Chapter 12
The Role of Nutrition in Attenuating Age-Related Skeletal Muscle Atrophy

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1 Introduction

Skeletal muscle contractions power human body movements and are important for maintaining stability. Skeletal muscle tissue accounts for about half of the human body mass and, in addition to its power-generating role, is a crucial factor in maintaining homeostasis. Given its central role in human mobility and metabolic function, any impairment in the contractile, material, and metabolic properties of skeletal muscle has an adverse effect on human health. Aging is related to a progressive loss of muscle mass, quality, and strength, a condition known as sarcopenia. Although this term is applied clinically to denote loss of muscle mass, it is often used to explain both some cellular processes (denervation, mitochondrial dysfunction, inflammatory and hormonal alterations) and some outcomes, such as reduced muscle strength, mobility, and function, a higher risk of falls, and decreased energy requirements (Fig. 12.1). Von Haeling et al. [1] have estimated its prevalence at 5–13% for the elderly population aged 60–70 years and at 11–50% for those aged 80 years or above. Lean muscle mass generally contributes up to 50% of total body weight in young adults, but decreases with aging to approximately 25% around 75–80 years of age. At the muscle fiber level, sarcopenia is described by specific type II muscle fiber atrophy, fiber necrosis, and fiber-type grouping. Several

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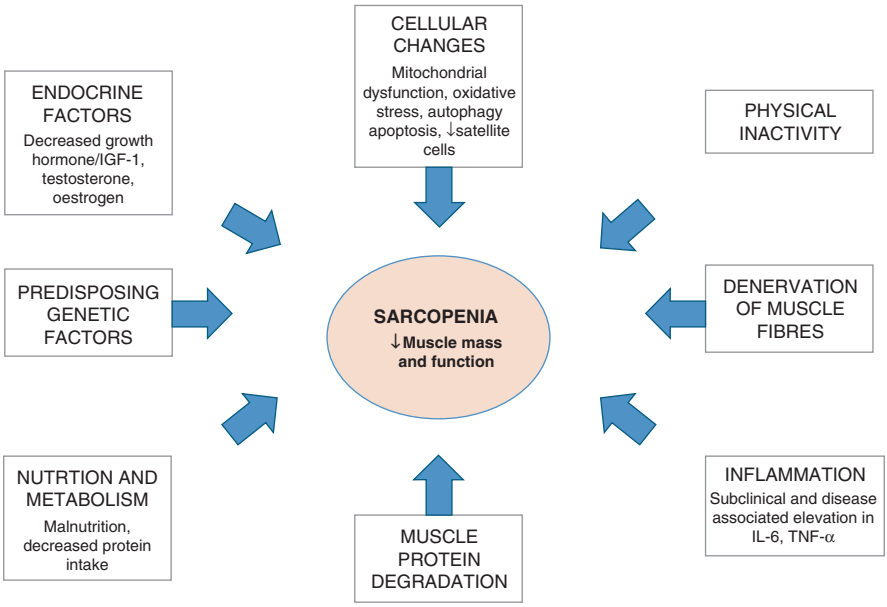

Fig. 12.1 Contributory factors of age-related muscle atrophy (sarcopenia)

probable mechanisms of age-related muscle atrophy have been reported. Age-related muscle loss is due to losses in the size and number of muscle fibers, possibly resulted from a multi-factorial process that includes physical activity level, nutrient intake, hormonal changes, metabolic homeostasis, oxidative stress, and lifespan. The specific contribution of each of these factors is unknown but there is growing evidence that the disruption of several positive regulators of muscle hypertrophy such as Akt and serum response factor (SRF) are an important feature in the progression of sarcopenia [2, 3]. Some studies demonstrated a functional defect in autophagy- and myostatin-dependent signaling in sarcopenic muscle [4–6]. In contrast, many researchers have failed to identify age-related increases in the levels of common negative regulators, such as atrophy gene-1 (atrogin-1), nuclear factor-kappaB (NF-κB) and calpain, in senescent mammalian muscles [2, 3, 7].

