Ana João Antunes da Costa e Silva

# Nutritional interventions in sarcopenia in older adults: a review of the literature

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Ana João Antunes da Costa e Silva

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Ana João Antunes da Costa e Silva

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Orientadora:
Professora Doutora Ana Sofia Sousa

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## iv. List of abbreviations and acronyms

BIA- Bioelectrical impedance analysis

CRP- C-reactive protein

CT- computed tomography

DHA- Docosahexaenoic acid

DXA -Dual-energy X-ray absorptiometry

EAA - Essential amino acid

EPA – Eicosapentaenoic acid

EWGSOP – European Working Group on Sarcopenia in Older People

HMB - ß-Hydroxy ß-Methylbutyrate

KNHANES – Korea National Health and Nutrition Examination Survey

MDS- Mediterranean diet score

MPS - Muscle protein synthesis

MRI – Magnetic resonance imaging

mTOR- Mammalian target of rapamycin

myoPS – Myofibrillar protein synthesis

PUFAs- Polyunsaturated fatty acids

RDA - Recommended Daily Allowance

SPPB - Short Physical Performance Battery

TUG - Timed-Up and Go Test

## v. Title/authors/academic affiliation

Ana João Costa e Silva (1), Ana Sofia Sousa (2)

(1) Estudante finalista do 1º Ciclo de Estudos em Ciências da Nutrição da Faculdade de Ciências da Saúde da Universidade Fernando Pessoa.

(2) Professora Auxiliar da Faculdade de Ciências da Saúde da Universidade Fernando Pessoa. Orientadora do trabalho complementar de final de curso.

Ana João Antunes da Costa e Silva
Faculdade de Ciências da Saúde da Universidade Fernando Pessoa
Morada: Rua Carlos da Maia, 296. 4200-150 Porto.
E-mail: 35360@ufp.edu.pt

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## vi. Abstract

Sarcopenia is defined as the progressive and generalized loss of skeletal muscle mass and functional performance and is considered a major threat to healthy ageing.

There is a growing body of evidence linking nutrition with sarcopenia parameters in the elderly.

Therefore, the present study aims to review the literature and to analyze the existent information regarding nutritional interventions for preventing or treating sarcopenia in older adults.

Nutritional interventions present as a promising strategy when it comes to prevent or delay the development of sarcopenia, especially in sedentary individuals.

The most studied approaches are a balanced diet, adequate intake of proteins (especially those rich in leucine) and there is also data regarding the role of supplementation with leucine or/and HMB in this condition. Moreover, there is also evidence linking omega-3 fatty acids to the management of sarcopenia.

The effect of minerals such as selenium and magnesium in sarcopenia are worth further exploring since the little evidence existing on this topic shows that they can be relevant on the prevention of sarcopenia.

In conclusion, there is promising evidence on nutrition and diet as key strategies to prevent and treat sarcopenia while promoting physical function and quality of life. Notwithstanding this, further studies are needed in order to strengthen the evidence and to establish specific nutritional recommendations for preventing or treating sarcopenia in older adults.

**Keywords:** sarcopenia; nutritional interventions; nutrients; food; dietary patterns; nutritional supplements; ageing

## vii. Resumo

A sarcopenia é definida como a perda progressiva e generalizada da massa muscular esquelética e do desempenho funcional e é considerada uma grande ameaça ao envelhecimento saudável.

Existe um conjunto crescente de evidência que associa a nutrição e a sarcopenia nos idosos.

Assim, o presente estudo tem como objetivo rever a literatura e analisar a informação existente sobre intervenções nutricionais que previnam ou tratem a sarcopenia em idosos.

As intervenções nutricionais apresentam-se como a estratégia mais promissora quando se trata de prevenir ou retardar o desenvolvimento da sarcopenia, especialmente em indivíduos sedentários.

As abordagens mais estudadas são uma alimentação equilibrada, a ingestão adequada de proteínas (especialmente as ricas em leucina) e existe também evidência sobre o papel da suplementação com leucina e/ou HMB nesta condição. Além disso, existem alguns estudos sobre a associação dos ácidos gordos ómega-3 com o tratamento da sarcopenia.

O efeito de minerais como o selénio e o magnésio na sarcopenia necessita de mais investigação, uma vez que a pouca evidência existente sobre este tópico mostra que podem ser relevantes para a prevenção da sarcopenia.

Em conclusão, existe informação promissora acerca da nutrição e da alimentação como estratégias-chave para a prevenção e tratamento da sarcopenia, além da promoção da função física e da qualidade de vida. No entanto, são necessários mais estudos para reforçar esta evidência de forma a que seja possível estabelecer recomendações nutricionais específicas para a prevenção ou tratamento da sarcopenia nas pessoas idosas.

**Palavras-chave**: sarcopenia; intervenções nutricionais; nutrientes; alimentos; padrões alimentares; suplementos nutricionais; envelhecimento

## 1. Introduction

Sarcopenia is a muscle disease that results in several adverse outcomes such as: falls, fractures, physical impairment, morbidity and mortality (1). Since 2016, this condition is recognized as a disease in the International Classification of Diseases code (2).

According to the European Working Group on Sarcopenia in Older People (EWGSOP2) consensus, sarcopenia is defined by low muscle strength and low muscle quantity/quality (1). Physical performance is an indicator of severity (1,3). Thus, this disease is identified when low muscle quantity or low muscle quality is confirmed.

To assess muscle strength, handgrip strength and the chair rise test are considered the reference methods by the EWGSOP2 consensus. The gold standard techniques to evaluate muscle mass are computed tomography (CT) and magnetic resonance imaging (MRI). However, Dual-energy X-ray absorptiometry (DXA) is the preferred alternative method since it is a more widely available instrument (1). Bioelectrical impedance analysis (BIA), although considered less precise and more sensitive to changes in water body content, is also a valid method to assess muscle mass (1,4). Furthermore, the gold standard to evaluate physical performance is the Short Physical Performance Battery (SPPB). However, gait speed and the Timed-Up and Go Test (TUG) are also valid methods (1). To assess muscle quality, CT, MRI or BIA-derived phase angle measurement are used although there is not a consensus on which one to use in clinical practice (1,5).

