to a lesser degree, providing evidence that these changes can be slowed.[21] If we want to prevent or delay sarcopenia, we should maximize muscle earlier in life

so that we reach old age in the best shape possible; this can be possible with lifestyle interventions, including exercise and nutrition.[3]

5.2. Nutrition Interventions

We can approach nutrition interventions for sarcopenia from two angles. First, we can address and correct specific deficiencies which are common in older adults. Second, after correcting the mistakes detected we can have nutrition interventions intended to optimize strength, muscle mass, and physical performance, and this way serve as a sarcopenia treatment.

Regarding general nutrition, there is a lot to correct in older adults. With aging, there is reduced nutritional intake, with reductions of about 25% from 40 to 70 years; this is explained by reduced hunger in older adults for which there are several contributing factors, such as eating slower, loss of taste, dementia, depression, poor dentition, and loss of motivation to eat.[18] This process is referred to as “anorexia of aging”. The reduced food intake is especially bad because of reduced protein consumption. Due to the anabolic resistance and altered protein metabolism that accompanies aging, older adults have been recommended to have higher intakes of protein, but community-dwelling older adults frequently fall below the minimum recommendations.[73] Besides deficiencies in energy and macronutrients, older adults frequently suffer from micronutrient deficiencies, such as calcium, vitamin D, vitamin B12, iron, magnesium, and zinc.[73] These nutritional deficiencies can be seen as targets for interventions when assessing older populations and we should correct them regardless of other supplemental strategies that can be used in sarcopenia.

As explained in the pathophysiology section, sarcopenia is associated with changes in protein metabolism – there is increased muscle breakdown, and decreased protein synthesis.[4,17] To counteract the effects of anabolic resistance, and further manage sarcopenia, older adults have been recommended to consume more protein although the evidence on the amount is not so straightforward.[74]

The ICSFR guidelines recommend that clinicians consider protein supplementation (PS)/a protein-rich diet for older adults with sarcopenia (conditional recommendation; low certainty of evidence).[60] They also give a conditional recommendation for the evaluation of protein and protein-energy intake, as well as discussing with patients the importance of adequate calorie and protein intake.[60] The reason for not giving strong recommendations arise from low certainty of evidence in their systematic review caused by small-scale studies, possible biases, non-use of current diagnostic criteria for sarcopenia, and ambiguity of results.[60] Regarding vitamin D supplementation the ICSFR guidelines agreed that at the time

there is insufficient evidence to recommend vitamin D supplementation for older adults with sarcopenia; supplementation should be decided on an individual basis.[60]

The SCWD position paper gives a conditional recommendation for a protein-rich diet or PS. They define this as doses of 1 to 1.5 g protein/kg/day or up to 2 g protein/kg/day when there is a severe illness, injury, or a pro-inflammatory/catabolic state.[63] They also acknowledge that the amount of evidence was small which explains the conditional recommendation.[63]

The clinical sarcopenia guidelines developed by a collaboration of the Japanese Association on Sarcopenia and Frailty, the Japan Geriatrics Society, and the National Center for Geriatrics and Gerontology found that the evidence level for nutritional interventions is very low.[66] These guidelines state that nutritional interventions for at least three months may contribute to an improvement in muscle strength.[66]

The Belgian Society of Gerontology and Geriatrics (BSGG) while developing their sarcopenia guidelines published the results of their working group on nutrition as an umbrella review.[75] They gave specific recommendations and classified them by quality of evidence (Table 2). Besides PS, they recommend leucine supplementation, a branched-chain amino acid that has been found to have an important role in protein synthesis; they also concluded that β-hydroxy-β-methylbutyrate (HBM), a leucine metabolite, may be considered to increase muscle mass.[4,75]

Table 2. BSGG nutrition recommendations. (Adapted from Gielen et al.[75])