Poor diet is one of the most common problems practitioners encounter when treating elderly people. Many individuals in this population have low nutrient intakes, for different reasons that range from physical deficits to economic problems. Dental problems in the elderly may make them more likely to choose softer foods that often lack protein and delayed gastric emptying can decrease appetite and hormonal alterations may lead to longer-lasting feelings of satiety. Physical disability may also make packaged, processed foods more appealing [8]. Such dietary problems are not impossible to overcome. If we can understand the lifestyle factors that affect the rate of decrease in muscle mass and strength in older age, we can develop strategies that will help to prevent or slow sarcopenia, and allow people to have a higher quality of life in old age. This chapter aims to address several recent strategies for inhibiting this phenomenon.

2 The Role of Nutrition

The diets of elderly people affect to a large extent their health, and particularly the potential for counteracting the possible physiological etiological factors of sarcopenia. In the following sections, the effects of dietary factors on muscle metabolism will be discussed.

2.1 Amino Acid Supplementation

Many reviews demonstrate that certain nutritional interventions such as a high protein intake or an elevated intake of essential amino acids and the branched chain amino acid (BCAA) leucine with resistance training may help to slow fiber atrophy in sarcopenic muscle by modulation of both anabolic and catabolic pathways [9]. In particular, leucine can be considered as a regulatory amino acid with unique features. It has several effects on muscle metabolism regulation, such as control of protein synthesis and glucose homeostasis. In addition, leucine has been shown to be a nitrogen donor for the synthesis of muscle alanine and glutamine. Considering these findings, the administration of leucine as an anti-atrophic agent is biologically justified [9].

It has been reported that amino acid supplementation has a synergistic impact on the contraction-induced escalation of muscle protein synthesis following acute resistance exercises [10]. Treatment with amino acids has been found to induce additional hypertrophy in response to continuous resistance training [11]. Recent human studies have shown that amino acids have an effect in the phosphorylation of translational initiation factors, especially eIF4F and p70S6K, through an mTOR-mediated mechanism [12]. On the other hand, several other studies have not reported advantages from protein supplementation [13, 14]. These studies administered a single bout or short-term (10 day) ingestion to evaluate the rate of myofibrillar synthesis or protein synthesis [13]. In contrast, Godard et al. [14] aimed to evaluate the long-term supplementation of several amino acids and carbohydrate combined with resistance training. Unfortunately, they performed the evaluation of total muscle cross-sectional areas only using magnetic resonance imaging (MRI), and did not conduct a detailed morphological analysis. Since the examination of muscle cross-sectional area by MRI seems to be affected by the inner amount of adipose tissue, connective tissue, or water, it is unknown whether or not the protein supplementation showed positive effects on the morphometry of muscle fibers. In another study, the administration of many essential amino acids has been shown to have a positive effect on muscle mass and protein synthesis under both normal states [2, 3, 15], and with resistance training [12]. Although a positive slowing impact on sarcopenia has been reported in almost all studies utilizing many essential amino acids and comprising high levels of leucine, supplementation with essential amino acids not enriched with leucine may fail to increase muscle protein synthesis in the elderly.

Moreover, a greater amount of leucine should be supplemented along with large amounts of isoleucine and valine in order to avoid an imbalance of branched-chain amino acid levels [15].