Sarcopenia is considered as severe if all the three parameters identified above are present (1,3). This condition is associated with a number of adverse outcomes such as: longer length of hospital stay (6), higher hospital costs and high personal and social burden. Also, mortality and morbidity rates are higher in sarcopenic individuals (7).

Sarcopenia can result only from the ageing processes, i.e., primary sarcopenia, or it can be a result from pathogenic mechanisms that are nutrition-related (e.g. protein deficiency), disease-related (e.g. cachexia) or activity-related (e.g. sedentarism), i.e. secondary sarcopenia (8).

The prevalence of sarcopenia ranges from 1% to 30 % in older adults, i.e., individuals aged 65 years or older (9).

As the global population ages, the prevalence of age-related sarcopenia is expected to increase. Thus, it is essential to develop standardized diagnostic, guidelines and treatment options in order to allow early identification and treatment (10).

Prevention strategies to maximize the peak of muscle mass as individuals get older should start in early life through the improvement of diet and nutrition alongside with physical exercise, if possible (4,11,12). Thus, ensuring diets of adequate quality throughout life may help to preserve muscle function for as long as possible (4,13).

Since there is no pharmacological treatment yet available to treat this condition, in the past few years, nutrition and exercise are possible strategies for the prevention and the management of sarcopenia (4).

Although physical exercise (e.g. resistance training) exerts positive effects on sarcopenia (4), most older adults are sedentary and either do not want or are unable to exercise so nutritional interventions might be the best approach to treat or prevent this muscle disease.

Over the past decade, evidence has been suggesting that there is an association between nutrition and muscle strength, mass and function in older adults (7,14).

Poor nutrition is common in older age and it is associated with adverse effects on muscle in older adults (11,15). As individuals grow older, besides the lower levels of physical activity and a decrease in energy needs, food consumption also declines and energy intakes tend to decrease (15).

The loss of appetite (‘anorexia of ageing’), poor oral health, changes in sensory perception and personal factors are some of the drivers of low food intake (15). Thus, this can lead to undernutrition which is a state resulting from lack uptake or intake of nutrition that will change body composition and body cell mass and it is considered one of the primary causes of sarcopenia (16). Adding to a poor nutritional status in a context of advanced age is the presence of anabolic resistance, which is characterized by a reduced response to anabolic stimuli (feeding), leading to higher needs of dietary protein compared to younger individuals (17). Moreover, oxidative stress and inflammation are present on sarcopenia’s etiology. Besides protein and amino acids (especially leucine), other specific nutrients such as: vitamin D, n-3 polyunsaturated fatty acids (n-3 PUFAs) and antioxidants have been studied, either as single supplements or in combination with other supplements for the treatment or management of sarcopenia. Also, evidence has shown the benefits of ‘a balanced diet for functional capacity on elderly (13,18).

Regarding the available information on the association between nutrition and sarcopenia, nutritional interventions are considered as promising approaches in the prevention and management of sarcopenia. (12,19).

Intervention studies involving specific nutrients such as proteins, especially those rich in leucine, ß-Hydroxy ß-Methylbutyrate (HMB**)**, vitamin D, minerals, n-3 PUFAs and antioxidant nutrients have been a focus of recent research. Also, food, the Mediterranean diet and combined oral supplements and their possible role on sarcopenia prevention and management were also studied.

Therefore, the present study aims to review the literature and to analyze the existent information regarding nutritional interventions for preventing or treating sarcopenia in older adults.

## 2. Methods

The article's search was conducted on the MEDLINE via PubMed database to identify suitable articles from 2008 to present. The search terms included the following: "sarcopenia AND?", "sarcopenic", 'nutritional interventions', 'nutrition', 'elderly', 'older age', 'protein', 'amino acid', 'leucine', 'vitamin D', 'oral nutritional supplements', 'muscle mass', 'diet', 'dietary patterns'. On PubMed, the filters were set to allow only 'human' studies, 'clinical trials' and 'review' and studies in English. Also, studies where participants had decreased functional status due to other specific health conditions such as diabetes, heart failure, chronic liver diseases, etc. were not included.

Using the search terms identified above, 1732 studies were identified through database searching. After removing duplicates, there were 1344 records left. Of these, 1178 studies were immediately excluded because they did not have any information about nutritional interventions or nutrition itself in the treatment or prevention of sarcopenia. Also, 88 studies were excluded either because their population were younger adults (<50 years old) or they focused on patients with chronic or acute diseases besides sarcopenia and/or frailty. Thus, a total of 65 articles were reviewed (Fig.1).

