



# Pharmacological Treatment of Sarcopenia

## *Tratamento medicamentoso da sarcopenia*

Caio Gonçalves de Souza<sup>1</sup> 

<sup>1</sup> Osteometabolic Diseases Group, Institute of Orthopedics and Traumatology, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), São Paulo, SP, Brazil

**Address for correspondence** Caio Gonçalves de Souza, PhD, Instituto de Ortopedia e Traumatologia do Hospital das Clínicas da FMUSP, Rua Ovídio Pires de Campos, 333, Cerqueira César, São Paulo, SP, 05403-010, Brazil (e-mail: caiogsouza@hotmail.com).

Rev Bras Ortop 2021;56(4):425–431.

### Abstract

#### Keywords

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

### Resumo

#### Palavras-chave

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

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.

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.

## Introduction

In 1989, Irwin Rosenberg proposed the term sarcopenia as an age-related decrease in skeletal muscle mass.<sup>1</sup> 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.<sup>2</sup> In addition, ageing and physical disability are also related to increased fat mass,

particularly visceral fat,<sup>3</sup> which is an important factor in the development of metabolic syndrome and cardiovascular diseases.<sup>4</sup> Therefore, sarcopenia with obesity in the elderly can synergistically increase its effect on metabolic, and cardiovascular disorders, and mortality, in addition to physical disability.<sup>5</sup>

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.<sup>6</sup> 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.

© 2020. Sociedade Brasileira de Ortopedia e Traumatologia. All rights reserved.

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

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.<sup>7</sup> 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.<sup>8</sup>

The prevalence of sarcopenia in the world population varies substantially, as this is closely correlated with the definition of this pathology.<sup>9</sup> 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.<sup>10</sup>

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).<sup>11</sup>

The reduction in muscle mass and strength with advancing age is associated with some comorbidities, including type 2 diabetes, cancer, metabolic syndrome,<sup>12</sup> reduced mobility, and physical disability, in addition to mortality.<sup>13</sup> It is also correlated with an increased risk of falls and fractures.<sup>14</sup> Current estimates suggest that about 200 million people worldwide have sarcopenia to a degree that could affect their health over the next 4 decades.<sup>15</sup> 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.<sup>16</sup>

Skeletal muscle mass is maintained, in large part, by combined changes in the rate of muscle protein synthesis<sup>12</sup> and the rate of muscle protein destruction.<sup>17</sup> 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.<sup>18</sup> 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<sup>19</sup> and to exercise.<sup>20</sup>

### 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.<sup>21</sup> 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.<sup>10</sup>

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.<sup>11</sup>

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.<sup>22</sup> The form suggested by the American Society of Hand Therapists<sup>23</sup> 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.<sup>11</sup>

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.<sup>24</sup> 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.<sup>25</sup>

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.<sup>11</sup>

### 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.<sup>26</sup>

### 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.<sup>27</sup> 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.<sup>18</sup>

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.<sup>28</sup>

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,<sup>27,28</sup> 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.<sup>29</sup> 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.<sup>19</sup> In fact, in older adults, the intake of 35 and 40 g of protein at rest<sup>30</sup> and after resistance exercises,<sup>31</sup> compared to 20 g in young individuals,<sup>32</sup> 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.<sup>19</sup>

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.<sup>33</sup> 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.<sup>34</sup>

### 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,<sup>35</sup> leucine is the key amino acid that leads to the beginning of this synthesis.<sup>36</sup>

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.<sup>37</sup>

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;<sup>38</sup> 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.<sup>39</sup> 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.<sup>40</sup> 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.<sup>41</sup>

### $\beta$ -hydroxy- $\beta$ -methyl butyrate

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

Oral supplementation with  $\beta$ -HMB increases plasma and intramuscular concentrations of this substance.<sup>44</sup>  $\beta$ -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  $\beta$ -HMB for 5 days before and during 10 days of bed rest in elderly patients attenuated muscle losses.<sup>45</sup> 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.<sup>46</sup>

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

In the longest study of supplementation of  $\beta$ -HMB more amino acids published so far, Baier reported that the elderly who received the combination of  $\beta$ -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.<sup>48</sup>