2.2 Protein

Proteins are continuously broken down and resynthesized, and skeletal muscle may account for about one-quarter of the total body protein turnover [16]. When protein intake is inadequate, turnover of tissue protein is decreased while the opposite may occur with elevated intake. However, in the elderly, the amount of protein turned over reduces compared to young adults [17]. Net protein balance in the skeletal muscle is the result of protein synthesis and protein breakdown. When muscle protein breakdown is greater than the rate of muscle protein synthesis, the net protein balance is negative, while the opposite correlates with positive balance. Balance is achieved when muscle protein breakdown equals muscle protein synthesis [18]. The occurrence of sarcopenia may be the result of an elevated basal-fasted rate of muscle protein breakdown and/or decreased basal muscle protein synthesis [19]. Nevertheless, muscle protein breakdown may also lead to restore the functionality of proteins by allowing impaired proteins to be removed and recycled into new muscle proteins [20]. Muscle protein synthesis is more responsive than protein breakdown to diet-associated alterations in healthy subjects, making it the main target to stimulate muscle protein balance and eventual protein accumulation [20]. In our study of women aged 40–60 years old, protein intake, adjusted for physical activity and weight, was positively and significantly associated with fat free mass percentage [21]. Considerable discussion exists about the amount of protein intake required for optimal health in older adults, particularly when evaluating it in the light of energy needs [22]. Gersovitz et al. [23] provided older adults with diets containing 0.8 g egg protein/kg/day, and concluded that this amount was not adequate for most of the participants. Campbell et al. [24] also proposed that 0.8 g protein/kg/day may not be sufficient to completely meet the needs of all elderly people. In a study to evaluate dietary protein intake and alterations in lean mass in community-dwelling older adults, subjects in the highest quintile of protein intake (1.2 ± 0.4 g protein/kg body weight/day) lost about 40% less lean mass than did those in the lowest quintile of protein intake (0.8 ± 0.3 g protein/kg/day) [25]. According to some researchers, the recommend intake for the prevention of sarcopenia is 0.8–1.2 g of high-quality protein/kg/day [26] or higher amounts, such as 1.6 g protein/kg/day [27].

Moreover, Paddon-Jones and Rasmussen [28] revealed that muscle protein synthesis was decreased in old people when the ingested protein was less than about 20 g per meal, and a value of 25–30 g of high-quality protein per meal was recommended to maximize the anabolic response. Hence, elevating the distribution of protein intake in approximately equal parts through breakfast, lunch and dinner may be also an important factor of protein effectiveness [29].

2.3 Beta-Hydroxy-Beta-Metylbutyrate (HMB)

HMB is a product of leucine metabolism that has been demonstrated to slow protein breakdown in muscle tissue [30]. HMB may be effective at limiting the demands placed on elderly people by acute stresses, such as sudden increases in physical activity, an immunologic challenge, or acute malnutrition [30, 31]. Daily supplementation of HMB (2 g/day), arginine and lysine for 12 weeks positively changed measurements of functionality, strength, fat-free mass and protein synthesis, proposing that the strategy of targeted nutrition has the ability to influence muscle health in elderly women [32]. Therefore, an adequate intake of proteins (1.2/g/kg/day) is essential to prevent sarcopenia and amino acid supplementation, especially branched chain amino acids (leucine 2.5 g/day) as well as the intake of beta-hydroxy butyrate (2 g/day), is a well-established intervention for treating sarcopenia.

2.4 Creatine

Creatine is known as a non-protein nitrogenous tri-peptide, composed of glycine, arginine and methionine. In the human body, creatine is synthesized in the liver and pancreas from these amino acids. In addition, creatine is present in foods (meat and fish) and is taken with the diet in the amount of 1–2 g per day. Approximately 95% of the creatine in the body is stored in skeletal muscle, with about two-thirds of this is stored as phosphocreatine (PCr) and the remainder as free creatine. The energy provided for the phosphorylation of adenosinediphosphate (ADP) to adenosine triphosphate (ATP) during and after intense exercise depends on the amount of PCr stored in the muscle. With depletion of PCr during intense exercise, the availability of energy reduces due to the inability to resynthesize ATP in the amounts needed to maintain the high-intensity exercise [33]. Age-related reductions of creatine/PCr in skeletal muscle have been indicated in some studies [34, 35], although not all studies agree [36, 37]. The reduction of muscle creatine is biologically plausible, due to aging and, possibly, to certain co-morbidities, such as sarcopenia, and/or alterations of behavior with age, including decreased physical activity and/or changes in dietary intake, such as reduced consumption of meat products due to denture issues. Type II muscle fibers have a higher content of PCr compared to type I fibers [38], and sarcopenia is characterized by a preferential atrophy of the former fiber type [39]. The progressive atrophy of type II fibers may therefore partly account for the decreased muscle creatine in the elderly. In addition, the reduction of creatine in the muscles of the elderly is in line with previous evidence that documents an increase in oxidative processes in aged skeletal muscles, such as a reduction of lactate dehydrogenase [40] and reduced dependence on glycolysis [41]. Smith et al. first demonstrated an elevation in muscle PCr in middle-aged adults (58 years-old) as a result of short-term intake of high doses of creatine (0.3 g/kg/day for 5 days) [34]. In a similar study, Rawson et al. showed a smaller elevation in muscle PCr (7 versus 35%) in 70 year-olds compared with 24 year-olds, in response to ingestion of