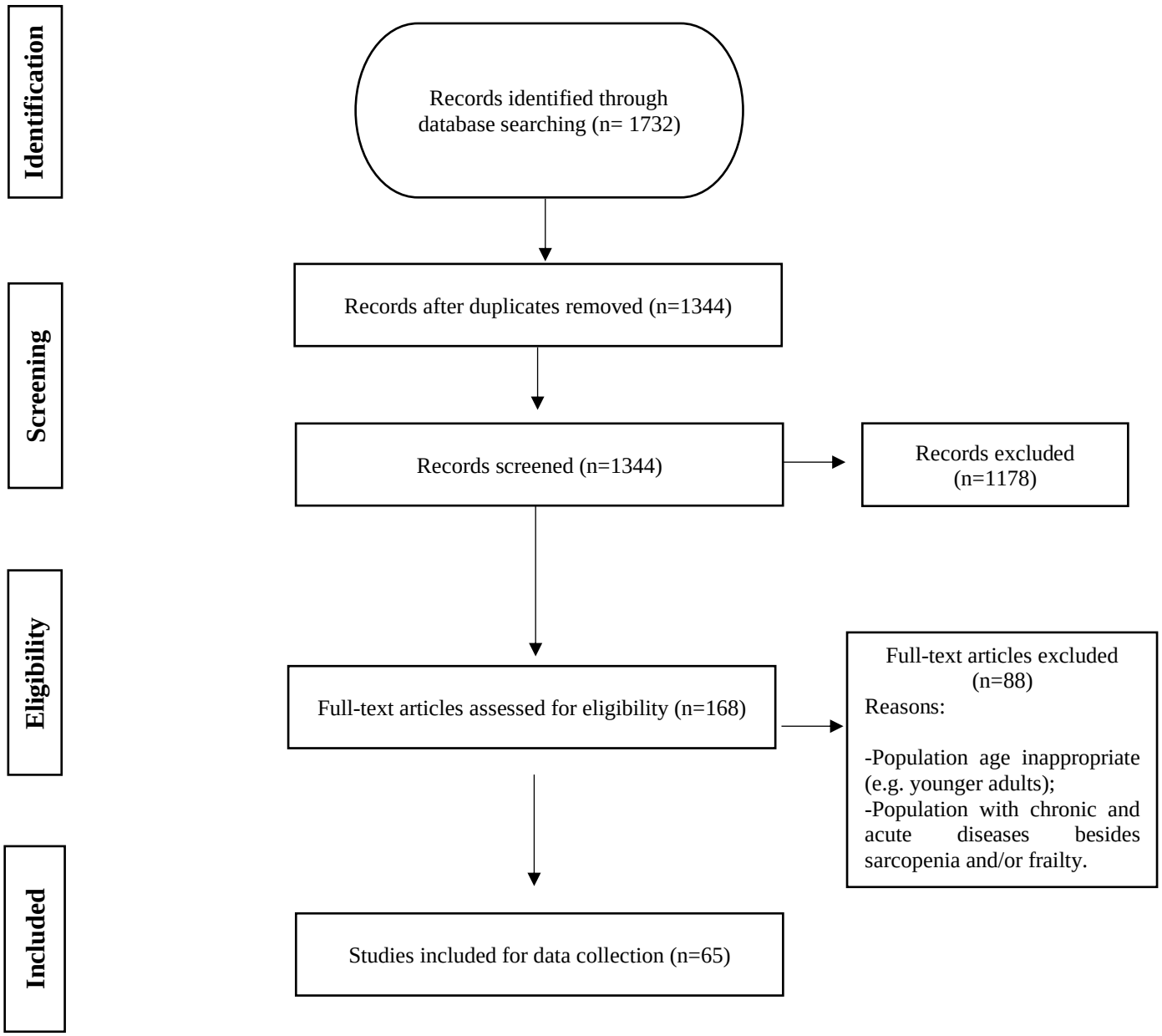


**Fig. 1.** Flow-chart of search strategy and study selection based on Preferred Reporting Items for systematic reviews and meta-analyses (PRISMA) guidelines (20).

## 3. Nutritional interventions in sarcopenia in older adults

Nutritional intervention studies regarding sarcopenia prevention or treatment are still scarce. However, there is evidence regarding interventions involving specific nutrients, food or dietary patterns.

Therefore, the following sections will provide an overview of current data on nutritional interventions and their role in the prevention and/or management of sarcopenia.

Table 1, displayed in attachments, summarizes the main studies regarding nutritional interventions in sarcopenia in older adults.

### 3.1 Protein

Dietary protein provides amino acids that are needed for the synthesis of muscle protein as well as acting as an anabolic stimulus, with direct effect on protein synthesis (12).

This macronutrient is of utmost importance in older age and in the pathogenesis of sarcopenia due to its role in counteracting anabolic resistance to protein ingestion, a phenomenon that is common in older individuals that limits muscle maintenance and growth. Also, dietary needs for protein appear to increase with age (15,21). Indeed, there is some observational evidence that links low protein intakes to the loss of muscle mass and strength in older individuals. Recently, two consensus studies, ESPEN Expert Group (21) and the PROT-AGE Study Group (22), recommended that diet should provide 1.0 to 1.2 g protein/kg body weight/day for healthy older individuals. These values are significantly higher than the recommended dietary allowance (RDA) that has been set for healthy adults of all ages: 0.8 g protein/kg bodyweight/day (12) supporting that the RDA is not enough to maintain nitrogen balance and prevent loss of muscle strength and mass in people aged 65 and older. Moreover, older individuals require more protein to offset inflammatory and catabolic conditions associated with chronic and acute diseases (23).

To strengthen the fact that protein dietary intake needs to be higher with ageing, Mitchell et al. (2017) conducted a 10-week randomized controlled trial in 29 men aged

>70 years who were provided with a complete diet containing either 0.8 (Recommended Daily Allowance (RDA) or 1.6, twice the Recommended Daily Allowance (RDA2) /g protein/kg bodyweight/day. While appendicular lean mass (the amount of lean mass of the upper and lower limbs) decreased in the RDA group, it remained unchanged in RDA2 group. Also, positive effects were found on leg power only in the RDA2 group. These findings support the importance of a higher protein consumption in older age (24).

Moreover, findings of the systematic review and meta-analysis conducted by Coelho-Júnior et al. (2018), suggest that better lower-limb physical performance is associated with a higher protein intake (1-1.2 g/kg bodyweight/day) when compared to the RDA (0,8 g/kg bodyweight/day) in community-dwelling older adults (aged > 60 years). Also, low protein intake (<1 g/kg bodyweight/day) was positively associated with lower grip strength (25).

Besides protein quantity, source and amino acid composition are also important. For instance, leucine, an essential amino acid, is considered as the most potent amino acid to stimulate muscle protein synthesis in older people. The biological pathways on which leucine act are the activation of the mammalian target of rapamycin (mTOR) which is a regulator of leucine effects on mRNA translation essential for skeletal muscle protein synthesis and it also interacts with proteolytic mechanisms by attenuating skeletal muscle breakdown (26).

Maybe due to its higher content in leucine, animal proteins seem to have a higher anabolic effect compared to plant proteins (27) and even in the animal protein group there are some proteins which are more effective at increasing muscle protein synthesis (MPS) than others. For example, whey protein, a milk protein, is considered as a 'fast protein' due to its association with the fast release of amino acids, will probably be more effective at simulating MPS compared to casein, another milk protein that is considered a 'slow protein' (22).

