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Review

# Nutritional approach to sarcopenia

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To maintain a good balance of skeletal muscle mass, it is important to consume high amount of proteins and specific amino acids. In fact, the main nutritional stimulus for protein synthesis is represented by amino acids derived from food protein; in particular, leucine is the main dietary regulator of muscle protein anabolism. It is also important to select the quality of proteins taken up with the diet. Proteins show specific absorption rates based on amino acid composition and are distinguished into "fast" or "slow" absorption proteins. Research has shown that proteins, essential amino acids, leucine, hydroxymethylbutyrate (HMB) and vitamin D play a role in the metabolism of skeletal muscle and are valid nutritional supplements. Being sarcopenia a complex geriatric syndrome, the most effective approach for its prevention and management is represented by multimodal interventions that mainly include physical exercise and nutritional intervention. The important role of nutrition in both prevention and management of sarcopenia is proven by the remarkable evidence linking nutrition with muscle mass and function. Therefore, the best strategy to prevent and treat sarcopenia in older people is to combine a specific exercise protocol and adequate amino acid intake, as expected in the multi-center European clinical trail "Sarcopenia and Physics fRailty IN elderly: multi-component treatment strategies" (SPRINTT).

**Key words**: Skeletal muscle, Diet, Protein

## INTRODUCTION

Malnutrition is one of the main causes of the onset of sarcopenia and frailty. Research showed that specific dietary interventions can prevent or treat the loss of muscle mass and strength related to age. Anorexia of aging consists in loss of appetite and/or reduction in food intake with serious consequences for the individual. This condition can in fact lead to muscle wasting, decreased immune-competence, depression, and an increase in the rate of complications of diseases. In particular, a reduction in food intake along with low levels of physical activity leads to significant loss of muscle mass and strength. Anorexia is strongly associated with a higher risk of quantitative malnutrition due to a reduced caloric intake, and especially in early stages can be related to a high risk of low qualitative intake of individual nutrients, particularly proteins and vitamins. In fact, sarcopenia can be correlated with the onset of selective malnutrition, for example, in terms of lack of individual macro or micronutrients.

Sarcopenia is characterized by a progressive atrophy of type II skeletal muscle fibers, which are mainly involved in the production of power. The turnover of muscle proteins is responsible for the composition and function of the muscle. A reduced synthesis of muscle proteins can be due to many factors, including an inadequate nutritional intake, and a deficit in protein synthesis after absorption because of incorrect response to nutrients, especially amino acids. Between 40 and 70 years a 25% average drop in energy requirement occurs and, consequently with increasing age, there is a progressive reduction in food intake secondary to physiological, psychological and social factors that influence appetite

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and food consumption. The changes that occur during the aging process include loss of taste, smell and vision, changes in secretion and peripheral action of the appetite hormones, effects on gastrointestinal motility, difficulty in chewing and swallowing. These modifications are often associated with functional limitations that negatively impact on the ability to access and prepare food, on depression and dementia, as well as on social problems (many elderly people live alone) [1].

The economic estimate of malnutrition related to the disease is high. Sarcopenia frequently coexists with malnutrition in older patients [2], and poor nutritional status is associated with the onset of frailty. During the International Conference on Frailty and Sarcopenia Research Task Force, in February 2018, the current state of research on nutritional interventions for sarcopenia was discussed; the effective efficacy of the combination of nutritional supplements with physical activity, and the role of nutritional intervention in sarcopenia obese individuals were evaluated. The Task Force concluded that nutritional supplementation should be integrated with pharmacotherapy and physical activity in order to have a substantial impact on individual patients and on the prevalence of sarcopenia [3].

## ENERGY AND DIETARY PROTEIN INTAKE

The amount of food intake and the energy consumed are of fundamental importance to maintain muscle mass and physical performance. In fact, the lack of energy derived from the food consumed, associated with the lack of some nutrients, can determine the onset of sarcopenia. An inadequate nutrient and energy intake triggers a catabolic process that involves both body fat and muscle. Older subjects present with a reduced energy intake, derived from multiple causes including a reduction of appetite (anorexia of aging) [4]. For example, in the InCHIANTI study, which enrolled 802 people aged 65 or over, frailty was found to be associated with an energy intake < 21 kcal/kg [5]. These data were confirmed by further studies, such as the Third National Health and Nutrition Examination Survey involving 4731 US participants over the age of 60, and it was inferred that daily energy intake was lower in people who were frail, followed by the pre-frail ones. On the other hand, subjects who were not frail presented a higher daily intake of energy [6]. The Fourth Korea National Health and Nutrition Examination Survey for sarcopenia reported that energy intake was significantly lower in sarcopenic participants [7]. So, in elderly and frail subjects, protein-energy malnutrition is one of the main risk factors for the development of sarcopenia and its association with adverse clinical outcomes [8].

### Effect of protein metabolism on muscle cells

Skeletal muscle mass is regulated by the balance between protein synthesis and breakdown, and most of the metabolism of muscle proteins depends on the intake of adequate amounts of proteins and amino acids with the diet. In fact, the consumption of high amounts of dietary proteins and/or specific amino acids promotes the synthesis of muscle proteins and inhibits protein degradation. Amino acids derived from food proteins greatly influence the muscle anabolic process, since essential amino acids are the main nutritional stimulus for protein synthesis. In particular, leucine is the main dietary regulator of muscle protein anabolism, because it is able to activate the mammalian target pattern of rapamycin and to inhibit the proteasome [9].

In older subjects, there is a reduction in the anabolic response at low doses of essential amino acids (EAA), whereas the administration of high doses of EAA (eg 10-15 g with at least 3 g of leucine) can stimulate protein synthesis similarly to what happens in adults [9]. Anabolic resistance is defined as the inability of skeletal muscle to stimulate protein synthesis in order to maintain protein mass, and this occurs in case of physical inactivity and muscle disuse. There are also many other mechanisms that can influence muscle metabolism including smoking, alcohol intake, the skin structure, and the presence of chronic inflammatory diseases [10]. Finally, insulin plays a very important role in protein metabolism stimulating, together with amino acids, muscle anabolism.

### Protein sources

For the maintenance of a proper muscle metabolism, it is important to select the quality of proteins taken up with the diet [11]. Various protein sources are characterized by specific anabolic properties according to the amino acid profile, digestibility and bioavailability. Proteins show specific absorption rates based on the amino acid composition, which characterizes “fast” or “slow” absorption proteins. The absorption rapidity of dietary amino acids by the gut is of fundamental importance, because it influences the rate of postprandial protein synthesis. Compared to fast absorption proteins (whey), slow-absorption proteins (casein) stimulate a greater post-prandial accumulation of proteins in the muscle of young individuals. An opposite model has been documented in older individuals. As a result, some authors have shown that whey protein intake stimulates post-prandial accumulation of muscle protein in older subjects more efficiently than casein or hydrolyzed casein [12]. There are few studies that considered the different effect of animal-derived proteins with respect to those of plant origin on skeletal muscle. However, it is known that plant-derived proteins generally contain smaller amounts of EAA and are less digestible than

those derived from animal proteins, since they include lower amounts of lysine, methionine and/or leucine. Recent studies conducted in older populations indicate that consumption of large amounts of plant-based proteins, as a strategy to improve muscle protein synthesis, might not be as effective as expected. Amino acids derived from soy protein are poorly involved in *de novo* muscle protein synthesis compared to amino acids derived from whey. It is therefore recommended to choose meat as a source of high-quality proteins, since it contains essential amino acids that are of fundamental importance for optimal muscle growth and bone development. Therefore, a nutritional intervention aimed at the prevention of sarcopenia should include the consumption of meat 3-4 times a week (white meat twice a week, lean red meat less than twice a week, and processed meat no more than twice a week).

The importance of animal protein intake for the prevention of sarcopenia was also confirmed by the VIP (Very Important Protein) study, conducted during the 2015 Expo in Milan, Italy. A population survey was conducted to evaluate main health parameters with particular attention to the relationship between protein intake derived from animals, muscle mass through the circumference of the calf and the mid-arm muscle circumference, and muscle strength of the upper and lower limbs assessed by means of a resistance test to the handle and repeated test of the support of the chair, respectively. Participants in the highest tertile of protein consumption showed better performance both in terms of grip strength and chair support test compared to the lowest tertile. The same results were found for calf circumference (CC) and mid-arm muscle circumference (MAMC). The results of the VIP survey suggest the presence of a synergistic effect on muscle parameters given by the intake of proteins derived from animals and carrying out physical activity [13].

### Dietary protein requirements

The amount of dietary protein required to meet nutritional needs and maintain the nitrogenous balance is defined as protein requirement. This quantity is widely variable, and is fundamental for the maintenance of muscular homeostasis. Most of the studies conducted on protein metabolism focused on the anabolic response to protein ingestion or individual amino acids, and on the calculation of the adequate daily-recommended dose of high-quality proteins. The European Geriatric Medicine Society, in collaboration with other scientific organizations, launched the PROT-AGE Study Group [14] with the aim of developing updated and evidence-based recommendations that regulate the daily protein needs of elderly subjects. Overall, the current recommendations for protein intake for men and women aged 19 or over indicate 0.8 grams per kg of body weight per day [15]. Recent research suggests a protein intake of 1.0-1.2 g/kg/day for the maintenance of muscle health during the aging process. Older subjects with acute or chronic diseases are recommended to take up 1,2-1,5 g/kg/day of proteins. A further increase in protein requirements occurs in older people with serious illness or malnutrition, for which a contribution of 2.0 g/kg/day of protein is recommended.

Recently, it has been shown that nutritional deficit including low protein intake can aggravate muscular atrophy in individuals with sarcopenia, increasing the rate of adverse events such as hip fractures [16]. A study conducted among older subjects hospitalized for hip fracture due to accidental falls at the Emergency Department of the Teaching Hospital “Agostino Gemelli”, Catholic University of the Sacred Heart (Rome, Italy) explored the relationship between food intake and muscle mass, calculated using bioelectrical analysis. Dietary assessment conducted on these patients showed that over 75% of the participants consumed less than 1.0 g kg-1 day of protein. This study showed that in older subjects with hip fracture there is a significant association between protein-calorie malnutrition and the presence of sarcopenia.

### Optimal timing of protein intake

To improve muscle health, it is important to consider the timing of protein intake, in particular in relation to the performance of physical activity. Most researchers agree that proteins should be introduced homogeneously during the day to ensure a more sustained 24-hour anabolic response. Thus, older people should eat a suitable portion (for example, 25-35 g) of high-quality protein sources at each meal [17], to take between 1.0 and 1.2 g/kg per body weight per day of proteins. To increase the anabolism of muscle proteins, it is important to optimize the timing of protein intake and to coordinate it with the exercise timing. Some data suggest that resistance and aerobic exercise offer the greatest benefit to muscle function when combined with protein intake. Training with resistance exercises determines a transient increase in skeletal muscle protein synthesis by activation of AMP protein kinase, and reduced phosphorylation of 4E-binding protein 1E and other key specific regulators of the initiation of translation. However, studies shown that the highest level of protein synthesis is observed 60 minutes after exercise, since the maximal synthesis rate of muscle proteins is restored and theoretically amplified by the activation of protein kinase B, mTOR, ribosomal protein S6 kinase beta-1, and eukaryotic elongation factor 2 [18]. Therefore, improving the availability of amino acids during this period could offer the greatest anabolic advantage, and

it is also important to maintain the appropriate dietary protein in the post-exercise period to facilitate adaptive muscle response.

## ORAL NUTRITIONAL SUPPLEMENTATION

Nutritional supplementation plays an important role in the prevention of sarcopenia and the treatment of protein-caloric malnutrition. Protein, essential amino acids, leucine, hydroxymethylbutyrate (HMB) and vitamin D are important factors in the management of sarcopenia. Table I summarizes the effects of the main metabolic treatments on the skeletal muscle.

### Essential amino acid

Several studies focusing on muscular anabolic responses following oral or intravenous intake of amino acid mixtures in adults and older people observed a large increase in muscle protein synthesis with an associated reduction in the rate of protein turnover, regardless of the type of mixture. These results suggest the importance of the amino acid intake; in fact, low doses of proteins do not stimulate muscle protein synthesis, since there is a threshold value of the amino acid quantity capable of stimulating protein synthesis. Furthermore, this threshold increases during the aging process and in the presence of inflammation.

Many protein supplementations containing essential amino acids demonstrated their effectiveness in randomized controlled trials, leading to an improved muscle-genesis. The essential amino acids can not be synthesized by the body and are necessary dietary components. A small study comparing a supplement containing only essential amino acids against a supplement containing a balance of essential and non-essential amino acids, suggests that the essential amino acids are responsible for stimulating amino acid-induced muscle protein synthesis [19].

Randomized controlled trials were conducted in Italy to test the efficacy of Aminotrofic®, a supplement composed of essential amino acids. The researchers reported that a dose of 4 grams of this supplement given twice a day between meals resulted in a significant increase in grip strength in the elderly and significant increases in lean mass among sarcopenic individuals. Recent studies have shown that protein-enriched amino acid sources such as leucine play a beneficial and protective role in muscle mass and function in older people; such effects occur at a set minimum dosage [20].

**Table I.** Effects of metabolic treatments on skeletal muscle.

| Metabolic treatments | Effects on skeletal muscle | Validated treatment |
|---|---|---|
| Leucine | • Activation of mTOR signal pathway<br>• Stimulation of protein synthesis/attenuate protein degradation<br>• Nitrogen donor for the synthesis of muscle alanine and glutamine | Yes |
| HMB | • Activation mTOR signal pathway<br>• Substrate for cholesterol synthesis<br>• Stabilization of muscle cell membrane<br>• Stimulation of protein synthesis/inhibition of protein degradation<br>• Inhibition of caspase 8 | Yes |
| Vitamin D | • Muscle fibers type effects<br>– increased number type II fibers<br>– increased size type II fibers<br>• Metabolic effects<br>– increased gene expression of protein<br>– increased metabolism of calcium<br>• Anabolic effects<br>– increased protein synthesis<br>– increased muscle cell growth<br>• Anti-inflammatory effects<br>– reduced cytokine other inflammatory effects | Yes |
| ***Other possible metabolic approches:*** | | |
| **Omega 3** | Mediators and regulators of inflammation<br>Action on the synthesis of muscle proteins through effects on mTOR signaling. | No |
| **Gut microbiota manipulation** | Regulation of inflammatory and redox status<br>Deposition of fat mass<br>Sensitivity to insulin | No |

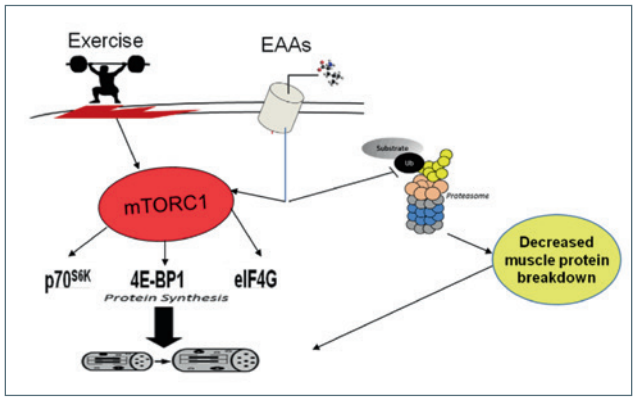


**Figure 1.** Protein ingestion combined with physical exercise stimulates initiation of protein translation via the mammalian target of ripamycin complex 1 (mTORC1). mTORC1 promotes protein synthesis by phosphorylating its substrates eIF4E, binding protein 1 (4E-BP1) and p70 rpS6 kinase (p70S6K). The inhibition of the proteasome by essential amino acids, in particular leucine, reduces muscle protein breakdown.

A study designed to evaluate the effects of a mixture of 6,7 g of essential amino acids enriched with leucine on the metabolism of muscle proteins in elderly and young individuals, showed that a higher percentage of leucine resulted in greater stimulation of the speed of muscle protein synthesis by essential amino acids in the elderly [21].

### Oral nutritional supplement with leucine

At present, the only definitive test is currently limited to the integration of proteins and/or single amino acids. Essential amino acids stimulate myofibrillar protein synthesis, and several animal studies have shown that leucine, a branched-chain essential amino acid, independently stimulates muscle protein synthesis by activating components of the mammalian rapamycin target (mTOR) cascade. Activation of mTOR leads to increased phosphorylation of ribosomal protein S6 kinase 1 (S6K1) and eukaryotic 4E-binding protein initiator factor, thereby increasing muscle protein synthesis rates. Leucine is also an important insulin secretagogue, and it has been suggested as an effective active ingredient for the prevention and treatment of sarcopenia and type-2 diabetes. Leucine stimulates insulin secretion because the intracellular catabolism of amino acids in the pancreatic beta cells increases the intracellular relationship of ATP/ADP, which leads to the activation of insulin. Leucine has been shown to be a nitrogen contributor for the synthesis of muscle alanine and glutamine, and it is able to interact with proteolytic degradation attenuating skeletal muscular atrophy [22]. All these effects have been shown to depend on the dose. Many studies examined muscular anabolic responses following oral or intravenous intake of amino acid mixtures in adults and older people [23].

The PROVIDE study showed that stimulation of the rate of muscle protein synthesis by essential amino acids can be achieved in older subjects taking sufficient quantities of enriched essential amino acids, regardless of physical exercise [24]. This study showed that a targeted nutritional supplement containing whey protein, enriched with leucine and vitamin D in a timely amount of bolus, induced muscle protein growth and muscle strength improvement regardless of exercise among non-malnourished sarcopenic older people at high risk of disability.

### Oral nutritional supplement with HMB

Leucine acts as the main diet regulator for the muscle cell, and it has been recently shown that HMB, a leucine metabolite, is able to stimulate protein synthesis and to improve muscle strength and body composition in the elderly. Therefore, nutritional supplementation with HMB could protect or restore muscle mass in the elderly who have a reduced lean mass. After its absorption, the dietary leucine is converted to $\alpha$-ketoisocaproate, which is further metabolized to isovaleryl-CoA or HMB. In normal conditions, most KICs are converted to isovaleryl-CoA, while only about 5% of leucine is metabolized to HMB. Therefore, to reach pharmacological levels of HMB, this compound should be administered directly, rather than by increasing the leucine dosage. HMB promotes muscle cell membrane stabilization, modulates protein degradation by selectively inhibiting intracellular inflammation, inhibits caspase-8 activation on the cell membrane, increases protein synthesis directly through mTOR activation, and its effects are enhanced by IGF-1. The results of a recent study have suggested that age-related decline in endogenous HMB plasma concentration was positively correlated with lean appendicular mass and muscle strength in young and old [25].

Recently, several clinical studies have been conducted to determine the importance of HMB supplementation as a contributor to the preservation of muscle mass in older subjects. This supplementation can be useful in preventing muscle atrophy induced by bed rest or other factors. Daily administration of a nutritional mixture comprising HMB (2 g), arginine (5 g), and lysine (1.5 g) for 12 weeks, to elderly women who did not exercise was shown to improve physical performance, muscle strength, lean mass and protein synthesis.

In a multicenter, randomized, placebo-controlled, double blind trial, Deutz and colleagues demonstrated that early administration (within 72 hours of admission) of a oral supplement containing high concentrations of protein and HMB in malnourished older subjects was

associated with decreased post-discharge mortality and improvement of nutritional status [26]. A further study was conducted to determine whether HMB was able to attenuate muscle decline in healthy older adults during full bed rest, and the results showed that supplementation with HMB preserved muscle mass [27]. Furthermore, a meta-analysis of seven randomized controlled trials of HMB supplementation in the elderly showed that there is a greater gain of muscle mass in the intervention groups, compared to the control groups [28].
A recent study evaluated the effects of 24-week intake of 2 high-quality oral nutritional supplements (ONS), different for the amount and type of key nutrients in older adult men and women. These supplements had a high caloric quantity (330 kcal): Control ONS (C ONS, 14 g of proteins, 147 IU of vitamin D3) against experimental ONS (E ONS, 20 g of proteins, 499 IU of vitamin D3, 1,5 g CaHMB) taken twice a day. Participants were assessed at baseline, 12 and 24 weeks for gait speed, gripping force, and muscle mass of left and right leg by dual energy X-ray absorptiometry. Both ONS groups (E ONS and C ONS) improved leg strength, grip strength, and gait speed from baseline, without treatment differences. Based on the results, the participants were classified into two groups: those with severe sarcopenia, and those with mild-moderate sarcopenia. High quality oral nutritional supplements improved strength results and leg muscle quality in malnourished elderly adults with mild-to-moderate, but not severe, sarcopenia [28]. These results suggest that CaHMB can improve resistance parameters associated with loss of function and performance.
In conclusion, HMB is emerging as a promising candidate for nutritional interventions against sarcopenia, but further extensive studies are needed to establish the precise effects of HMB on muscle strength and physical function in the elderly, the optimal dosage and possible side effects resulting from chronic supplementation.

### Other possible nutritional supplementation

Vitamin D

Vitamin D deficiency often occurs in elderly patients with reduced muscle mass and predisposes individuals to falls. For example, more than a decade ago, Visser and colleagues showed that older people enrolled in the Longitudinal Aging Study Amsterdam study who had serum 25 (OH) D concentrations below 25 nmol/L were twice as likely to be sarcopenic [29]. The action of vitamin D is mediated by the vitamin D receptor expressed in muscle tissue, and it has been shown that the number of VDRs present in human muscle tissue tends to decrease with age. However, recent studies have shown that the expression of VDR can be modified by vitamin D supplementation. A 4-month RCT demonstrated that women with reduced mobility administered with 4000 IU of vitamin D3 showed a greater variation in the concentration of intra-nuclear VDR than the placebo group [30].
In muscle tissue, vitamin D modulates the expression of the IGF-1 factor-binding protein-3 gene, and the calcium channels of the muscle membrane fibers, together with a neuro-trophic effect on nerve conduction. Therefore, vitamin D deficiency is associated with muscle atrophy, reduced muscle strength and power, reduced balance ability, and consequently increased risk of falls and recurrent fractures.
Factors influencing vitamin D deficiency are reduced sun exposure, decreased renal absorption, and reduced expression of vitamin D receptors. Furthermore, vitamin D exerts an important anti-inflammatory effect, as demonstrated for example in the InCHIANTI study, which showed an inverse association between serum concentration of 25 (OH) D and the proinflammatory cytokine IL-6 in the elderly [31]. Vitamin D deficiency is associated with a lower limb strength deficit, preferentially affecting type II muscle fibers. Since vitamin D deficiency is common in many older subjects, much attention has been focused on the potential therapeutic benefits of such supplementation. A meta-analysis consisting of about 29 vitamin D supplementation studies confirmed a small positive effect on muscle strength [32]. To date, ten meta-analyses of falls prevention studies have been published and, except for one meta-analysis which did not show the benefits of supplementation [33], the remaining studies described a reduction in fall rates from 37% to 12% after vitamin D supplementation. Moreover, considering the strong role played by both vitamin D and physical activity on muscle mass and strength, their combination use can represent an ideal strategy for the treatment of sarcopenia.
Clinical studies showed that muscle strength can improve as a result of vitamin D supplementation. 800 IU of vitamin D significantly improved lower limb strength or 4-11% function after 2-12 months of treatment in individuals aged 65 and over. In conclusion, it is recommended to measure the plasma value of vitamin D in frail older people, particularly in those who live in nursing homes, and to carry out vitamin D supplementation to patients with a plasma level below 40 nmol/L [34]. In order to increase serum vitamin D levels to the optimal value of 75-100 nmol/L, the recommended daily dose (between 400 and 600 IU) may not be sufficient. In contrast, intake between 700 and 1,000 IU per day could facilitate the achievement of satisfactory plasma levels of vitamin D.

Omega 3

Essential fatty acids are involved in muscle metabolism.

Since eicosanoids derive from polyunsaturated fatty acids with 20 carbon atoms, fatty acids are among the mediators and regulators of inflammation, which act on the synthesis of muscle proteins through mTOR signaling.
These evidences raise the possibility that dietary intakes of long-chain polyunsaturated n-3 and n-6 acids and their balance in the diet may be important. Omega-3 fatty acids, including linolenic acid and its metabolic products, such as eicosapentaenoic acid and docosahexaenoic acid present in fish oil, promote muscle anabolism, while a high ratio of omega-6/omega-3 may cause higher IL-6 levels, which interfere with IGF-1 mediated processes by blocking the p70s60k protein phosphorylation, necessary for protein synthesis activation [35]. A recent study conducted on 3,000 elderly adults reported that increased consumption of fish oil is associated with increased gripping force [36]. In particular, the long-chain n-3 polyunsaturated fatty acids may be powerful anti-inflammatory agents and may exert direct effects on the synthesis of muscle proteins via mTOR signaling. Therefore, supplementation of n-3 fatty acids could increase muscle mass in older subjects. In a randomized controlled study, the supplementation with n-3 long-chain polyunsaturated fatty acids in elderly patients resulted in an increase of rate of muscle protein synthesis. In a muscle strengthening trial, the use of fish oil supplements (2 g/day) led to greater improvement in muscle strength and functional capabilities compared to a strength training program.
Integration with LCPUFA n-3 (1.86 g of eicosapentaenoic acid, 1.50 g of docosahexaenoic acid acid) in subjects aged between 60 and 85 years old was associated with increased muscular volume of the thigh over the 6-month follow-up period, as compared with subjects that were given corn oil. Muscle strength at follow-up was also higher in the integrated group [37]. These data offer the promise of a simple and low-cost approach to guarantee the prevention and treatment of muscle mass reduction and muscular functions in old age. However, not all tests have confirmed the efficacy of treatment with essential fatty acids in sarcopenia.

Gut microbiota manipulation

The interaction between the human host and its symbiotic microbial inhabitants plays an essential role in defining the health status of the host [38]. The gastrointestinal tract hosts more than 1,000 distinct bacterial species, with important implications for the bioavailability of nutrients, glucose and lipid metabolism, conditioning the immune system response, protection against pathogens, metabolism and drug toxicity. Some diseases such as obesity, type 1 and 2 diabetes mellitus, cardiovascular disease, inflammatory bowel disease, colorectal cancer, fatty liver disease, multiple sclerosis, and autism, have been hypothesized to result from an imbalance between the host and the microbial species caused by changes in the function of the gastrointestinal tract and other age-related events. This human-microbial imbalance can lead to chronic low-grade inflammation, increased susceptibility to systemic infections, malnutrition, drug side effects and possibly accelerated progression of chronic diseases, fragility, and sarcopenia. In view of these observations, appropriate manipulation of the intestinal microbiota could be exploited to achieve therapeutic gain in old age.
A better understanding of the symbiotic relationship between the aging human host and the intestinal microbiota is also of utmost importance in sarcopenia, since this microbial ecosystem is involved in the regulation of inflammatory and redox status, in the splanchnic extraction of nutrients, in the deposition of fat mass, and in insulin sensitivity. Furthermore, the intestinal microbiota can influence (and can be influenced by) the bioavailability and bioactivity of most of the proposed nutritional factors as remedies against sarcopenia.
Three main approaches are currently available to manipulate the composition and function of intestinal microbiota: probiotics, prebiotics and symbiotics. Probiotics are defined as “live microorganisms which, when administered in adequate quantities, confer benefits to the host”. Prebiotics are “non-digestible food ingredients that positively affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already residing in the colon” (eg. galacto-oligosaccharides, fruit- oligosaccharides, inulin and lactitol). Finally, symbiotics are food supplements that combine probiotics and prebiotics, the administration of which produces health benefits deriving from the synergistic actions of the two components. These three approaches can improve intestinal function, modulate the function of the immune system, and improve the bioavailability of nutrients. However, no study has yet specifically analyzed the effects of these interventions on muscle aging. Therefore, further research is justified to explore the potential application of its manipulation for the management of sarcopenia.

## NUTRITIONAL INTERVENTIONS AGANIST SARCOPENIA IN CLINICAL STUDIES

Being sarcopenia and frailty complex geriatric syndromes, multimodal strategies that include exercise and nutritional intervention seem to be the most sensitive approach for the prevention and improvement of these conditions. The “Sarcopenia and Physics fRailty IN elderly: multi-componenT Treatment strategies “(SPRINTT) is an ambitious multi-center European trial

that attempts to demonstrate the effect of multimodal interventions in frail and sarcopenic older subjects. This study was launched by the Joint Initiative for Innovative Medicines Initiative (IMIJU 11561) in 2014 and has recently completed the registration of 1500 participants residing in communities aged 70 or over who are at high risk for developing disability [39]. Eighty researchers from 11 countries conduct the randomized controlled phase III trial, which is aimed at preventing disability mobility with a multi-component intervention (MCI) consisting of a long-term structured physical activity program, personalized nutritional counseling. The control group will receive a healthy lifestyle education program (HALE).

The SPRINTT clinical trial includes an intervention that can support the nutritional program of the planned physical activity; this intervention consists of two phases. In the first phase, all the participants (MCI and HALE) are subjected to a nutritional screening through the Mini-Nutritional Assessment – Short Form (MNA-SF); in the second phase, the participants randomized to the MCI group will receive personalized nutritional recommendations and will be followed for the entire duration of the clinical trial by the nutritionist/dietician, with the support of the study physician and the participant's general practitioner. The nutritionist/dietician must keep in mind various problems that may be present, including oral/dental problems, difficulty swallowing, gastrointestinal problems, poly-pharmacy, chronic pain, depression, any allergies or intolerances, unfavorable social and financial conditions.

Participants of the SPRINTT study receive a personalized diet program from a dietician/nutritionist who elaborates this plan based on anthropometric data, blood chemistry tests, and concomitant clinical problems. The food preferences of the subjects are also considered. Participants in the MCI group complete a three-day dietary record at baseline and at each annual clinical visit, and based on this registration, the dietician/nutritionist determinate the macro and micronutrient to elaborate the diet plan. The nutritional objectives to be achieved are: a total daily energy intake between 25 and 30 kcal/kg, and a daily protein intake between 1.0 and 1.2 g/kg. These objectives can be customized based on the participant's current nutritional status, and on comorbidities (severe kidney dysfunction, obesity, diabetes). In patients with obesity, the total energy requirements should be calculated based on the correct body weight and not on the actual body weight.

In patients with mild chronic kidney disease it is not necessary to reduce the protein intake provided by the SPRINTT protocol. In patients with moderate CKD it is possible to prescribe a protein intake as foreseen in the protocol, but it is necessary to check the creatine values twice a year. In patients with severe CDK, the daily protein intake should not exceed 0.8 g/kg per day. In patients with diabetes mellitus, it is necessary that the dietician finds strategies to increase the protein intake without altering the glycemic compensation.

In case of further situations that require specific dietary measures, for example patients suffering from hypertension that must follow a low sodium diet, it is necessary that the nutritionist/dietician formulate the dietary strategies to obtain the nutritional target foreseen by the study. Finally, the dietician/nutritionist will provide recommendations on how to improve the intake of vitamin D with the diet.

## CONCLUSIONS

Nutrition plays an important role both in the prevention and in the management of sarcopenia due to the remarkable evidence linking nutrition with muscle mass and function. However, further high-quality studies are needed to allow an understanding of the dose and duration effects of individual nutrients, to clarify the mechanical connections, and to define optimal profiles and nutrient intake schemes for the elderly. In older populations, wider efforts should be made to promote a quality diet alongside a physically active lifestyle, with the aim of preventing disability. Therefore, the best strategy to prevent and treat sarcopenia in older people is to combine a specific exercise protocol and an adequate intake of amino acids. Moreover, although several promising pharmacological approaches are currently under investigation, these are not yet available to treat sarcopenia in frail older people. HMB supplements showed promising effects in muscle improvement mass and function parameters. Protein supplements did not show consistent benefits on muscle mass and function. For the prevention and treatment of sarcopenia, a balanced diet can be proposed: it is advisable to adhere to the Mediterranean diet and to improve physical activity to obtain a significantly lower risk of sarcopenia and frailty.

### Conflict of interest

The authors have no conflict of interest to declare.

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