creatine (20 g/day for 5 days) [37]. Brose et al. found an increase in total muscle creatine (30% men, 17% women) in 70 year-old participants who underwent 14 weeks of resistance training and intake of 5 g/day creatine [42], a result that is in line with the increases shown in younger adults [43, 44]. Eijnde et al. reported increases of 5% and 21% in total muscle creatine and free creatine, respectively, following 6 months of an exercise program for muscular endurance combined with 5 g/day creatine supplementation [45]. Hence, it appears that the muscle creatine in the elderly can be elevated with oral creatine supplementation at a dose of 5 g/day but the magnitude of the response can be significantly influenced by initial muscle creatine levels. Wyss et al. have proposed that the increase in extracellular creatine may reduce the absorption of creatine in muscle [46]. One of the most important findings was an improvement in fatigue resistance, which has been shown in several studies using different exercise tests [47–51]. Some researchers have indicated an increase in strength [49, 50] but this has not always been reported [47, 48]. Some researchers have shown that creatine supplementation may help to increase the performance of tasks identified in the activities of daily living (activity daily living; ADL) [50, 52, 53]. The is an important finding because of the relationship between the performance of ADL, fall risk and mortality. Among the studies that have investigated muscle mass, the majority found a greater increase in lean mass accretion after ingesting creatine in combination with resistance training [42, 54, 55] and Dalbo et al. mentioned that creatine is an effective intervention to counteract sarcopenia [56]. The timing of creatine ingestion (before and after resistance training sessions) can be more relevant than the amount of creatine [33]. In conclusion, an adequate creatine supplementation could be a useful intervention to combat sarcopenia, in particular fatigue associated with sarcopenia, although clinical studies are required to support this.

2.5 Long-Chain Polyunsaturated Fatty Acids (LCPUFAs)

Sarcopenia is recognised as an inflammatory status driven by cytokines and oxidative stress [57]. Since eicosanoids derived from 20-carbon polyunsaturated fatty acids are among the regulators of inflammation [58], this raises the probability that variations in intake of n-3 and n-6 LCPUFAs, and their balance in the diet, could be of importance. In particular, n-3 LPUFAs have the potential to be potent anti-inflammatory agents [58]. Although biochemical processes underlying the impacts of pro-inflammatory cytokines on skeletal muscle remain to be established [59], elevated circulation levels of cytokines including interleukin (IL)-6, C-reactive protein (CRP) and tumor necrosis factor (TNF)-α receptor II, may have harmful impacts on protein synthetic rates [60, 61]. However, these inflammatory processes may be decreased by n-3 LPUFAs, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are found in foods such as fatty fish [62, 63]. There is some observational evidence to support the effect of n-3 LCPUFA status on muscle function, as higher grip strength was reported in elderly men and women who had greater oily fish consumption [64]. In line with this finding, several studies of patients with

rheumatoid arthritis have indicated that supplementation with fish oil led to improvement in grip strength [58].

In a randomized controlled trial study to investigate the effects of n-3 LCPUA on the rate of muscle protein synthesis in older adults, 8 weeks of daily supplementation with 1.86 g EPA plus 1.50 g DHA had no effect on the basal rate of muscle protein synthesis, but amplified the hyper-aminoacidaemia–hyperinsulinaemia-stimulated elevation in the rate of muscle protein synthesis, which may be important to counteract the anabolic resistance related to aging [65]. Moreover, the intake of oily fish was related to an increase in grip strength in community-dwelling older adults, which raised the hypothesis of an anti-inflammatory impact of n-3 LCPUFA and a possible effect of these nutrients in the prevention of sarcopenia [66].

