Pharmacological Treatment of Sarcopenia

Tratamento medicamentoso da sarcopenia

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Rev Bras Ortop 2021;56(4):425–431.

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Abstract

Sarcopenia has been acquiring a growing importance in the scientific literature and in doctors' offices. As the population ages, it becomes increasingly essential to know, prevent, and treat this clinical condition. The purpose of the present review is to bring up the current evidence on the diagnosis of this pathology, in a practical way, as well as the main current treatment options.

Keywords

- sarcopenia/diagnosis
- sarcopenia/therapy
- leucine
- creatine
- testosterone

Resumo

A sarcopenia vem ganhando cada vez mais importância na literatura científica e nos consultórios médicos. Com o envelhecimento da população, essa condição clínica se torna cada vez mais imprescindível de se conhecer, se prevenir e de se tratar. O objetivo desta revisão é trazer as evidências atuais sobre o diagnóstico dessa patologia, de forma prática, bem como as principais opções atuais de tratamento.

Palavras-chave

- sarcopenia/diagnóstico
- sarcopenia/terapia
- leucina
- creatina
- testosterona

Introduction

In 1989, Irwin Rosenberg proposed the term sarcopenia as an age-related decrease in skeletal muscle mass.[1] It was not just the creation of a new word. It was the finding of a pathology still unknown. The concept of sarcopenia is not yet widely known by the medical profession, especially by orthopedists. It is usually accompanied by physical inactivity, reduced mobility, slow gait, and low physical resistance, which are also common features of frailty syndrome.[2] In addition, ageing and physical disability are also related to increased fat mass, particularly visceral fat,[3] which is an important factor in the development of metabolic syndrome and cardiovascular diseases.[4] Therefore, sarcopenia with obesity in the elderly can synergistically increase its effect on metabolic, and cardiovascular disorders, and mortality, in addition to physical disability.[5]

A progressive loss of muscle mass occurs from approximately 40 years of age. This loss was estimated at around 8% per decade until the age of 70, after which the loss increases to 15% per decade.[6] There is also loss of muscle strength. A 10 to 15% loss of leg strength per decade is observed up to 70 years of

received
October 21, 2019
accepted
January 27, 2020
published online
September 22, 2020

DOI https://doi.org/10.1055/s-0040-1709732.
ISSN 0102-3616.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

age, after which a more rapid loss occurs, ranging from 25 to 40% per decade.[7] It is estimated that a 10.5% reduction in the prevalence of sarcopenia could lead to a reduction in health care costs of $ 1.1 billion per year in the United States.[8]

The prevalence of sarcopenia in the world population varies substantially, as this is closely correlated with the definition of this pathology.[9] In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) published a definition of sarcopenia that aimed to promote advances in the identification and care of people with sarcopenia. In early 2018, the Working Group met again (EWGSOP2) to update the original definition to reflect the scientific and clinical evidence that was built in the last decade.[10]

These researchers identified a strong correlation between sarcopenia and negative clinical outcomes. Initially, sarcopenia was associated only with elderly individuals, but it is now recognized that the development of sarcopenia starts before ageing. They also started to consider it a muscle failure, whose main symptom is weakness. Loss of strength has become more important than measuring muscle mass as a trigger for diagnostic investigation. This fact alone will greatly change the prevalence of this disease.

The association of sarcopenia with lower muscle mass and worse muscle performance of sick patients (low muscle quality) remains important, but these parameters should now be used mainly in clinical research or in the confirmation of some cases of the disease. This is due to the fact that both muscle mass and muscle quality are technically difficult to measure accurately, as they depend on more complex diagnostic tools and cost more than the measurement of muscle strength, which can be done with the Five Times Sit to Stand Test (5XSTT).[11]

The reduction in muscle mass and strength with advancing age is associated with some comorbidities, including type 2 diabetes, cancer, metabolic syndrome,[12] reduced mobility, and physical disability, in addition to mortality.[13] It is also correlated with an increased risk of falls and fractures.[14] Current estimates suggest that about 200 million people worldwide have sarcopenia to a degree that could affect their health over the next 4 decades.[15] In financial terms, sarcopenia is costly for health systems. The presence of sarcopenia increases the risk of hospitalization and increases the cost of care during hospitalization.[16]

Skeletal muscle mass is maintained, in large part, by combined changes in the rate of muscle protein synthesis[12] and the rate of muscle protein destruction.[17] Protein intake and resistance exercise are potent stimuli for synthesis; however, when combined, there is synergistic interaction between these stimuli, which leads to an accumulation of skeletal muscle mass.[18] Currently, there are data that suggest that ageing leads to an attenuated response of synthesis (and possible increased destruction) to the intake of amino acids[19] and to exercise.[20]

Assessment and Diagnosis of Sarcopenia

To identify individuals at risk for sarcopenia, the EWGSOP2 recommends using the Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls (SARC-F) questionnaire (**Annex 1**) or clinical research to find symptoms associated with sarcopenia.[21] The EWGSOP2's current definition of probable sarcopenia is low muscle strength. If, in addition, the patient has low muscle volume or low muscle quality, his diagnosis of sarcopenia will be confirmed. The combination of the three factors will lead to the diagnosis of severe sarcopenia.[10]

To assess the evidence of probable sarcopenia, EWGSOP recommends the use of grip strength or the 5XSTT, with specific cutoff points for each test.