### 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.<sup>49</sup>

The benefits of creatine are not limited to athletes, but also to elderly patients. Some studies,<sup>47</sup> but not all,<sup>50</sup> 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.<sup>51</sup> 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,<sup>50</sup> 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.<sup>52</sup>

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.<sup>53</sup> 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.<sup>53</sup>

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.<sup>54</sup> 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.<sup>55</sup>

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.<sup>56</sup> 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.<sup>57</sup>

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.<sup>58</sup>

### 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.

#### References

- Rosenberg IH, Roubenoff R. Stalking sarcopenia. *Ann Intern Med* 1995;123(09):727–728
- Cesari M, Leeuwenburgh C, Lauretani F, et al. Frailty syndrome and skeletal muscle: results from the Invecchiare in Chianti study. *Am J Clin Nutr* 2006;83(05):1142–1148
- Riechman SE, Schoen RE, Weissfeld JL, Thaete FL, Kriska AM. Association of physical activity and visceral adipose tissue in older women and men. *Obes Res* 2002;10(10):1065–1073
- Ryan AS, Nicklas BJ. Age-related changes in fat deposition in mid-thigh muscle in women: relationships with metabolic cardiovascular disease risk factors. *Int J Obes Relat Metab Disord* 1999;23(02):126–132
- Stenholm S, Harris TB, Rantanen T, Visser M, Kritchevsky SB, Ferrucci L. Sarcopenic obesity: definition, cause and consequences. *Curr Opin Clin Nutr Metab Care* 2008;11(06):693–700
- Grimby G, Saltin B. The ageing muscle. *Clin Physiol* 1983;3(03):209–218
- Goodpaster BH, Park SW, Harris TB, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci* 2006;61(10):1059–1064
- Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The health-care costs of sarcopenia in the United States. *J Am Geriatr Soc* 2004;52(01):80–85
- Abellan van Kan G. Epidemiology and consequences of sarcopenia. *J Nutr Health Aging* 2009;13(08):708–712
- Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019;48(01):16–31
- Lira VA, Araújo C. Teste de sentar-levantar: estudos de fidedignidade. *Rev Bras Ciên Mov* 2000;8(02):11–20
- Gong Z, Muzumdar RH. Pancreatic function, type 2 diabetes, and metabolism in aging. *Int J Endocrinol* 2012;2012:320482
- Srikanthan P, Karlamangla AS. Muscle mass index as a predictor of longevity in older adults. *Am J Med* 2014;127(06):547–553
- Schaap LA, van Schoor NM, Lips P, Visser M. Associations of Sarcopenia Definitions, and Their Components, With the Incidence of Recurrent Falling and Fractures: The Longitudinal Aging Study Amsterdam. *J Gerontol A Biol Sci Med Sci* 2018;73(09):1199–1204
- Janssen I. The epidemiology of sarcopenia. *Clin Geriatr Med* 2011;27(03):355–363
- Cawthon PM, Lui LY, Taylor BC, et al. Clinical Definitions of Sarcopenia and Risk of Hospitalization in Community-Dwelling Older Men: The Osteoporotic Fractures in Men Study. *J Gerontol A Biol Sci Med Sci* 2017;72(10):1383–1389
- Rennie MJ, Wackerhage H, Spangenburg EE, Booth FW. Control of the size of the human muscle mass. *Annu Rev Physiol* 2004;66:799–828
- Cermak NM, Res PT, de Groot LC, Saris WH, van Loon LJ. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. *Am J Clin Nutr* 2012;96(06):1454–1464
- Moore DR, Churchward-Venne TA, Witard O, et al. Protein ingestion to stimulate myofibrillar protein synthesis requires greater relative protein intakes in healthy older versus younger men. *J Gerontol A Biol Sci Med Sci* 2015;70(01):57–62