α-Linolenic acid (ALA) is the major plant-based n-3 LCPUFA and its effects may also occur via its conversion to EPA and DHA, when dietary intake of marine PUFAs is low [67, 68]. Although the precise efficacy of metabolic conversion of ALA to EPA and/or to DHA is an unresolved question, it has been established that desired tissue levels of EPA and DHA could be better achieved by consumption of these two nutrients [69]. Since LCPUFA synthesis occurs mainly in the liver, it is possible that natural alterations in physiological condition occurring with aging, or any additional pathologic states that may exist, influence the availability of these nutrients in different tissues [67]. However, considering the antithrombotic effects of n-3 LCPUFA, special attention should be given to the risks of potential severe adverse events after high doses ingestion, such as bleeding [62] or a slight rise in LDL cholesterol [70], particularly in older adults. In a review of Calder [63] evaluating the consumption of fish oil supplements by healthy adults and its effect on inflammatory processes, it was demonstrated that EPA and DHA intake higher than 2 g/day appeared to be needed to produce anti-inflammatory effects. The existence of Dietary Reference Intakes for EPA and DHA is still a matter for discussion, but consumption levels for an adult of up to 500 mg/day do not seem to raise safety concerns [69]. In addition, Villani et al. [62] conducted a systematic review on fish oil administration in elderly people, and concluded that the potential for adverse events associated with omega-3 supplementation appeared mild to moderate at worst. However, data are limited to establish definitive conclusions about the safety of these nutrients. In another randomized controlled clinical trial, supplementation of older adults with EPA and DHA led to an elevated anabolic response to amino acid and insulin infusion. While these novel data propose that the stimulation of muscle protein synthesis by n-3 LCPUFA supplementation could be beneficial for the prevention and treatment of sarcopenia [71], further evidence is required to establish the therapeutic potential of n-3 LCPUFAs in inflammatory states.

2.6 Antioxidant Supplementation

Free radicals are highly reactive molecular species with a single unpaired electron in the outer orbit seeking to pair with another free electron. In particular, reactive oxygen species (ROS), deriving from oxidative metabolism, have higher reactivity

than O_2. ROS are constantly generated in cells of aerobic organisms, in particular skeletal muscle, by the addition of a single electron to the oxygen molecule with subsequently injury of biological macromolecules, such as lipids and DNA. The interaction of ROS with normal cellular structures results in potentially nonreversible changes, with subsequent cellular loss of function and death. ROS generation has been found to be elevated in skeletal muscle during aging. During the aging process, it is probable that elevated levels of ROS lead to the alterations of mitochondrial DNA and to increases in myonuclear apoptosis. Hiona and Christiaan Leeuwenburgh [72] reviewed the potential mechanisms by which mitochondrial DNA mutations related to aging that favor mitochondrial dysfunction may influence the skeletal muscle, and concluded that mitochondrial DNA mutations may contribute to sarcopenia. Based on the mitochondrial "vicious cycle" hypothesis related to the free radical theory of aging, chronic ROS production and oxidative stress can favor mitochondrial DNA mutations, which in turn may result in an elevated mitochondrial ROS production, promoting a cycle of oxidative damage that may lead to muscle cell death [72], which in turn may contribute to sarcopenia [73]. The presence of elevated levels of pro-inflammatory cytokines that may occur with aging also contribute to an elevation of oxidative stress in skeletal muscle [74]. Hence, counteracting oxidative stress by exposure to anti-oxidants may be an important strategy to prevent sarcopenia [75].

The primary and auxiliary extra- and intracellular anti-oxidant protection systems include nutritive anti-oxidants (e.g. vitamin C, vitamin E, carotenoids, conjugated dienoic isomers of linoleic acid, carnosine, anserine and histidine), non-nutritive anti-oxidants (e.g. natural and synthetic phenols, and furanones/furfurals), enzymes (e.g. glutathione peroxidase/transferase or glutathione disulphide reductase that catalyze anti-oxidants regeneration), transition metals (e.g. iron, copper) binders and exporters (e.g. the glutathione conjugate transporter) [76].