Protein supplementation
Protein supplementation alone may be considered as an intervention to increase muscle mass (low QoE).
Protein supplementation in combination with progressive resistance training is recommended to achieve optimal effects on muscle mass (minimum 24 weeks) and muscle strength in older adults, particularly those who are obese (moderate QoE).
EAA supplementation
EAA supplementation alone and on top of physical exercise should not be considered an intervention to increase muscle mass, muscle strength, and physical performance (high and low QoE, respectively).
Leucine supplementation is recommended for sarcopenic older people to increase muscle mass (moderate QoE).
HMB supplementation alone may be considered an intervention to increase muscle mass (high QoE).
Creatine supplementation on top of progressive resistance training may be considered an intervention to increase muscle mass and muscle strength (low QoE).

QoE, quality of evidence; EAA, essential amino acids; HMB, β-hydroxy-β-methylbutyrate.

Creatine is one of the most studied supplements for muscle mass and strength in healthy adults, so it may be of use in sarcopenia. A meta-analysis by Phillip et al.[76] found that creatine supplementation in older adults during RT resulted in increased lean mass and strength. Further studies using sarcopenic individuals are needed.

Regarding prevention, the recommendations for older adults (≥65 years), besides a generally healthy diet, are to increase protein intake.[74] The specific amount is still debated, but most agree that it should be above 1.0 g protein/kg/day, going as far as 2.0 g protein/kg/day in specific situations; since sarcopenia can start earlier in life these amounts may even be beneficial in younger people.[63,74,77] Per-meal protein amount also matters and the total protein intake should be divided into, at least, two or three large meals to maximize muscle protein synthesis; each meal should contain a minimum of around 25-30 g of protein.[77]

There are many benefits to increased protein intake but there is also fear that high-protein diets will have deleterious effects, especially to the kidneys. The European Society for Clinical Nutrition and Metabolism says that for older adults with healthy kidneys these protein recommendations are safe.[74] For patients with moderate or severe chronic kidney disease they recommend an individual approach; clinicians need to balance the risk of worsening kidney function with the risk of disability/morbility.[74]

5.3. Synergistic effect

The evidence for nutritional interventions alone in the management of sarcopenia is not yet clear.[62,69] On the other hand, the beneficial effect on sarcopenia of nutrition interventions in association with exercise is more straightforward.[63,68,69] This can be explained by the synergistic effect of exercise and nutrition.

Exercise, especially RT, promotes muscle protein synthesis as does protein consumption, and this cumulative effect should be used when approaching sarcopenia treatment and/or prevention.[78] Exercise sensitizes muscles to other anabolic stimuli, increasing protein synthesis up to 24 hours after training with a peak at around 3 hours.[79] Regarding nutrition, essential amino acids (EAA) play a big role in promoting protein synthesis, especially leucine.[78]

A recent meta-analysis[80] supports this synergistic effect as it found that protein supplementation (PS) in addition to RT is effective in promoting gain in muscle mass and strength, and in enhancing performance in physical mobility in elderly adults when compared with the placebo, PS-alone, or RT-alone controls.

5.4. Other types of treatment

There are other types of interventions for the treatment of sarcopenia that were proposed and/or are being tested, mainly pharmacological ones. Drugs with anabolic properties have been proposed as a possible tool for sarcopenia treatment, examples are growth hormone, testosterone, and more recently selective androgen receptor blockers (SARMs).[4,13] Angiotensin-converting enzyme inhibitors and myostatin inhibition may also have a beneficial effect on sarcopenia but further studies are needed.[4,24]

The pharmacological working group from BCSGG published an umbrella review on pharmacological interventions for sarcopenia to improve muscle mass, strength, and physical performance in older people.[81] They looked at the efficacy of ten different pharmacological interventions: vitamin D, combined estrogen-progesterone, dehydroepiandrosterone, growth hormone, growth hormone-releasing hormone, combined testosterone-growth hormone, insulin-like growth factor-1, pioglitazone, testosterone, and angiotensin-converting enzyme inhibitors.[81] They concluded that only vitamin D in women with low baseline levels (< 25 nmol/l), and testosterone in men with low testosterone serum levels (< 200-300 ng/dl) can be justified in daily clinical practice to improve muscle mass, muscle strength, and/or physical performance.[81]