- Kumar V, Selby A, Rankin D, et al. Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men. *J Physiol* 2009;587(01):211–217
- Barbosa-Silva TG, Menezes AM, Bielemann RM, Malmstrom TK, Gonzalez MC, Grupo de Estudos em Composição Corporal e Nutrição (COCONUT). Enhancing SARC-F: Improving Sarcopenia Screening in the Clinical Practice. *J Am Med Dir Assoc* 2016;17(12):1136–1141
- Roberts HC, Denison HJ, Martin HJ, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing* 2011;40(04):423–429
- Fess EE. Grip strength. In: Casanova JS, editor. *Clinical assessment recommendations*. 2nd ed. Chicago: American Society of Hand Therapists; 1992:41–45
- Morley JE. Sarcopenia: diagnosis and treatment. *J Nutr Health Aging* 2008;12(07):452–456
- Heymsfield SB, Smith R, Aulet M, et al. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. *Am J Clin Nutr* 1990;52(02):214–218
- Horstman AM, Dillon EL, Urban RJ, Sheffield-Moore M. The role of androgens and estrogens on healthy aging and longevity. *J Gerontol A Biol Sci Med Sci* 2012;67(11):1140–1152
- Leenders M, Verdijk LB, van der Hoeven L, van Kranenburg J, Nilwik R, van Loon LJ. Elderly men and women benefit equally from prolonged resistance-type exercise training. *J Gerontol A Biol Sci Med Sci* 2013;68(07):769–779
- Mitchell CJ, Churchward-Venne TA, West DW, et al. Resistance exercise load does not determine training-mediated hypertrophic gains in young men. *J Appl Physiol* (1985) 2012;113(01):71–77
- Churchward-Venne TA, Burd NA, Mitchell CJ, et al. Supplementation of a suboptimal protein dose with leucine or essential amino acids: effects on myofibrillar protein synthesis at rest and following resistance exercise in men. *J Physiol* 2012;590(11):2751–2765
- Pennings B, Groen B, de Lange A, et al. Amino acid absorption and subsequent muscle protein accretion following graded intakes of whey protein in elderly men. *Am J Physiol Endocrinol Metab* 2012;302(08):E992–E999
- Yang Y, Breen L, Burd NA, et al. Resistance exercise enhances myofibrillar protein synthesis with graded intakes of whey protein in older men. *Br J Nutr* 2012;108(10):1780–1788
- Witard OC, Jackman SR, Breen L, Smith K, Selby A, Tipton KD. Myofibrillar muscle protein synthesis rates subsequent to a meal in response to increasing doses of whey protein at rest and after resistance exercise. *Am J Clin Nutr* 2014;99(01):86–95
- Geirsdottir OG, Arnarson A, Ramel A, Jonsson PV, Thorsdottir I. Dietary protein intake is associated with lean body mass in community-dwelling older adults. *Nutr Res* 2013;33(08):608–612
- Tieland M, van de Rest O, Dirks ML, et al. Protein supplementation improves physical performance in frail elderly people: a randomized, double-blind, placebo-controlled trial. *J Am Med Dir Assoc* 2012;13(08):720–726
- Volpi E, Kobayashi H, Sheffield-Moore M, Mittendorfer B, Wolfe RR. Essential amino acids are primarily responsible for the amino acid stimulation of muscle protein anabolism in healthy elderly adults. *Am J Clin Nutr* 2003;78(02):250–258
- Anthony JC, Yoshizawa F, Anthony TG, Vary TC, Jefferson LS, Kimball SR. Leucine stimulates translation initiation in skeletal muscle of postabsorptive rats via a rapamycin-sensitive pathway. *J Nutr* 2000;130(10):2413–2419
- Sancak Y, Bar-Peled L, Zoncu R, Markhard AL, Nada S, Sabatini DM. Ragulator-Rag complex targets mTORC1 to the lysosomal surface and is necessary for its activation by amino acids. *Cell* 2010;141(02):290–303
- Moore DR, Robinson MJ, Fry JL, et al. Ingested protein dose response of muscle and albumin protein synthesis after resistance exercise in young men. *Am J Clin Nutr* 2009;89(01):161–168