Also, meal distribution of dietary protein and its effects on sarcopenia have been an emerging topic of interest. There are several studies that showed that the equal distribution of daily protein intake across three meals containing 25 to 30 g of protein per meal can stimulate MPS (22,28,29). However, there are also other studies that showed that with a main high protein meal (pulse feeding), anabolic benefits can also be reached (30). Bouillanne et al. (2012) conducted a prospective randomized study in 66 malnourished and at-risk elderly patients (30). The participants consumed 1.3 g/kg/day

from a diet that provided either an amount that was divided into four meals or >70% proteins at lunch (bolus). The results of the study showed that lean body mass only increased in the group that was fed with the protein bolus diet (30,31).

### 3.2 Leucine

Since leucine is found in almost all proteins, leucine intake is practically impossible to dissociate from total protein intake. Thus, most of the evidence found on leucine effects is from supplementation studies (31).

A recent randomized and placebo-controlled trial published by Martínez-Arnau et al. in 2020, who studied the effects of leucine supplementation in 50 participants aged 65 and over showed that the administration of 6 g/day of leucine improved physical performance measured by walking speed and also improved lean mass index (32).

In 2018, a randomized, controlled trial conducted by Devries et al. tested the twice-daily consumption of 15 g milk protein containing 4.2 g leucine against 15 g of mixed protein (soy and milk) containing 1.3 g leucine, as part of a diet providing 1 g protein/kg/day in 22 healthy older women aged between 65 and 75 years (33). Results showed greater acute (hourly) and integrated (daily) myofibrillar protein synthesis (myoPS) responses over six days with the 15-g protein-containing beverage with 4.2 g leucine (31,33) suggesting that leucine has an important role on stimulating MPS.

Moreover, a meta-analysis by Martínez-Arnau et al. published in 2019 included 23 studies that tested the effect of leucine or leucine-enriched protein in the treatment of sarcopenia in a wide variety of participants. In these studies, supplemented leucine was administered alone, in leucine-enriched casein/whey protein or in an essential amino acid (EAA) mixture at doses ranging from 1.2-6 g/day and in nine of them leucine was co-supplemented with vitamin D (34). The duration of the nutritional interventions varied from 1 day to 17 weeks. The meta-analysis revealed that leucine-supplementation, with or without co-supplementation of vitamin D, increased lean mass in 63% of the studies. Furthermore, other parameters such as muscle strength and walking speed also improved in several studies supporting the idea that leucine presents beneficial effects on sarcopenia parameters (34).

Findings of the systematic review and meta-analysis conducted by Xu et al. (2014) that included nine randomized controlled trials in which most participants were aged 65

or more also showed that leucine significantly increases muscle protein synthesis in older individuals and that it can have positive impacts in those who are sarcopenic (35).

### 3.3 ß- Hydroxy ß-Methylbutyrate (HMB)

HMB is an active metabolite of leucine that has been studied as a potential supplement to improve muscle quality and therefore to prevent or treat sarcopenia. HMB acts by modulating protein degradation and it has also been shown to directly upregulate protein synthesis through the activation of mTOR signaling pathway (26). It also promotes muscle tissue response to insulin-like growth factor (IGF-1), an endogenous growth hormone (26,36). There is a rationale for supplementation with HMB in sarcopenic older adults since it is known that there is an age-related decline in its concentrations (4,37).

In a randomized controlled double-blinded trial carried out by Deutz et al. (2013) in 24 older adults (four men and 20 women) showed that HMB supplementation was able to preserve muscle mass in older adults who were confined to complete bed rest, a wasting condition, for ten days (38). Also, a recent double-blind placebo controlled trial conducted by Din et al. in 2018 that analyzed the effects of HMB supplementation (and exercise) on muscle mass and function in 16 healthy older men concluded that supplements containing HMB free acid were associated with improvement in muscle mass in the intervention group (39).

Wu et al. (40) conducted a systematic review that included seven randomized controlled trials to explore the effects of HMB supplements on muscle loss in older adults. It included 287 older adults aged 65 or more in which 147 of them received the HMB supplementation and 140 were in the control groups. The results showed that supplementation not only contributed to preserve muscle mass but also to prevent muscle atrophy in older adults (40).

### 3.4 Vitamin D

Vitamin D is a fat-soluble vitamin that regulates and modulates the function and physiology of several human systems, including the skeletal muscle (41). For that reason, vitamin D is essential for the normal development and growth of muscle (41,42).

Vitamin D deficiency is a common health problem, particularly in elderly and maybe due to low dietary intake and also insufficient exposure to the sun (41). This vitamin deficiency is associated with many adverse outcomes such as reduced muscular strength and power, poor physical performance and an increased risk of falls and fractures (42).

For all these reasons, it is plausible to hypothesize that an older person with vitamin D deficiency might be at risk of developing sarcopenia.

Over the last few years, several authors studied the effects of vitamin D supplementation on muscle mass and function. Pfeifer et al. conducted in 2009 an interventional study in 242 community-dwelling older adults (≥70 years old) which were supplemented with either 1000 mg of calcium or 1000 mg of calcium plus vitamin D for twelve months. Results showed that, compared to the control group, the group supplemented with calcium plus vitamin D demonstrated improvements not only in muscle strength (hand grip strength and knee extension strength) but also in physical performance measured by the TUG test (43).

In a recent narrative review (2019) conducted by Remelli et al., the association between vitamin D deficiency and sarcopenia was studied. Several potential positive effects of supplementation with vitamin D were shown on appendicular muscle strength assessed by handgrip and knee extension strength and on physical performance in older individuals who had vitamin D deficiency (41). Also, a systematic review conducted by Lamberg-Allardt et al. in 2013 including 35 studies showed that vitamin D supplementation was also shown to exert benefits on hip muscle strength, handgrip strength and lower limb strength in elderly (44).