The 5XSTT has a very simple application. It consists of making the patient get up and sit on a chair five times, without supporting or unbalancing. The grading of the actions is done by time. The patient must do the 5 repetitions in less than 15 seconds.[11]

The grip strength test is the method most widely cited in the literature on the subject. It consists of a portable dynamometer that measures the handgrip strength in kilograms (kg) in an easy-to-apply test that lasts a few minutes. Usually, the test is done in both hands, alternately, with three repetitions on each side.[22] The form suggested by the American Society of Hand Therapists[23] is with the patient seated, with the elbow flexed in a 90 degrees position. As cut-off points, the standard established by the EWGSOP2 is 16 kg for women and 27 kg for men.[11]

For the confirmation of sarcopenia, the detection of the smallest muscle volume should be performed. Dual-energy X-ray absorptiometry (DXA) is considered one of the ideal methods for assessing muscle mass.[24] It has the advantage of speed in its realization and minimal exposure to radiation, determining the amounts of muscle mass (lean) and fat mass with accuracy.[25]

In order to determine the severity of the disease, a performance assessment must be made. The method recommended by the EWGSOP2 is the gait test, due to its simplicity. This test consists of covering 400 m, previously marked by the examiner, in which only gait speed is assessed.[11]

Treatment

Currently, there are no viable pharmaceutical interventions to slow the progression of sarcopenia. Some articles cite hormone replacement with testosterone, but more evidence is needed on this, as we will see below.[26]

Resistance Training

Resistance training (RT) is a highly effective strategy to compensate for sarcopenia and has numerous beneficial effects. The main relevant results for this review are obvious increases in muscle mass, strength and functional performance in older individuals.[27] Resistance exercise stimulates the synthesis of new muscle protein by the action of the mTORC1 (mechanistic target of rapamycin complex 1) protein.

A recent meta-analysis of randomized controlled trials found that dietary protein supplementation during RT (over 6 weeks) resulted in greater gains in lean mass and body strength than RT alone in young and elderly adults.[18]

Contrary to belief and prescriptive guidelines for the elderly, it is not necessary to lift heavier loads to induce muscle hypertrophy. A scientific article showed similar gains

in muscle mass in young adults after 12 weeks of low-load, high-repetition or high-load and low-repetition RT.[28]

Resistance training is effective in terms of muscle mass gain and to prevent skeletal muscle loss, in addition to promoting strength gains and functional improvement. Although recent meta-analyses have found greater strength gains with higher intensity RT,[27,28] it is suggested that these differences are functionally unimportant because they did not translate into differences in functional performance in elderly patients.

Protein Supplementation

Protein consumption, especially those composed of essential amino acids, that is, those that our bodies cannot form endogenously, can act synergistically with resistance exercise to improve the response of muscle protein synthesis.[29] We know that protein can act independently of exercise to increase protein synthesis rates; however, the protein's ability to stimulate the creation of these new muscle proteins is diminished in the elderly.[19] In fact, in older adults, the intake of 35 and 40 g of protein at rest[30] and after resistance exercises,[31] compared to 20 g in young individuals,[32] was necessary to stimulate muscle synthesis as much as possible. Recently, an attempt was made to define the protein dose, relative to body mass, required per meal in young and elderly individuals. Briefly, data from the literature already published investigating the effects of protein dose-response on muscle in young and elderly individuals were analyzed. The finding of this study confirmed different needs for protein doses in young and elderly individuals, so the synthesis was stimulated to the maximum by 0.24 g of protein per kg per meal in young individuals, and 0.40 g of protein per kg per meal in elderly individuals.[19]

Additional evidence supporting recommendations for higher protein intake in older adults comes from studies showing that, in elderly patients, the highest protein intake is protective against loss of lean mass.[33] Furthermore, the addition of 15 g of protein for breakfast and lunch, which increased the protein content of these meals to at least 25 g, increased strength and physical performance in frail elderly people.[34]

Leucine

The quality of protein supplementation is a result of its amino acid content, digestibility, and bioavailability. Although several amino acids are needed to allow muscle protein synthesis,[35] leucine is the key amino acid that leads to the beginning of this synthesis.[36]