The ICSFR guidelines recommend against pharmacological interventions as first-line treatment for sarcopenia as they found that there was inadequate data in persons with sarcopenia to recommend the use of any of the studied drugs for the management of sarcopenia.[60] They also concluded that there was insufficient evidence to recommend anabolic hormone supplementation for older adults with sarcopenia based on studies using testosterone and SARMs.[60]

5.5. Recommendations for further research

The difficulty with developing an evidence-based management protocol for sarcopenia has to do with the available research and its shortcomings. Many of the international associations that study sarcopenia have acknowledged the research pitfalls in this area and have given recommendations for future studies.[3,60,62,63]

Some important considerations for further research are as follows:

- Sarcopenia diagnostic criteria, like the ones by EWGSOP2, should be used so evidence can be applied to sarcopenic patients and comparison between studies is possible.
- Populations need to be well-defined.
- Interventions should be validated for effectiveness on sarcopenic obesity and secondary sarcopenia.
- Outcomes should be well-defined, well-assessed, and clinically relevant to sarcopenia diagnosis: muscle strength, muscle mass, muscle quality, and physical performance.
- Large-scale studies with long follow-ups are needed.
- Quality of life, as an outcome, should be assessed.
- Exercise interventions:
    - Improved standardization is needed on exercise programs to reduce heterogeneity.
    - Effects of different exercise modalities should be interpreted independently as different types of exercise can give different results.
    - Longer studies are needed as exercise results can take time.
    - Outcomes should be assessed at similar times for comparison across studies.
- Nutrition interventions:
    - Studies that try to look at the effect of exercise and nutrition should have four arms: exercise, nutrition, both, and none.
    - Baseline nutritional status should be considered before specific interventions and should be reported.
    - Calorie intake needs to be addressed and both control and intervention groups should have equal calorie intake to eliminate confounding factors.
    - Most studies are based on protein and vitamin D; other nutrients, food groups, and diet types should also be studied.

6. CONCLUSION

Sarcopenia is an age-related condition that impacts an increasing number of people with the aging of the global population. Having an accepted definition and standardized diagnostic criteria is imperative and will help guide clinical management research. In the last few years, there was major progress in this subject and now we have a consensus definition of sarcopenia that focuses on low muscle strength.

The pathophysiology of sarcopenia is complex, but many mechanisms are now known, which creates many possible targets for treatments. For many years the consensus has been that sarcopenia should be addressed with exercise and nutrition, specifically resistance exercise and increased protein intake. In this study, we show that this has been found to be true, but the quality of evidence is low, and we still do not have a universally accepted approach for sarcopenia. No medical therapies have been shown, without a doubt, to be effective in the treatment of sarcopenia, but many that are still in development could become important tools in the future.

Regarding specific recommendations:

- A high-intensity RT program is advised for the treatment and prevention of sarcopenia.
- Older adults (≥65 years) or adults at risk for sarcopenia have increased protein requirements of 1.0-1.2 g protein/kg/day and in specific cases 2 g protein/kg/day.
- Due to the synergistic effect of nutrition and exercise interventions increased protein intake in conjunction with RT is recommended.
- Leucine and creatine supplementation may help.
- Vitamin D is recommended if there are low serum values.

More high-quality and large-scale studies are needed; this is easier as now we have a consensus definition of sarcopenia and a few guidelines for interventions.

Sarcopenia starts developing earlier in life and lifestyle factors such as exercise and nutrition have a great preventive role on sarcopenia. With this study, we tried to raise awareness and help with the understanding of this condition so it can be approached in an evidence-based way leading to better care and better outcomes for older adults.

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