- 39 Churchward-Venne TA, Breen L, Di Donato DM, et al. Leucine supplementation of a low-protein mixed macronutrient beverage enhances myofibrillar protein synthesis in young men: a double-blind, randomized trial. *Am J Clin Nutr* 2014;99(02):276–286
- 40 Koopman R, Wagenmakers AJ, Manders RJ, et al. Combined ingestion of protein and free leucine with carbohydrate increases postexercise muscle protein synthesis in vivo in male subjects. *Am J Physiol Endocrinol Metab* 2005;288(04):E645–E653
- 41 Katsanos CS, Kobayashi H, Sheffield-Moore M, Aarsland A, Wolfe RR. A high proportion of leucine is required for optimal stimulation of the rate of muscle protein synthesis by essential amino acids in the elderly. *Am J Physiol Endocrinol Metab* 2006;291(02):E381–E387
- 42 Molino A, Gioia G, Rossi Fanelli F, Muscaritoli M. Beta-hydroxy-beta-methylbutyrate supplementation in health and disease: a systematic review of randomized trials. *Amino Acids* 2013;45(06):1273–1292
- 43 Cruz-Jentoft AJ, Landi F, Schneider SM, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). *Age Ageing* 2014;43(06):748–759
- 44 Wilkinson DJ, Hossain T, Hill DS, et al. Effects of leucine and its metabolite  $\beta$ -hydroxy- $\beta$ -methylbutyrate on human skeletal muscle protein metabolism. *J Physiol* 2013;591(11):2911–2923
- 45 Deutz NE, Pereira SL, Hays NP, et al. Effect of  $\beta$ -hydroxy- $\beta$ -methylbutyrate (HMB) on lean body mass during 10 days of bed rest in older adults. *Clin Nutr* 2013;32(05):704–712
- 46 Wilson GJ, Wilson JM, Manninen AH. Effects of beta-hydroxy-beta-methylbutyrate (HMB) on exercise performance and body composition across varying levels of age, sex, and training experience: A review. *Nutr Metab (Lond)* 2008;5:1. Doi: 10.1186/1743-7075-5-1
- 47 Stout JR, Sue Graves B, Cramer JT, et al. Effects of creatine supplementation on the onset of neuromuscular fatigue threshold and muscle strength in elderly men and women (64 - 86 years). *J Nutr Health Aging* 2007;11(06):459–464
- 48 Baier S, Johannsen D, Abumrad N, Rathmacher JA, Nissen S, Flakoll P. Year-long changes in protein metabolism in elderly men and women supplemented with a nutrition cocktail of beta-hydroxy-beta-methylbutyrate (HMB), L-arginine, and L-lysine. *JPEN J Parenter Enteral Nutr* 2009;33(01):71–82
- 49 Gotshalk LA, Kraemer WJ, Mendonca MA, et al. Creatine supplementation improves muscular performance in older women. *Eur J Appl Physiol* 2008;102(02):223–231
- 50 Devries MC, Phillips SM. Creatine supplementation during resistance training in older adults—a meta-analysis. *Med Sci Sports Exerc* 2014;46(06):1194–1203
- 51 Kersey RD, Elliot DL, Goldberg L, et al. National Athletic Trainers' Association. National Athletic Trainers' Association position statement: anabolic-androgenic steroids. *J Athl Train* 2012;47(05):567–588
- 52 Silva TA, Frisoli A Junior, Pinheiro MM, Szejnfeld VL. Sarcopenia associada ao envelhecimento: aspectos etiológicos e opções terapêuticas. *Rev Bras Reumatol* 2006;46(06):391–397
- 53 Vaisberg M, Mello MT. Exercícios na saúde e na doença. Barueri, São Paulo: Manole; 2010
- 54 Isidori AM, Giannetta E, Greco EA, et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clin Endocrinol (Oxf)* 2005;63(03):280–293
- 55 Sinha-Hikim I, Cornford M, Gaytan H, Lee ML, Bhasin S. Effects of testosterone supplementation on skeletal muscle fiber hypertrophy and satellite cells in community-dwelling older men. *J Clin Endocrinol Metab* 2006;91(08):3024–3033
- 56 Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013;310(17):1829–1836
- 57 Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *J Androl* 2009;30(06):726–733
- 58 Kanayama G, Brower KJ, Wood RI, Hudson JL, Pope HG Jr. Anabolic-androgenic steroid dependence: an emerging disorder. *Addiction* 2009;104(12):1966–1978

**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 $\geq$ 33cm	[0] Men $\geq$ 33cm
[10] Women < 33cm	[10] Men < 33cm
Sum of points (0-20) _____	Sarcopenia $\geq$ 11 points

J Am Med Dir Assoc. 2016 Dec 1;17(12):1136-1141

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