The stimulatory impact of the branched-chain amino acid leucine on muscle tissue is associated with leucine's ability to activate the mTORC1 protein, which, subsequently, targets signaling protein kinases that facilitate translation initiation and stimulation of protein synthesis.[37]

The potency of leucine was demonstrated when individuals consumed a lower protein dose (6 g), which previously proved to be less effective in muscle stimulation;[38] however, with the addition of leucine, this effectively led to the same response in muscle tissue as with a higher protein dose (25 g) in young individuals.[39] Likewise, after a resistance exercise session, the addition of leucine to a protein and carbohydrate drink improved muscle synthesis in a more significant way than the protein and carbohydrate drink alone.[40] These findings indicate that proteins with a higher leucine content would be more effective than those with a lower leucine content for muscle tissue. This may be particularly true in elderly patients, in whom there appears to be reduced sensitivity to leucine.[41]

β-hydroxy-β-methyl butyrate

β-hydroxy-β-methyl butyrate (β-HMB) is a leucine metabolite that also has anabolic properties. In a recent systematic review of studies involving β-HMB, Molfino concluded that a meta-analysis of the effects of β-HMB in the elderly was not possible, mainly because of the heterogeneity of the studies and the lack of studies between isolated β-HMB and a placebo.[42] However, a recent review states that supplements with essential amino acids plus β-HMB show good effects in improving the muscle mass and function parameters.[43]

Oral supplementation with β-HMB increases plasma and intramuscular concentrations of this substance.[44] β-HMB fame of being an exercise substitute comes from studies that show its effectiveness in preventing muscle mass loss at rest. For example, supplementation with 3 grams of β-HMB for 5 days before and during 10 days of bed rest in elderly patients attenuated muscle losses.[45] Such findings may have clinical relevance for those individuals who experience periods of short-term muscle disuse, for example, hospitalization. However, his most important reports are of improved muscle function and strength when combined with resistance exercise.[46]

Interestingly, a study shows that leucine (3.42 g) is at least as powerful, when compared in grams, as the β-HMB.[47] It is also important to realize that the change in muscle protein synthesis in response to the intake of β-HMB is not always detected by articles in the literature.[45]

In the longest study of supplementation of β-HMB more amino acids published so far, Baier reported that the elderly who received the combination of β-HMB (2 g) more protein supplementation showed greater gains in body muscle composition than those who received only amino acids. These authors reported greater gains after 12 months of supplementation. It is important to note that there were no associated functional gains (such as strength) compared to the control group, only differences in body composition.[48]

Creatine

Creatine is a nitrogenous organic acid that exists naturally in the body, being synthesized in the liver and kidneys from some amino acids. It is stored in the muscle and acts as a quick reserve of energy during high-intensity exercise. It is reversibly converted to phosphocreatine by creatine kinase during periods of low muscle activity. At the beginning of high-intensity exercise, phosphocreatine donates a high-energy phosphate to adenosine diphosphate (ADP), serving as a quick source of anaerobic energy to support exercise; however, it runs out quickly.

Its main function is to be an important reserve of energy in transitions from rest to workloads, being particularly important in short-term muscle contractions (less than 30 seconds), high intensity activities, such as running and resistance exercise, and allowing high muscle power to be obtained.[49]

The benefits of creatine are not limited to athletes, but also to elderly patients. Some studies,[47] but not all,[50] investigated the effects of creatine supplementation alone and found positive effects on strength and functional performance in the elderly. A recently completed meta-analysis showed that creatine consumed concomitantly with RT had a greater effect than RT alone on improving body composition, strength, and functional performance in elderly men and women.[51] This meta-analysis was based on the results of 8 randomized, placebo-controlled studies, which included a total of 252 elderly people. Although there was a disparity in results between trials, general creatine supplementation increased total body fat-free mass, the strength of the pectorals on the bench press, and the number of times a subject could lift from the chair over a period of 30 seconds by 2 repetitions more than just with the RT. These findings confirm the role of creatine intake (5 g) paired with RT to alleviate sarcopenia.

As mentioned earlier, not all studies have shown a greater effect of creatine alone or when added to RT to improve body composition, strength and/or performance,[50] indicating some degree of variability in response to creatine between assays or subjects. As such, the recommended strategies for using creatine for sarcopenic elderly are to consume 5 g of creatine along with a progressive RT program, recognizing that those with naturally higher muscle creatine before supplementation will not respond to supplementation.