Although sufficient intake of anti-oxidants may be considered as an important strategy to prevent sarcopenia [77], Chaput et al. [78] found no significant differences in anti-oxidant intake between the elderly participants with sarcopenia and the nonsarcopenic group. However, it should be noted that the intake of anti-oxidant nutrients in older adults with sarcopenia did not reach the Dietary Reference Intakes (DRIs) in the group of participants without sarcopenia. Nutritional approaches that have been suggested to prevent oxidative stress or benefit muscle protein metabolism via anti-oxidant approaches include resveratrol [79], vitamin E, vitamin C [80], carotenoids [81], vitamin A [82], dehydroepiandrosterone, ornithine, cysteine, N-acetylcysteine, carnitine, epigallocatechin gallate [83] zinc and selenium [82]. Considering that oxidative stress may favor the initiation of sarcopenia [73, 75, 84], future research should clarify specific protein targets for oxidative damage [85] and the mechanistic pathways by which anti-oxidants in foods or supplements may reduce oxidative stress.

In diabetes, antioxidant supplementation appears to prevent muscle atrophy [86]. The impact on cancer cachexia is partial although significant. In contrast, the data on antioxidant supplementation for mammalian sarcopenia are limited and controversial, despite the clinical relevance and large interest. A number of studies have

evaluated the possibility of delaying the aging process by elevating anti-oxidative capacity. For example, resveratrol, a natural polyphenol found in grapes, peanuts, and berries, has demonstrated a protective impact against oxidative stress in skeletal muscle. Although most human studies analyze the association between dietary antioxidant supplementation and physical performance or muscle strength measures, the effect is still debatable. As suggested by Bonetto et al. [86], oxidative stress probably would behave as an additional factor that would certainly amplify wasting stimuli but may not play a leading role in other cases for which the effectiveness of antioxidant therapy was not indicated. A recent statement from the Society on Sarcopenia, cachexia and wasting disease does not mention antioxidant supplementation as a possible tool to manage sarcopenia in older persons [87].

Future randomized controlled trials using single or several anti-oxidants, in supplements or food preparations, should also be investigated for efficacy to decrease oxidative stress in the muscle, and increase net protein balance in older adults.

2.7 Vitamin D

Vitamin D has been traditionally considered as a key regulator of bone metabolism, and calcium and phosphorus homeostasis through negative feedback with parathyroid hormone. Currently, approximately one billion people worldwide have vitamin D deficiency and most of these are elderly. The prevalence of low vitamin D concentrations in people older than 65 years of age has been estimated to be about 50%, but this statistic is variable because it is influenced by sociodemographic, clinical, therapeutic and environmental factors. Similarly, there is an age-dependent decrease found in vitamin D receptor expression in skeletal muscle. Prolonged vitamin D deficiency has been related to severe muscle weakness, which is found to be ameliorated with vitamin D supplementation. A large body of evidence indicates that low vitamin D levels represent an independent risk factor for falls in the elderly [88]. Supplementation with vitamin D in a clinical trial was found to elevate muscle strength and performance and decrease the risk of falling for community-living, elderly and nursing home residents with low vitamin D levels [89]. In contrast, several groups reported no positive impact of vitamin D supplementation on fall event outcomes [90]. Cesari et al. [91] attributed these discrepant findings to the selection criteria adopted to enroll study participants, compliance with the intervention, or the extreme heterogeneity of cut-off points defining the condition of deficiency. A more comprehensive knowledge of vitamin D-related mechanisms may provide a useful tool for preventing muscle atrophy in older persons.

The genomic impact of vitamin D on muscle includes changes in mRNA that will cause de novo protein synthesis involved in controlling cell proliferation and induction of terminal differentiation. In addition, the non-genomic impact of vitamin D on muscle includes the activation of protein kinase C (PKC) and Ca^{2+} in the cytosol. This effect leads to the active transportation of Ca^{2+} into the sarcoplasmic reticulum by Ca^{2+}-ATPase, elevating the calcium pool which is necessary for

muscle contraction [92]. Moreover, the activation of PKC has an impact on protein synthesis in the muscle cells. On other hand, because inflammation is a potential risk factor for sarcopenia, the anti-inflammatory impacts of vitamin D could lead to the improvements in skeletal muscle composition [92].