Although there are several studies that support the beneficial effects of vitamin D on the prevention or treatment of sarcopenia, the available literature on this theme is still controversial (41). In a randomized double-blind placebo-controlled trial conducted by Levis and Gómez-Marín in 2016, with a sample composed of 130 sedentary men with ages between 65 to 90 years, a daily capsule containing 4,000 IU cholecalciferol (vitamin D3) was given to the intervention group for nine months in order to test its effect on physical function. The results showed that, although the vitamin D3 supplement did increase serum levels of 25-hydroxyvitamin D in the intervention group, no improvements in SPPB score or gait speed were seen suggesting that supplements

containing vitamin D are ineffective at preventing function decline in sedentary older individuals (45).

Also, another randomized controlled trial conducted by Shea et al. (46) in 2019 analyzed the effects of vitamin D supplementation on lower-extremity power and function on 100 healthy people aged 60 years or older who presented vitamin D deficiency with serum levels ranging from 8 to 20 ng/ml. The intervention group took a vitamin D supplement (880 IU vitamin D3/day) for twelve months. Results showed that, although vitamin D serum levels increased in the intervention group, the vitamin D supplement did not affect lower-extremity power, strength or lean mass in healthy older adults (46).

### 3.5 Minerals: calcium, selenium and magnesium

Minerals are crucial for regulatory and structural body functions, playing a role in muscle metabolism and particularly in muscle function (47). Thus, it is plausible to hypothesize that minerals may contribute to prevent and treat sarcopenia.

**Calcium** is considered the main regulatory signaling molecule for muscle fibers so its deficiency can potentially lead to the development of sarcopenia (14). For example, the results of the fourth Korea national health and nutrition examination survey (KNHANES IV) (48) showed that daily calcium intake was positively correlated with appendicular skeletal muscle mass in 1339 older individuals, 592 men and 707 women. This study also showed that subjects in the highest tertile for daily calcium intake had a lower odds ratio for sarcopenia when compared to participants in the lowest tertile, suggesting a strong inverse association between daily calcium intake and the development of sarcopenia (48). Moreover, a cross-sectional study carried out by Petermann-Rocha et al. in 2019, using UK Biobank data, analyzed 396,383 European participants in order to study the associations between different factors and sarcopenia, revealed that higher levels of dietary calcium were associated with a lower prevalence of sarcopenia (49).

However, not all studies showed an association between calcium and sarcopenia or muscle parameters. The Maastricht Sarcopenia Study (2016) which included 227 community-dwelling older adults did not found any significant difference in daily calcium consumption between the sarcopenic and non-sarcopenic individuals (50).

**Selenium** is another essential trace element (14) and one of the most important antioxidants in humans (51). There are several studies which support the benefits of this

mineral on muscle parameters in elderly individuals. Chen MD et al. (2014) conducted a study that aimed to investigate the association between serum selenium levels and skeletal muscle mass in 327 elderly individuals. The results showed that low serum selenium levels were associated with a higher risk of low skeletal muscle mass (51). Also, in a case-control study conducted by Verlaan et al. in 2017, with a sample of 66 older participants, a significant lower intake of selenium in the sarcopenic group was found (52).

**Magnesium** is an essential ion for the maintenance of health and it is involved in over 600 enzymatic reactions, including protein synthesis (53). As a result, magnesium is potentially associated with beneficial effects on muscle parameters such as muscle mass and consequently physical performance.

A cross-sectional analysis of 396,283 European participants conducted by Petermann-Rocha et al. in 2019, revealed that higher levels of dietary magnesium were associated with a lower prevalence of sarcopenia (49). Another cross-sectional study carried out by Welch et al. in 2015 that included 2570 women aged 18 to 79 years showed that dietary magnesium was positively associated with indices of skeletal muscle mass and leg explosive power, in women of all ages (54).

Thus, although further studies are needed to clarify and confirm magnesium effects on muscle parameters, considering its dietary intake or supplementation on the prevention of sarcopenia appears to be relevant.

### 3.6 N-3 Polyunsaturated Fatty Acids (PUFAs)

A chronic low-grade inflammation associated with age (‘inflammaging’) is implicated in the aethiology of sarcopenia and it involves increases in the production of inflammatory factors such as C-reactive protein (CRP) and interleukin-6 (IL-6) (12,15). Lowering inflammation with anti-inflammatory agents such as PUFAs might offer a window of opportunities to treat or prevent sarcopenia (55).

In the Hertfordshire Cohort Study that was conducted by Robinson et al. in 2008 in 3000 older individuals, each additional portion of fatty fish (rich in PUFAs) consumed per week was positively associated with a significant gain in grip strength in both men and women (56).

Abbatecola et al. in a study conducted in 2009 which included 884 participants suggested that higher plasma levels of n-3 fatty acids may play a protective role on physical performance decline in older individuals (57). Moreover, in a cross-sectional study from 2014 carried out by Welch et al., a higher dietary consumption of PUFAs has been positively associated with a greater improvement of skeletal muscle mass in women aged 18-79 years (58).

Also, a recent review conducted in 2016 that studied the effects of dietary omega-3 on muscle quality and composition in older adults concluded that fish-oil has the capacity to overcome anabolic resistance and, therefore, stimulate muscle mass growth (59).

Altogether, the results of the above mentioned studies suggest that a higher dietary consumption of PUFAs (e.g., fatty fish) might be a low-cost strategy to prevent or even treat sarcopenia in older adults.

There is also current evidence on supplementation with omega-3 PUFAs alone and how it can exert benefits on the treatment or prevention of sarcopenia in elderly.

Yoshino et al. in a study conducted in 2016, with a sample composed of 20 healthy men and women 60-85-year-old, showed that n-3 PUFA supplementation was associated with changes in the muscle transcriptome that contributes to stimulate skeletal muscle anabolism and therefore, attenuate anabolic resistance in older adults (55,60).

An intervention study conducted by Smith et al. (2015) evaluated the efficacy of fish oil-derived n-3 PUFA therapy on muscle mass and function in 44 older men and women (60-85 years). The intervention group followed a six-month, 4g/day n-3 PUFA supplementation and, compared to corn oil placebo (control group), n-3 PUFA therapy (1.86 g eicosapentaenoic acid (EPA), 1.5 g docosahexaenoic acid (DHA)) increased thigh muscle volume, hand grip strength and one repetition maximum (1-RM) upper-and lower-body muscle strength in the healthy older individuals (61).