Testosterone and Analogs

Androgens are steroid hormones synthesized mainly in the gonads and adrenal glands, such as dihydrotestosterone, dehydroepiandrosterone, androstenediol, androstenedione, and testosterone. Among them, testosterone is the main androgen that promotes male characteristics, in addition to facilitating protein synthesis.[52]

Anabolic androgenic steroids (AAS) are considered a synthetic therapeutic class of testosterone analogs. Some examples are nandrolone decanoate, oxandrolone, stanozolol, methandrostenolone, boldenone acetate and testosterone enanthate.

Elderly people around 80 years old show a decline in testosterone levels and adrenal androgens with age, with a relationship between drop in testosterone and decline in muscle mass and strength evidenced by epidemiological studies.[53] Thus, it seems logical to investigate the use of testosterone or the like for the treatment or prevention of sarcopenia.

There are two mechanisms of testosterone for increasing lean mass and increasing muscle strength: the direct and the indirect. The direct occurs through the interaction with the androgenic receptors of the cell cytoplasm. This interaction causes a signal for protein synthesis. Another possibility of increasing lean muscle mass and strength by testosterone directly is in the better use of amino acids and in the greater expression of androgenic receptors in muscle tissue. In the indirect form, there is a greater affinity of testosterone with glucocorticoid receptors, thus suggesting an antagonistic action to glucocorticoids. Another indirect action on muscle tissue hypertrophy occurs similarly to the insulin process (IGF-1), that is, as a growth factor, this can be seen in the elderly treated with testosterone, in whom there are increased levels of mRNA of IGF-1 in muscle tissue.[53]

A meta-analysis of 29 randomized clinical trials, with periods of 9 months of testosterone administration, with a mean age of 64.5 years and without RT, showed an increase of 1.6 Kg of lean muscle mass (2.7% of initial lean mass) and a 6.2% reduction in the percentage of initial fat.[54] Another article researched which dosage of anabolic steroids would allow better muscle hypertrophy. Men without comorbidities aged between 60 and 75 years were studied, divided into groups that received 25, 50, 125, 300 or 600 mg of intramuscular testosterone enanthate. At the end of 20 weeks, it was observed, by means of imaging exams and muscle biopsy, the increase in the area of the muscle cross section with the administration of dosages of 300 mg and 600 mg of testosterone enanthate, in addition to a greater number of satellite cells in the region. However, there was no test regarding strength and function.[55]

We must emphasize that this class of medications is only indicated for patients with androgenic deficiency and serum levels below the reference values. Even so, there is a risk to be weighed. A study with testosterone administration in the elderly from 65 to 75 years old, who had mobility limitations and had free testosterone below the normal level, but with a tendency to cardiovascular diseases, had to be stopped prematurely due to increased cardiovascular risks. Therefore, safety in individuals with a history of heart disease or stroke is low, and its recommendation should be avoided.[56] As for prostate cancer, the patient should be investigated, and its existence discarded before the start of therapy. It is known that one of the side effects of using testosterone supplementation is an enlarged prostate. However, in a study carried out over a period of 52 weeks, no changes were observed by blood methods (prostate specific antigen - PSA) and digital rectal examination.[57]

The most common adverse effects found with the use of testosterone analogs are: increased risk of thrombotic events, such as myocardial infarction or stroke; left ventricular hypertrophy; sudden death; increased aggressiveness and withdrawal symptoms that may include severe depression, addiction, suppression of gonadal steroidogenesis, amenorrhea, clitoral hypertrophy, testicular atrophy, disproportionate growth of the prostate, acne, deepening of the voice in women and infections at the application site.[58]

Conclusion

The pharmacological treatment of sarcopenia still has a lot to evolve. Currently, its diagnosis and importance are the focus of most research, and treatment remains largely based on

resistance exercises and some supplements. We hope that in the next decade this picture will change substantially.

Conflict of Interests

The author declares that there are no conflicts of interest.

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Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls + calf circumference (CC)

SARC-F + CC

How much difficulty do you have in lifting and carrying 5 kg		
[0] None	[1] Some	[3] A lot or unable
How much difficulty do you have walking across a room?		
[0] None	[1] Some	[3] A lot, use aids or unable
How much difficulty do you have transferring from a chair or bed?		
[0] None	[1] Some	[3] A lot or unable without help
How much difficulty do you have climbing a flight of 10 stairs?		
[0] None	[1] Some	[3] A lot or unable
How many times have you fallen in the past year?		
[0] None	[1] 1-3 falls	[3] 4 or more falls

+

Average of the two measurements of the right calf:_____cm	
[0] Women ≥ 33cm	[0] Men ≥ 33cm
[10] Women < 33cm	[10] Men < 33cm
Sum of points (0-20)_____	Sarcopenia ≥11 points

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Annex 1 SARC-F questionnaire (based on Barbosa-Silva et al).[21] Abbreviations: CC, calf circumference; SARC-F, Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls.