Novel dietary strategies to manage sarcopenia

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Purpose of review
Sarcopenia is a wasting disease, mostly age-related in which muscle strength and mass decline, such as physical performance. With aging, both lower dietary protein intake and anabolic resistance lead to sarcopenia. Moreover, aging and sarcopenia display low-grade inflammation, which also worsen muscle condition. In this review, we focused on these two main targets to study dietary strategies.

Recent findings
The better understanding in mechanisms involved in sarcopenia helps building combined dietary approaches including physical activity that would slow the disease progression. New approaches include better understanding in the choice of quality proteins, their amount and schedule and the association with antioxidative nutrients.

Summary
First, anabolic resistance can be countered by increasing significantly protein intake. If increasing amount remains insufficient, the evenly delivery protein schedule provides interesting results on muscle strength. Quality of protein is also to consider for decreasing risk for sarcopenia, because varying sources of proteins appears relevant with increasing plant-based proteins ratio. Although new techniques have been developed, as plant-based proteins display a lower availability, we need to ensure an adapted overall amount of proteins. Finally, specific enrichment with leucine from whey protein remains the dietary combined approach most studied and studies on citrulline provide interesting results. As cofactor at the edge between anabolic and antioxidative properties, vitamin D supplementation is to recommend. Antioxidative dietary strategies include both fibers, vitamins, micronutrients and polyphenols from various sources for positive effects on physical performance. The ω_3-polyunsaturated fatty acids also display positive modifications on body composition. Gut microbiota modifiers, such as prebiotics, are promising pathways to improve muscle mass and function and body composition in sarcopenic patients. Nutritional interventions could be enhanced by combination with physical activity on sarcopenia. In healthy older adults, promoting change in lifestyle to get near a Mediterranean diet could be one of the best options. In sarcopenia adults in which lifestyle changes appears unprobable, specific enrichement potentialized with physical activity will help in the struggle against sarcopenia. Longitudinal data are lacking, which makes it hard to draw strong conclusions. However, the effects of a physical activity combined with a set of nutrition interventions on sarcopenia seems promising.

Keywords
dietary, elderly, muscle, proteins, sarcopenia

INTRODUCTION

Musculoskeletal aging appears as one of the main systems to target in the global understanding of the aging processes. Sarcopenia is defined as a global skeletal muscle decline in both mass, strength and physical function. This wasting condition exposes to various noxious effects, such as falls, disability and death. The current ESGWOP2 definition seems the most operational at this state of art [1]. In the elderly, sarcopenia overlaps with malnutrition and frailty, highlighting the therapeutical role of both physical activity and adapted nutritional support.

Several studies focused on the pathophysiology of age-related sarcopenia and highlighted the

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KEY POINTS

- Diet adaptation is crucial for sarcopenia treatment, targetting anabolic resistance, oxidative stress, and inflammation.
- Lifestyle changes (mediterranean diet) seem more suited to prevention, when supplementation and combinations of supplements target sarcopenia care.
- Protein intake should include higher amounts, source blending, and higher digestibility of proteins.
- The multicomponent approach (rapid whey protein, vitamin D, essential aminoacids) is one of the most promising leads for sarcopenia nonpharmacological treatment.
- Dieatary strategies for sarcopenia are strengthened by physical exercise.

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biological mechanisms underlying decline in muscle strength and mass with aging.

The first mechanism to report is the impairment of protein metabolism (whole body and muscle) with aging. Anabolic resistance includes a loss of efficiency in muscle protein synthesis in response to protein intake, as well as the loss of proteolysis inhibition. Thus, targeting anabolic resistance is a priority in muscle loss. In addition, an increase of splanchnic extraction of amino acids in elderly subjects has also been reported, limiting amino acids bioavailability for muscle. Inactivity, hormonal and growth factors changes also affect negatively protein synthesis. Physical activity remains the first line therapy on muscle protein synthesis enhancement, with specific guidelines in sarcopenia [2]. Nonetheless, modification of dietary habits also optimizes muscle protein synthesis in sarcopenia. In the elderly with sarcopenia, increasing the protein intake to 1–1.2 g/kg/day, by food or supplements, is recommended [3]. Many other parameters should be taken into account, such as the quality of these proteins, their distribution throughout the day, their animal or plant-based source [4].

Redox signaling and oxidative damage are among the other accepted mechanisms underlying the decline of muscle mass and strength with aging. At the cellular scale, neural plaque changes, mitochondrial dysfunction and cellular loss (motoneuron and satellite cell) also contribute to the increase in oxidative stress, inflammation, protein catabolism and apoptosis. In sarcopenia, ESPEN micronutrient guideline [5] reported that deficiency in vitamin B1, B12 and D, carnitine and zinc are in favor of disease development [6].

Dietary fibers, micronutrients, omega-3 polyunsatured fatty acids, such as plant-based proteins all display antioxidant properties that could limit this inflammation circle. Vitamin D is the last main factor to be cited with positive effects on the musculoskeletal system through several pathways including inflammation.

The current global approach to limit sarcopenia tries to combine all the previous elements. Hence, both industrial combinations of high amount of proteins, specific enrichment [essential amino acids (EAAs), vitamin D, micronutrients, and so on] and lifestyle modifications approaches (Mediterranean diet for instance) have been tested to define the best strategy to manage sarcopenia. Multimodal approaches combining nutritional approaches with physical activy will are also promising but will not be discussed in this review.

In the present review, we will develop the positive effects of dietary approaches to reduce aged-related sarcopenia without focusing on the effect of physical activity, developed elsewhere.

TARGETING ANABOLIC RESISTANCE

Amount of proteins

As protein anabolism is proportional to net protein intake in a certain limit, the current recommendations for protein intake (1–1.2 g/kg/day) are sufficient in healthy older adults. However, the intake in many elderly patients remain below, especially in stress conditions justifying an increase in protein intake to reach the same muscle protein synthesis. Hence, in elderly men, a diet providing a double ration for protein had beneficial effects on lean body mass and leg power compared to those remaining at the recommended dietary allowances (RDAs) [7]. The increased protein intake was also related to a better lower limb physical functioning and walking speed performance in a meta-analysis comparing high and low protein intake groups [8].

In addition, higher protein intake kept its effects over two decades upon maintenance of physical function, especially in high-functioning women [9▪].

Hence, sex difference should also be considered, as protein intake enhancement provided an increase in appendicular lean mass in older men [10] contrary to postmenopausal women [11].

Protein intake enhancement with oral nutritional supplements (ONS) with 14–20 g of proteins also provides muscle strength improvement in a 24-week intervention randomized control study, even if this effect was only displayed in those with mild-moderate sarcopenia but not with severe sarcopenia

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[12]. The other combinations of protein enrichment with other strategies are developed below and in Table 1.

Distribution schedule

Every situation in which meal schedule is disturbed decreases dietary protein intake, such as programmed bed rest in hospitalized old men [13]. The linear relationship and the per-meal threshold are the two main hypotheses for the explanation of the relationship between protein intake and muscle response. With similar daily protein intake, protein distribution throughout day was more likely related to robust participants, when uneven distribution was to frailty and fatigue ones [14]. Evenly mealtime protein intake also provided a higher muscle strength composite score in the NuAge study [15]. Furthermore, sarcopenia risk is inversly related to protein intake in a dose–response relationship, even after adjustment on demographic, medical, and lifestyle factors [16▪]. However, protein pulse feeding has a positive effect on lean mass in malnourished elderly [17]. As an increased sensibility to protein synthesis occurs just after exercise, the adequate timing according to physical exercise is also to consider.

Protein quality and sources

Quality of proteins is related to its ability to deliver all of the EAAs in proportion to their individual dietary requirements. Moreover, the digestibility of protein will affect the availability of EAA digested and absorbed. Animal-based proteins provides a higher digestibility and more EAA. Among milk proteins, digestion of whey (rapid protein) is faster than casein. Although peak plasma EAA levels are higher after whey intake, plasma EAA levels will remain elevated longer after casein intake. As casein proteins aggregate into the stomach, the delivery to the intestine is delayed leading to lower hyperaminoacidemia, as compared to whey [18]. With carbon print and financial issues influencing our protein consumption, the choice between either plant or animal-based (meat, dairy, chicken, eggs, fish) protein source becomes crucial. Plant-based proteins (vegetables, nuts, soy, beans, and so on) display a lower anabolic capacity but recent biotransformation processes could overcome the limitations of decreasing the micronutrients assimilation [19].

In a recent work in healthy young men, supplementation with a 400 ml beverage containing either 30 g of milk protein or of 30 g of plant-derived protein (15 g wheat, 7.5 g corn, and 7.5 g pea protein) similarly increased the myofibrillar protein synthesis (MPS) rates [20]. Nonetheless, the amount of wheat protein required in healthy older men is twice higher than casein to reach the same level of MPS in another study [21]. Blending sources of proteins may enhance performance of plant-derived proteins. In healthy older adults, a protein-rich diet with 500 g of meat per week could be achieved with lean meat and several plant proteins [22]. In addition, the risk for sarcopenia is reduced when increasing plant protein intake at the expense of animal, for the same protein intake [16▪]. Moreover, low plant protein intake were associated with poor probability of successful aging, in a combined analysis [23]. No specific plant-based protein type is yet to recommend. And no difference were found between protein supplement type between whey, soy, or whey-soy blended protein in a 6-month supplementation, although both maintained lean muscle mass and physical performance with no difference in muscle strength [24]. Privde information on population Futhermore, no difference between milk or soy-milk supplementation were found upon muscle mass and strength in sarcopenia patients in nursing home [25]. The impact of dietary plant protein in older people has been recently reviewed [26▪]. Innovations in food processing and nutritional strategies may improve the quality of plant-based proteins. The diversification is related to several health benefits. However, their efficiency on postprandial muscle protein synthesis remains to be evaluated.

Specific protein and amino acids enrichment

Among all amino-acid supplementation, citrulline and leucine are among the most studied. Supporting data in older sarcopenia individuals were mostly found on leucine, in which muscle mass was improved in a recent umbrella review [27]. Leucine is an essential and branched chain amino acid. Leucine is more quickly absorbed than other amino acids are. To improve the synchronization between leucine signal and amino acid availability, rapidly digested whey proteins are often associated with leucine [28]. In nonsarcopenic healthy older men, EAA supplementation could improve lean body mass, strength, and physical function, with no physical exercise program [29]. However, long-term use (3 months) fails to display the same positive outcome [30]. Nonetheless, all randomized control trials supporting data for leucine supplementation upon sarcopenia patients remain short-term interventions, with a maximum duration of 13 weeks [31–37,38▪▪]. Moreover, a single bolus strategy of a leucine-enriched whey protein intervention failed to provide any difference in muscle protein

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Table 1. Main outcomes from interventional studies

Ref		Intervention type	FUP	RCT	Population	Main outcome in the intervention group
Amount of proteins						
Mitchell *et al.*	[7]	- complete diet containing either 0.8 g/kg/day (RDA) - 1.6 g/kg/day (2RDA) Before treatment and afte	10w	Y	29 men aged 70 y, RDA ($n=15$) 2RDA ($n=14$)	- increase in whole-body lean mass in 2RDA ($P=0.001$;1.496 1.30 kg, P, - increase in appendicular lean mass in 2RDA ($P=0.022$).
Kim and Park	[9▪]	0.8, 1.2, or 1.5 g/kg/day of protein	12w	N	96 community-dwelling older adults Prefrail or frail participants aged 70–85 years with risk of malnutrition were recruited	- increased protein intake of >0.54 g/kg/day was positively associated with changes in appendicular skeletal muscle mass (ASM)/weight (B = 0.591, $P=0.026$), ASM/BMI (B = 0.615, $P=0.023$), and ASM:fat ratio (B = 0.509, $P=0.030$) in older men..
Rossato *et al.*	[11]	- higher protein intake (~1.2 g/kg/day of protein) - normal protein (~0.8 g/kg/day)	10w	Y	26 postmenopausal women (63.2 ± 7.8 years) higher protein intake (HP) ($n=11$) normal protein (NP) ($n=12$)	increase in lean body mass both in HP (37.1 ± 6.2 to 38.4 ± 6.5 kg, $P=0.004$) and in NP (37.6 ± 6.2-38.8 ± 6.4 kg, $P<0.001$), with no differences between the groups ($P=0.572$).
Cramer *et al.*	[12]	- Control ONS (14gprotein;147IUvitaminD3) - Experimental ONS (20 g protein; 499 IU vitamin D3;1.5 g CaHMB) Both 330 kcal, vitamins, minerals, and nutrients in varying amounts.	24w	Y.	Malnourished and sarcopenic men and women, 65 years and older (n = 330).	- strength improvements (EONS > CONS, $P=.032$) in those with normal grip strength mild and moderate sarcopenia
Distribution schedule						
Bouillanne *et al.*	[17]	- Spread diet (SD): dietary protein was spread over the four daily meals. - Pulse diet (PPD): 72% of dietary protein (1.31 g/kg weight/d on average) in one meal at noon.	6w	Y	66 elderly malnourished or at-risk patients in an inpatient rehabilitation unit. n (SD) = 36, n (PPD) = 30	- improvement of lean mass index ($P=0.005$) - ASMM index ($P=0.022$)
Protein quality and sources						
Gorissen *et al.*	[21]	35-g bolus of wheat protein hydrolysate compared with casein and whey protein and hydrolysates.	–	Y	60 healthy older men [mean 6 SEM age: 71 6 1 y; $n=12$ 35 g wheat protein; $n=12$ 35g-whey protein; $n=12$ 35g wheat protein hydrolysate; $n=12$ 60g wheat protein hydrolysate; $n=12$ 35g micellar casein	- Increase in EAA concentrations after Whey > after casein and WPH - Higher Myofibrillar protein synthesis rates after casein > WPH ($P=0.03$). - Increase in leucine concentrations Whey > WPH-60 ($P<0.01$)
Li *et al.*	[24]	10 g blended protein containing - Whey (7.98) - Soy (8.80 g), - Whey-Soy 8.39 g	26w	Y	123 older > 65y with low lean mass n (Whey) = 31; n (Soy) = 31; n (Whey-soy) = 31; Habitual diet ($n=30$)	no differences in outcomes among treatment groups (ALM, SMI, LM…) Short Physical Performance Battery score were maintained in the treatment groups and decreased in the control group $P<.01$
Chiang *et al.*	[25]	2 x 200 ml/day - milk (96 kcal, 5.2 g protein, 2.6 g fat, 12 g carbohydrates, 260 mg Ca, 620.9 mg leucine) - soy milk (97.4 kcal, 6.4 g protein, 3.0 g fat, 11.2 g carbohydrates, 220 mg Ca, 458.6 mg leucine) + mild resistance exercise training program three times a week (30 min/time).	12w	Y	(>75 years) 35 individuals with sarcopenia in a nursing home $n=12$ control $n=11$ soy milk $n=12$ milk	no difference in supplementation upon muscle mass and strength
Specific protein and amino acids enrichment						
Bírsheim *et al.*	[29]	11 g of EAA arginine two times a day, between meals	16w	N	12 glucose intolerant individuals (67.0 years,7females,5males)	Increase in lean body mass at 12-w but do not at w-16 Improvements in usual gait speed ($P=0.002$), timed 5-step test ($P=0.007$), and timed floor-transfer test ($P=0.022$).
Verhoeven *et al.*	[30]	Leucine with each main meal (7.5 g/day, 5caps/d) or placebo (2.5 g/day, 5 caps/d)	13w	Y	30 healthy elderly men, age 71 y Leucine group $n=15$	No changes in skeletal muscle mass or strength were observed over time
Barichella *et al.*	[31]	- Standard hospital diet +150 kcal complement with Whey Protein (20 g) Leucine (3 g) and Vitamin D (800 IU) per serving - Standard hospital diet	4.5w	Y	Parkinson disease patients $n=150$	- Increased distance walked (mean difference, 18.1 m [0.9–35.3], $P=0.039$) - 4-m walking speed ($P=0.032$) - TUG ($P=0.046$) - SMM index ($P=0.029$)
Liberman *et al.*	[33]	Complement 2/d or isolcaloric control product Complement: 20 g whey protein, 3 g total leucine, 9 g carbohydrates, 3 g fat, 800 IU	13w	Y	Sarcopenic adults (low skeletal muscle mass) aged ≥ 65 years. Active group ($n=137$) Control group ($n=151$)	-IL-6 a significant time × treatment interaction ($P=0.046$): increase was attenuated in the active group
Rondanelli *et al.*	[34]	Moderate level exercise fitness + 40 g of powder (vanilla or strawberry flavor), twice a day providing - 150 kcal and containing 20 g of whey proteins, 2.8 g of leucine, 9 g of carbohydrates, 3 g of fat, 800 IU of vitamin D, and a mixture of vitamins, minerals (calcium, 500 mg), and fibres. - maltodextrins (control group)		Y	$N=127$ age 81 ± 6 years with sarcopenia $n=64$ experimental $n=63$ placebo	- gait speed (0.063 m/s/month [0.043–0.082], $P<0.001$) - muscle mass $P<0.03$
Bauer *et al.*	[36]	Complement 2/d or isolcaloric control product Complement: 20 g whey protein, 3 g total leucine, 9 g carbohydrates, 3 g fat, 800 IU	13w	Y	380 sarcopenic independent-living older adults. Active group ($n=184$) Control group ($n=150$)	- improved chair-stand test (-1.01 s [-1.77 to 0.19], $P=.018$. - appendicular muscle mass (0.17 kg [0.004;-0.338), $P=0.045$.

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Table 1 (*Continued*)

Ref		Intervention type	FUP	RCT	Population	Main outcome in the intervention group
Verlaan *et al.*	[38▪▪]	Posthoc analysis of the PROVIDE study	13w	Y	cf. 36	patients with higher baseline 25(OH)D and protein intake had greater gain in ASMM ($P=0.034$)
Kramer *et al.*	[39]	Leucine-enriched whey protein nutritional supplement containing 21 g of protein, 9 g of carbohydrate, and 3 g of fat.	–	N	15 healthy (69 ± 1 y) and 15 sarcopenic (81 ± 1 y) older men	Muscle protein fractional synthetic rates are not different between groups ($P=0.45$)
Murphy *et al.*	[40]	Leu-enriched protein (3 g leucine, 10 g protein) with/without long chain ω 3-PUFA supplementation (0.8 g eicosapentaenoÿc acid, 1.1 g docosahexaenoÿc acid) with D_2O and muscle biopsies	24w	Y	107 men and women ≥ 65 years with low muscle mass or strength $n=38$ control; $n=38$ Leucine; $n=38$ Leucine + PUFA	No effect of both supplementation on ALM, handgrip strength, physical performance, myofibrillar protein synthesis
Bouillanne *et al.*	[41]	oral dose of 10 g of citrulline or an equimolar mixture of six nonessential amino acids 3 weeks	3w	Y	24 (18 women and six men) malnourished older patients [80;92] years; in inpatient rehabilitation units.	- decrease in splanchnic extraction of dietary amino acid ($P=0.09$) - no difference for BMI, lean mass, ASMM, whole body protein synthesis between groups
Marcangeli *et al.*	[42]	High-intensity interval training with or without citrulline supplementation	12w	Y	81 obese adults	- fat mass decrease (1.04 ± 2.42%, $P<0.05$) - handgrip increase (+4.28 ± 9.36%, $P<0.05$)
Antioxidant and anti-inflammatory nutrients						
Alway *et al.*	[44]	Exercise with or without Resveratrol supplementation 500 mg/day	12w	Y	Older men ($n=12$) and women ($n=18$) 65–80 years. $n=15$/ group (same distribution for each sex)	- increase mitochondrial density - decrease muscle fatigue - increase muscle peak torque (8%) -increase muscle power (14%) - increase mean fiber area by 45.3% and total myonuclei by 20%.
Franceschi *et al.*	[45]	- exercise and balanced diet including proteins - + 1 g curcumin-based supplementation - + 1 g curcumin + supplementation (vitamin D 800 IU/day; Vitamin C 500 mg/day; Isoleucin 3 g/day; Carinitine 1 g/day	12w	N	86 patients 73-y three groups: $n=33$ standard; $n=31$ std + curcumin; $n=22$ std+ curcumin + others	Slight improvement in supplementations group in hangrip test
Smith *et al.*	[46]	− ω3 FA (1.86 g eicosapentaenoic acid (EPA, 20 : 5n23) and 1.50 g docosahexaenoic acid) - equivalent amount of corn oil	8w	Y	16 healthy older adults 10 men and 6 women ≥ 65-y	- no effect on the rate of muscle protein synthesis
Smith *et al.*	[50]	- fish oil–derived n–3 (v-3) PUFA - corn oil	26w	Y	60 healthy 60–85-y-old men or women $n=40$ PUFA $n=20$ corn oil	-increase muscle volume (3.6% [0.2%,7.0%]) - increase handgrip strength (2.3 kg [0.8,3.7])
Da Boit *et al.*	[51]	- long-chain n–3 PUFA (3 g fish oil/d) + exercise; - resistance exercise		Y	50 men and women men: $n=27$, age: 70.6-y; $n=23$ intervention; $n=27$ control	increase in maximal isometric torque in women ($P<0.05$)
Vitamins and minerals						
Nilsson *et al.*	[67]	- Fruit and vegetable intake x 5/d - vs. habitual diet	10w	Y	66 individuals (65–70 years)	no changes in CRP, IL6, TNF-α, MIP-1α, and β, and IL-18
Tominaga *et al.*	[72]	Prebiotic 1-kestose, 10 g/day	12w	N	6-year-old Japanese patients with sarcopenia	- Increase in SMI 3.8 ± 1.0→4.2 ± 1.1, $P<0.01$, - Increase in SMM 12.8 ± 2.3→13.9 ± 2.5, $P<0.01$ - Increase in *Bifidoacteria*
Buigues *et al.*	[73]	- inulin (3.4 g) + fructooligosaccharides (3.5 g) - placebo maltodextrin	13w	Y	50 participants (15 men, 35 women) in nursing homes	handgrip strength ($P<0.05$)
Multimodal						
Bernabei *et al.*	[78▪▪]	- multicomponent intervention - education on healthy aging	78w	Y	1519 individuals aged 70 years or older with physical frailty and sarcopenia,	- SPPB score 0.8 points [0.5–1.1] $P<0.001$ - Smaller decline in Handgrip strength 0.9 kg [0.1–1.6] $P=0.028$ - smaller loss of appendicular lean mass at 36 months 0.49 kg [0.26–0.73] $P<0.001$)

synthesis between nonsarcopenic and sarcopenic older men, after a similar postprandial increase in both groups [39]. However, compared to isocaloric milk or casein product for breakfast, this single bolus supplementation displayed faster and higher muscle protein synthesis rate [37]. Combined in a mixture with leucine-enriched protein in a three-arm randomized control study during 24 weeks in well nourished older adults, leucine alone, and leucine+polyunsaturated fatty acids affected appendicular lean mass, handgrip strength, and physical performance [40].

Citrulline is an amino acid not extracted in the splanchnic area, an interesting condition when considering sarcopenia older patients. According to preclinical studies, citrulline acts through the mTOR signaling pathway with a muscle specific action. Nevertheless, citrulline supplementation in older malnourished patients did not affect whole-body protein synthesis, although increasing lean mass

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and appendicular skeletal muscle mass in malnourished women [41]. When added to physical activity, citrulline enhanced results in modifying body composition by decreasing fat mass ($1.04 \pm 2.42\%$, $P < 0.05$) and increasing muscle strength (handgrip: $+4.28 \pm 9.36\%$; quadriceps: $+10.32 \pm 14.38\%$, $P < 0.05$) in obese adults [42], even in older individuals with obesity [43].

OTHER TARGETS

Antioxidant and anti-inflammatory nutrients

Oxidative stress is involved in skeletal muscle decline with production of serum protein carbonyls. Reactive oxygen species (ROS) are generated in excess with aging and favor damages to muscle proteins and DNA. A low-grade systemic inflammation also occurs that affects muscle metabolic response.

Polyphenols, classified as phenolic acids, stilbenes (resveratrol), lignans, flavonoids, and other polyphenols (curcumin), exhibit antioxidant and/or anti-inflammatory properties. In 65 to 80-year-old individuals following a 12-week training program, resveratrol supplementation did not show a decrease of cardiovascular risk further than exercise alone but increased resistance to muscle fatigue and increased muscle fibers, as compared to control groups [44]. In frail aging adults, curcumin seems to participate in maintaining muscle strength and physical performance [45].

Oils from different sources can provide potential positive effects on muscle. For instance, fish oil is one of the main sources of vitamin D and its ω_3-polyunsaturated fatty acid (ω_3-PUFA) enhanced muscle mass and function [46]. Moreover, ω_3-PUFA showed anti-inflammatory properties and reduction of insulin resistance [47]. Furthermore, low dietary ω_3-PUFA is observed in sarcopenia patients. In a recent meta-analysis, dietary ω_3-PUFA reduced the risk of sarcopenia by 59% [odds ratio (OR) = 0.41, 95% confidence interval (95% CI): 0.26–0.65; $P = 0.0001$] [48]. Supplementation affected lean mass (effect size 0.27, 95% CI 0.04–0.51) and skeletal muscle mass (effect size 0.31, 95% CI 0.01–0.60) [49▪]. Results remains tight in the positive studies evaluating ω_3-PUFA supplementation alone [50]. However, combined with physical exercise, fish-oil supplementation increased muscle function and ameliorated muscle quality in older women only [51].

Alternatives, as olive oil, provided antioxidant properties related to the specific presence and concentration of tocopherols, carotenoids, and phenolic compounds in contrast to other oils [52]. However, consumption fails to change body composition in adults [53].

Vitamins and minerals

Vitamin D displays pleiotropic effects through the VDR (Vitamin D receptor). First described in intestinal cells, the VDR expression is observed in muscle cells, especially in satellite cells. As the number of VDR decreases with aging, systematic supplementation could be done in older people. Vitamin D downregulates the FOXO signaling pathway involved in muscle atrophy and provides an anabolic effect on muscle protein synthesis via the mTORC1 signaling [54]. Vitamin D also reduces production of ROS, improving mitochondrial functioning [54]. Finally, vitamin D acts positively through all pathways involved in muscle decline.

As the effect on muscle strength improvement is more prominent in individuals with serum 25(OH) D concentrations less than 30 ng/ml, vitamin D supplementation should be firstly devoted to these patients [55].

However, 25(OH)-vitamin D measurement should be limited to adapt the correction of the insufficiency for the intial treatment for pharmacological purposes (such as fallers, fractured or patients suffering for bone mineral disorders, renal impairment, or malabsorption), before the maintenance treatment. Supplementation to reach an adapted intake in nonpathological situations do not need 25(OH)-vitamin D dosage. Alone, vitamin D supplementation did not improve grip strength and back muscle strength [56]. In presarcopenic elderly people with deep vitamin D insufficiency (mean 25 (OH)-D 13 nmol/l), a 30 000IU/week supplementation during 6 months showed significant improvement in appendicular skeletal muscle mass but not in handgrip strength [57]. However, the effect of vitamin D supplementation seems enhanced when combined with protein (10–44 g/day), and affects muscle strength but not muscle mass [58]. Combined with leucine-enriched protein supplements, supplementation exhibited an increase in lean mass [37]. With the same kind of mixture, the PROVIDE study confirmed the need to get above the threshold of 50 nmol/l of 25(OH)-vitamin D [38▪▪]. Another analysis of the PROVIDE study suggested a putative effect on low-grade inflammation with a time-treatment interaction with IL-6 [33].

B-vitamin intake and sarcopenia remains poorly reported yet. However, sarcopenia, low skeletal muscle mass index, low body mass, and dynapenia were frequently found in geriatric patients displaying serum vitamin B_{12} levels less than 400 pg/ml [59]. In addition, higher intake of either B_6 or B_9 vitamins are related to a decrease in odds of sarcopenia [60].

Vitamin C (ascorbic acid) is the main hydrophilic antioxidant, needed to make carnitine, serotonin, norepinephrine, and collagen. Vitamin

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C supplementation enhances grip strength upon short terms studies but fails to maintain this effect in long-term analysis [61]. Concerning vitamin E (α-tocopherol), a low serum concentration is related to lower muscle strength. Finally, carotenoids levels are independently associated with muscle strength [62]. In a longitudinal approach (Framingham Offspring Study) including sarcopenia outcomes in non sarcopenic participants, carotenoid intake was related to lower grip strength decline and lower gait speed decline over time [63]. If the authors failed to replicate these findings within the Cardiovascular Health Study, the advanced age (≥ 65 yo) of participants suggests that prevention should be earlier and committed with lifestyle modification.

Serum selenium was found positively associated with grip strength among 676 moderatly disabled community-dwelling women in the Women's Health and Aging [64]. Moreover, serum concentrations of selenium were also positively associated with muscle mass in a systematic review. In addition, the intake of minerals (magnesium, selenium) was positively related to a better physical performance in older adults and was negatively associated with the prevalence of sarcopenia [65]. Combined with physical activity, magnesium supplementation improves physical performance in healthy elderly women [66].

Fibers and prebiotics

Increasing fiber vegetable consumption provides a positive effect on levels of inflammatory biomarkers in a population of older adults [67]. Moreover, a direct and protein independent effect on muscle seems related to fibers consumption in a cohort of older adults from the Nu-AGE study [68]. Gut microbiota composition is altered in elderly people [69▪▪] and physical activity induced modification in the gut microbiota composition [70]. In prefail older adults, galacto-oligosaccharide supplementation was able to modifiy gut microbiota composition with an increase in *Bifidobacteria*, but the authors did not evaluate the muscle mass or function [71]. Prebiotic (1-kestose) was studied in six older old japanese patients with sarcopenia during 12 weeks, displaying a greater skeletal muscle mass index and a decrease in body fat percentage that was also associated with an increase in *Bifidoacteria* [72]. However, in this latter study, the effect disappeared after the end of supplementation. Finally, the combination of inulin and fructo-oligosaccharides during 13 weeks slightly reduced exhaustion and grip strength in frail individuals but was associated with an increase of adverse events such as abdominal discomfort [73]. Yet, the PROMOTe study aims to target the gut microbiome with prebiotics to overcome anabolic resistance [74].

INTEGRATIVE APPROACHES

Dietary patterns

A dietary pattern including variety (fruits, legumes, nuts, whole grains, unsaturated vegetable oils, fish, and lean meat) is associated with a lower all-cause mortality in the elderly [75]. Fruit consumption is related to a lower odd for sarcopenia, mostly in women with sarcopenia. In this analysis, vegetable consumption was not related to sarcopenia [76]. Meditarreanean diet seems to be inversly related to muscle catabolism factors such as inflammation, oxidative stress, and insulin resistance. This diet represents an association of high monounsaturated/saturated fat ratio, high intake of α-linoleic acid, high ω_3/ω_6 fatty-acid ratio, high dietary fiber intake, vitamins, micronutrients, antioxidants, such as moderate alcohol intake. Mediterranean diet is related to successful aging [23]. The Mediterranean dietary pattern is associated with a 40% lower risk for sarcopenia in an adjusted model in a cross-sectional work on postmenopausal women [77].

Multimodal approach

Multimodal approach appears as a smart approach that could potentialize all dietary approaches. However, only a few evidence support this approach in sarcopenia in older adults. The SPRINTT study, upon sarcopenia patients (1519 individuals randomized between either multicomponent intervention or education on healthy aging) and with long-term follow-up (26.4 months), shows that nutritional support (personalized dietary plans with a 25–30 / kcal/kg/day and daily protein intake over 1–1.2 g/kg/day target) is sufficient to lower muscle decline [78▪▪]. Nutritional supplementation (including PUFA, vitamin D & protein supplementation) added benefit to physical exercise in increasing appendicular skeletal mass and lower limb muscle mass at 12 weeks [79]. Nonetheless, evidence about the effect of dietary supplements remains limited partially due to the variations in the dietary supplementation protocols.

CONCLUSION

In primary prevention on sarcopenia, lifestyle modifications as adopting the Mediterranean diet could be a key in successful aging. Inspired from this strategy in already sarcopenic patients, multiple approaches including long-term and multimodal

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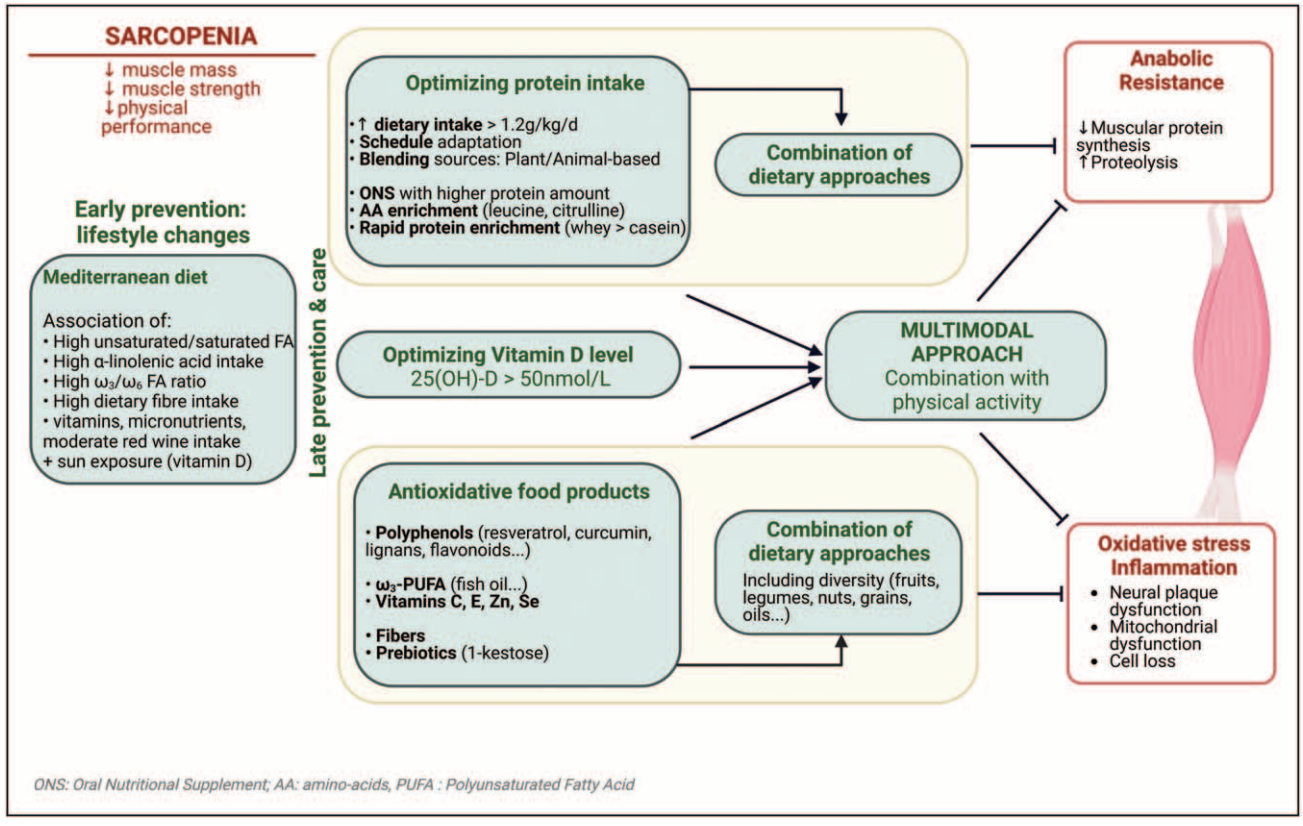

FIGURE 1. Dietary strategies for sarcopenia. This synthetic figure suggests a two-step approach. First, with lifestyle changes in early prevention and secondly in late prevention and care of sarcopenia. In late stages, three options and their combinations are available, in order to target either anabolic resistance or oxidative stress and inflammation in sarcopenia. EAA, essential amino acids; ONS, oral nutritional supplement; PUFA, polyunsaturated fatty acids.

interventions seems the best strategy (Fig. 1). Dietary intervention should focus on upgrading amount, schedule and variety of proteins, adequate level of vitamin D and dietary antioxidative nutrients.

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Conflicts of interest

There are no conflicts of interest.

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