Moreover, Hutchins-Wiese et al. (2013) showed that fish oil supplementation (2 capsules per day for 6 months) improved physical performance, measured by change in walking speed, in 126 postmenopausal women (62).

Notwithstanding this, not all studies on PUFAs supplementation showed effective results. An interventional study carried out by Krzymińska-Siemaszko in 2015 did not demonstrate any effect of 12 weeks of omega-3 supplementation (containing 660 mg EPA and 440 DHA a day) on muscle strength, gait speed (physical performance) or muscle

mass in 53 older adults with low muscle mass (63). The authors hypothesized that the ineffectiveness of omega-3 PUFAs supplementation may be due to several aspects such as low sample size, low dosage of EPA and DHA, low duration of the study and even due to the characteristics of the population in study (4,12,31,55).

### 3.7 Antioxidant nutrients

Oxidative stress is a factor involved in the ethiology of sarcopenia (4). Oxidative damage occurs due to an imbalance between the production of reactive oxygen species and the antioxidant defenses (4) which contributes to losses of muscle mass and strength in older adults (16). Thus, a diet rich in antioxidants, such as carotenoids, selenium, flavonoids and tocopherols among others, might present beneficial effects by attenuating oxidative stress and, therefore, prevent decline of physical function (12,16). Indeed, a recent observational study by Chen et al. (2014) demonstrated that low selenium levels were associated with low muscle mass in 327 Taipei older individuals (51). Also, the InCHIANTI (2014) study showed that community-dwelling older adults with higher plasma carotenoid levels had a lower risk of developing poor knee, hip and grip muscle strength over a period of 6 years (64). Higher plasma carotenoids levels were also associated with a lower risk of developing severe walking disability in older adults (65).

Thus, the above mentioned studies suggest that a diet rich in antioxidants (found in fruits and vegetables) can promote antioxidant protection and lower oxidative damage.

However, authors alert to the fact that high-dose antioxidant supplementation usually is not beneficial and can even be harmful to older individuals. (4,66). In an interventional study from 2016, carried out by Bjornsen et al. concluded that a high-dose supplementation with vitamin C and E blunted increases in total lean body mass in 34 older men (aged 60-81 years) after strength training (12,67).

Thus, a number of authors suggest that more research is needed to understand and clarify its conflicting reports and its role in sarcopenia (68).

### 3.8 Food

Although this is a rapidly growing area of interest, observational data associating whole foods to its benefits in muscle parameters is still scarce (69–72).

However, there is some research suggesting benefits of higher consumption of dairy foods (69,70) and fruit and vegetables in sarcopenia in older adults (71). In a single-blind randomized clinical trial (2014) that investigated the effectiveness of dairy product intake in the prevention of sarcopenia, Alemán-Mateo et al. concluded that the daily addition of 210 g of ricotta cheese to the habitual diet (18 g protein) during 12 weeks improved appendicular skeletal muscle mass, balance-test scores and it also attenuated the loss of muscle strength in 100 healthy older individuals (50 men and 50 women) (69,70).

Moreover, in a cross-sectional study conducted by Radavelli-Bagatini (2013) that included 1456 older community-dwelling women aged 70 to 85 years, high dairy consumption including: milk, yogurt and cheese was associated with greater appendicular skeletal muscle mass and lean mass, greater grip strength and better physical performance (72).

In the KNHANES IV, an inverse association between frequent vegetables and fruits consumption and the development of sarcopenia in elderly was observed. This study concluded that, compared with men in the lowest quintile of fruits and vegetables consumption, men in the highest quintile had a 68% reduced risk of sarcopenia (71).

Evidence is very limited concerning this subject. More trials are needed to confirm the beneficial effects of these whole foods in the prevention or treatment of sarcopenia in older adults.

### 3.9 Dietary Pattern

#### Mediterranean Diet

Mediterranean Diet is considered a healthy eating pattern characterized by a high intake of vegetables, fruits, whole grains, fish and nuts, a moderate consumption of olive oil and alcohol and a low consumption of red meat (14).

There has been a growing body of evidence showing that the Mediterranean Diet could reduce the risk of experiencing sarcopenia by preserving muscle mass and physical ability in older adults (14,73).

In a recent cross-sectional study (2016) including 2570 northern European women aged 18-79 showed that a higher adherence to the Mediterranean Diet score (MDS) was positively related with a significant increase in leg explosive power and FFM% (fat-free

mass/weight x 100) (74). Also, the KNHANES (2008-2011) which included 3488 older adults (60 years or older), investigated the role of Healthy (similar to the Mediterranean Diet) and Western dietary patterns (which was characterized by high intake of red meat, bread, fast-food, rice cake, soft drinks, noodles and poultry) on appendicular skeletal muscle mass (75). Authors concluded that the Healthy dietary pattern was positively associated with higher muscle mass in older men (75).

Moreover, a longitudinal study that included 2225 elderly (70 years and older) recruited from the Health, Aging and Body Composition (Health ABC) cohort study, concluded that 20 m walking speed was faster among the participants who had a higher MDS even after eight years, suggesting that diet might have a long-term effect on older individuals' physical performance (76).

However, not all studies found an association between Mediterranean Dietary adherence and sarcopenia. For example, a recent prospective cohort study of 2948 Chinese community-dwelling older people (65 years or older) could not establish an association between Mediterranean diet adherence and sarcopenia after a 4-year follow-up in both men and women (77).

Nevertheless, there is a growing body of evidence that supports the protective role and beneficial effects of Mediterranean Diet on muscle parameters in elderly. Thus, to reach a higher level of evidence, authors suggest standardized methods for defining dietary patterns, specific studies on different populations and longer follow-ups (73).

### 3.10 Combined supplements

The impact of combined supplementation with several nutrients and its effects on measures of sarcopenia (muscle mass, muscle strength and physical performance) has been a focus of current research (78–80).

The PROVIDE study, a recent randomized, double-blind, placebo-controlled trial evaluated the effects of a vitamin D leucine-enriched whey protein nutritional supplement on measures of sarcopenia in 380 sarcopenic older adults. Results showed that the oral nutritional supplement containing 20 g of whey protein with 3 g of leucine and 800 IU vitamin D improved appendicular muscle mass and lower-extremity function in sarcopenic older adults after 13 weeks of intervention (compared to the control group) (78).

Also, another randomized, double-blind, placebo-controlled trial conducted in 24 healthy older men showed that participants who received a medical nutrition drink containing 21 g of leucine-enriched whey protein and 800 IU vitamin D (intervention group) at breakfast increased their muscle protein synthesis after breakfast and their skeletal muscle health after 6 weeks of intervention (compared to the placebo group) (79).

Bo et al. showed that the intake before breakfast and dinner of a combined supplementation containing whey protein, vitamin E and D exerted beneficial effects on relative skeletal mass index (measured by bioimpedance analysis) and on muscle strength (handgrip strength) in 60 sarcopenic older adults aged 60 to 85 years old (80).

## 4. Discussion

In recent years, a growing body of evidence has been associating nutritional interventions with muscle mass, strength and physical performance in older individuals.

Considering the current literature, nutrients and diet seem to be the most suitable approach to prevent or manage sarcopenia since there is no pharmacological treatment yet available and although physical exercise is effective at improving muscle health, many older adults are sedentary and/or are unable to practice physical exercise (32).

Also, through this literature review, it can be understood that individual responses to nutrients, alone or combined, on muscle parameters are quite variable in the elderly due to several factors such as lifestyle, environmental and genetic factors.

Studies which focused on protein showed that a higher intake of this macronutrient might be crucial to prevent the decline of muscle mass, strength and physical performance although further trials are needed in order to establish the optimal timing, type and amount of protein intake needed to offer beneficial effects. Regarding amino acids, studies involving leucine supplementation showed that it is the most potent amino acid at stimulating muscle protein synthesis and it also exerted benefits on lean body mass and muscle strength. Moreover, it seems that supplementation with HMB (an active metabolite of leucine) is considered safe and useful in the prevention or management of sarcopenia due to its contribution in preserving muscle mass and preventing muscle atrophy in elderly. However, further studies are still necessary to understand HMB role on muscle strength and function.

There is also evidence suggesting a protective role of vitamin D supplementation on sarcopenia criterion although the available literature on this theme is very controversial. Thus, additional evidence is needed to clarify the effects that Vitamin D supplements have on muscle (mass, strength or function) and its optimum serum levels to guarantee an adequate physical function in elderly (46).

In terms of micronutrients, there were several studies that showed associations between calcium, selenium and magnesium and sarcopenia (47). Although there is some evidence that links higher levels of dietary calcium to lower prevalence of sarcopenia, not all studies could make that association so further trials are needed to prove the effect of daily calcium intake on sarcopenia.

Moreover, although more evidence is needed to support these findings, selenium and magnesium appear to have an important role on muscle mass and physical performance in older individuals so it might be interesting to include them on sarcopenia's management.

Concerning PUFAs, results suggest that a higher intake of omega-3 (ex: fatty fish) might work as a low-cost strategy to prevent or even treat sarcopenia in older adults due to its positive effects on muscle mass and strength. Regarding omega-3 PUFAs supplementation, further research is required to stablish the exact dosage, use, frequency and efficacy of its supplementation on elderly since there are several observational studies that did not show any associations between its supplementation and muscle mass.

There is some current evidence on the role of antioxidant nutrients such as carotenoids and selenium (found in fruits and vegetables) in sarcopenia since they have the power to lower oxidative damage and might also have a role at preventing muscle strength decline. However, authors alert to the fact that high doses of antioxidant supplementation might cause harm to older individuals and for that reason, at present, it should not be considered as a nutritional strategy to treat sarcopenia.

In terms of both adherence to the Mediterranean Diet and the consumption of vegetables and fruits, authors suggest that following this healthy dietary pattern (which is also characterized by high consumption of fruits and vegetables) might help to slow down the progression of aging and also prevent the development of sarcopenia by preserving muscle mass and physical ability (71,76).

However, evidence is very limited. More trials are needed to confirm the beneficial effects of the Mediterranean diet and of these whole foods in the prevention or treatment of sarcopenia in older adults.

Relatively to combined supplementation, recent studies suggest that supplements containing high-quality proteins, leucine, vitamin D and E are considered safe and might have positive effects at stimulating muscle protein synthesis and at improving muscle mass and function, especially in older individuals who cannot exercise (78–80).

Several limitations were found in a number of studies included in this review such as short follow-ups, low duration of the studies, low sample size, low dosages, lack of specific studies in different populations and the lack of standardized measures (e.g. standardized methods to define dietary patterns). Thus, in order to avoid controversial results and to get the best evidence, further studies are needed and there must be a standardization in order to allow reproducibility. Besides, the determination of doses and quantities of supplemented nutrients is also needed.

Therefore, studies with longer follow-ups/duration, standardized methods, a larger number of participants and more randomized controlled trials could contribute to strengthen the body of evidence concerning this subject.

Furthermore, there are still nutritional interventions that need more investigation to prove its effectiveness in sarcopenia criteria. For example, although there is evidence that links vitamin D to the management of sarcopenia (41–43), the clinical relevance of the association between its intake and muscle parameters is still questionable and controversial thus further exploration is necessary.

Antioxidant nutrients (e.g. vitamin C and E) also need more research to understand and clarify its conflicting reports and its role in sarcopenia.

Further evidence is also needed about the role of Mediterranean Diet and whole foods, as in sarcopenia onset and management although there is current evidence showing their positive effects in this disease (74,76).

Regarding strategies to prevent sarcopenia, it is important that older individuals follow healthy dietary patterns (e.g. Mediterranean Diet) that ensure adequate intakes of protein (and leucine), omega-3 PUFAs, minerals, antioxidants and vitamin D and also practice physical exercise.

Regarding treatment strategies for sarcopenia, personalization of diet and individualized approaches are crucial. Also, it is important to combine the preventive

strategies described above with other approaches (e.g. increasing protein intake). Supplementation with protein (including leucine and HMB), vitamin D, omega-3 PUFAs and/or minerals should be integrated if older individuals, for some reason, are unable to follow a healthy diet or if they are deficient or at high risk of deficiency of these important components.

Nevertheless, physical exercise and personalization of the diet are still the main approaches to treat sarcopenia thus, nutrition should be combined with exercise programs whenever possible. Furthermore, it is worth noticing that efforts to prevent sarcopenia should start earlier in life and not just when muscle health starts to decline. Thus, optimizing diet and nutrition throughout the lifecycle is the best approach to prevent this condition (11).

In conclusion, there is promising evidence on nutrition and diet as key strategies to prevent and treat sarcopenia while promoting physical function and quality of life. Notwithstanding this, further studies are needed in order to strengthen the evidence and to establish specific nutritional recommendations for preventing or treating sarcopenia in older adults.

## 5. Critical reflection and practical application

Considering the current literature, nutritional interventions might be the most promising approach to treat or prevent sarcopenia in older adults, especially in those who cannot or do not want to perform physical exercise.

Thus, nutritionists should focus on personalized approaches, i.e. individualized diet, according to the patient needs since it might be the main step to prevent or treat sarcopenia. Also, it is essential to assess nutritional status and body composition frequently in older individuals particularly in those who are at risk for sarcopenia.

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## 7. Attachments

**Table 1. Summary of the effect of nutrition on sarcopenia in studies meeting the inclusion criteria.**

| Authors | Year | Study type | Sample size, age | Methods | Conclusions |
|---|---|---|---|---|---|
| **Mart et al. (32)** | 2020 | Randomized and placebo-controlled clinical trial | 50 men and women living in nursing homes aged 65 and over | L-Leucine in powder form (6g/day) versus placebo (lactose) | L-leucine supplement improved physical performance (measured by walking speed) and also lean mass index in elderly individuals. |
| **Deutz et al. (38)** | 2013 | Randomized, controlled, double-blinded, parallel-group clinical trial | 24 healthy men and women (confined to complete bed rest for 10 days) | HMB (calcium salt, 1.5 g twice daily – total 3 g/day) | HMB supplementation prevented the decline in lean body mass over 10 days of bed rest. |
| **Pfeifer et al. (43)** | 2009 | Randomized, double-blinded placebo-controlled clinical trial | 242 community-dwelling older adults (≥70 years old) | 1000 mf of calcium plus 800 IU of vitamin D versus 1000 mg calcium | Supplementation with calcium plus vitamin D proved superior to calcium alone at improving muscle function (better quadriceps strength and faster performance of TUG) and reducing the number of falls in older adults. |

**Table 1. Summary of the effect of nutrition on sarcopenia in studies meeting the inclusion criteria. (cont.)**

| Authors | Year | Study type | Sample size, age | Methods | Conclusions |
|---|---|---|---|---|---|
| **Seo et al. (48)** | 2009 | Cross-sectional study | 1339 older men and women (over 60 years) | Analysis of data from the fourth Korea National Health and Nutrition Examination Survey (KNHANES) conducted in 2009 | Daily calcium intake was positively correlated with appendicular skeletal muscle mass in 1339 older individuals. Participants in the highest tertile for daily calcium intake had an odds ratio for sarcopenia of 0,295 when compared to participants in the lowest tertile |
| **Petermann-Rocha et al. (49)** | 2020 | Cross-sectional study | 396,283 participants, age 38-73 years | Analysis of data collected at the UK Biobank baseline clinic in order to assess the associations between different factors and sarcopenia. | A self-reported higher intake of minerals such as potassium, calcium and magnesium was associated with lower odds of sarcopenia. |
| **Smith et al. (61)** | 2015 | Double-blind randomized clinical trial | 60 healthy 60-85-year-old men and women | n-3 PUFA therapy (1.86 g EPA, 1.5 g DHA) (4g/day) | n-3 PUFA therapy increased thigh muscle volume, hand grip strength and one repetition maximum (1-RM) upper-and lower-body muscle strength in healthy older individuals. |

**Table 1. Summary of the effect of nutrition on sarcopenia in studies meeting the inclusion criteria. (cont.)**

| Authors | Year | Study type | Sample size, age | Methods | Conclusions |
|---|---|---|---|---|---|
| **Lauretani et al. (64)** | 2008 | Longitudinal study | 948 participants (at a baseline) aged 65 and older | Plasma carotenoids were measured at enrollment and muscle strength was measured at enrollment and six years later | Community-dwelling older adults with higher plasma carotenoid levels had a lower risk of developing poor knee, hip and grip muscle strength over a period of 6 years. |
| **Kim et al. (71)** | 2015 | Cross-sectional study | 1,912 men and women aged 65 and older | Analysis of cross-sectional data from the KNHANES 2008-2009;<br>Food frequency questionnaire (FFQ) was used to obtain the frequency of food group consumption;<br>Body composition was measured with DEXA (dual-energy-X-ray absorptiometry). | A frequent combined vegetables and fruits consumption was associated with a 68% reduced risk of sarcopenia in older men |

**Table 1. Summary of the effect of nutrition on sarcopenia in studies meeting the inclusion criteria. (cont.)**

| Authors | Year | Study type | Sample size, age | Methods | Conclusions |
|---|---|---|---|---|---|
| **Shahar et al. (76)** | 2012 | Longitudinal study | 2225 elderly aged ≥ 70 years | Analysis of data of 2,225 participants from the Health-ABC cohort study; Dietary assessment was evaluated using a FFQ and also a MedDiet score; Walking speed (20 m course) was measured to evaluate mobility performance. | 20 m walking speed was faster among the participants who had a higher Mediterranean Diet (MedDiet) score even after eight years. |
| **Bo et al. (80)** | 2019 | Randomized, double-blind, placebo-controlled trial | 60 sarcopenic older adults aged 60 to 85 years older | Combined supplementation containing whey protein, vitamin E and D | Combined supplements exerted beneficial effects on relative skeletal mass index muscle strength (handgrip strength) in older adults with sarcopenia. |