Vitamin D metabolites may influence muscle mass and function through indirect mechanisms such as hypophosphataemia [93] or secondary hyperparathyroidism of vitamin D deficiency [94]. Direct impacts may also occur through the 1,25(OH)2D3 receptor in muscle tissue [95]. In a systematic review investigating the impacts of exposure to vitamin D on muscle function, Rejnmark [94] identified 16 randomized controlled trials, and all except one of the studies were conducted in individuals above 50 years of age. Over seven studies, vitamin D supplementation resulted in positive impacts on muscle strength [94, 96]. Another systematic review and meta-analysis by Muir and Montero-Odasso [97], which evaluated the efficacy of vitamin D supplementation on muscle strength in elderly population aged over 60 years, found that all studies with ingested doses of 800–1000 IU per day reported useful impacts on muscle strength. In our study, vitamin D supplementation (1000 IU, daily, for 3 months) in vitamin D deficient middle-aged women (40–55 years-old) resulted in improvements in muscle function in the intervention compared to the placebo group. In addition, fat mass percentage was significantly reduced in vitamin D group at the end of intervention but the changes did not reach statistical significance compared with the placebo group. In both groups muscle strength did not differ significantly at the end of the intervention [98]. This might be explained by the possibilities of an insufficient dose of vitamin D supplementation in the vitamin D-deficient women, the period of vitamin D supplementation was not long enough, or the combination of both factors. In addition, baseline vitamin D status or baseline muscle strength or mass might have impacts on the response to vitamin D supplementation [98]. Furthermore, low vitamin D levels are a risk factor for falls in the elderly [99, 100], and its supplementation was demonstrated as an important strategy to decrease the risk of falls among ambulatory or institutionalized older individuals [101]. However, evidence on whether vitamin D supplementation influences muscle mass is scarce [102]. Although vitamin D functions include an important role for muscle health [103], an insufficient vitamin D nutritional status is frequently observed in older adults. In a study with older adults from 11 European countries, 36% of men and 47% of women had circulating concentrations of less than 12 ng/mL in wintertime, this being the lowest mean level found in Southern European countries [104]. Serum vitamin D concentrations may vary widely between participants from different countries [105] and variations in vitamin D status appear to be associated with contrasts in nutritional intake, sunlight exposure and clinical, therapeutic, sociodemographic and environmental factors [106].

2.8 Ursolic Acid

Ursolic acid, a water-insoluble pentacylic triterpenoid, is the major waxy component in apple peels. It is also found in many edible plants. Kunkel et al. [107] reported that ursolic acid decreased skeletal muscle atrophy in the setting of two

distinct atrophy-inducing stresses (fasting and muscle denervation). Ursolic acid might elevate muscle mass by inhibiting atrophy-related skeletal muscle gene expression. The above study found that acute ursolic acid treatment of fasted mice decreased atrogin-1 and MuRF1 mRNA levels in association with decreased muscle atrophy. Similarly, chronic ursolic acid treatment of unstressed mice decreased atrogin-1 and MuRF1 expression and induced muscle hypertrophy. Although ursolic acid elevated skeletal muscle Akt phosphorylation in vivo, the study could not determine if it acted directly on skeletal muscle, how quickly it acted, or if the effect needed insulin-like growth factor (IGF)-I or insulin, which are always present in healthy animals, even during fasting. To investigate these issues, Kunkel et al. [107] evaluated serum-starved skeletal myotubes and found that ursolic acid rapidly stimulated IGF-I receptor and insulin receptor activity, but only if IGF-I or insulin was also present. Altogether, their data suggests that ursolic acid first elevates the capacity of pre-existing IGF-I and insulin to activate skeletal muscle IGF-I receptors and insulin receptors, respectively. However, ursolic acid alone was not sufficient to increase phosphorylation of the IGF-I or insulin receptors, and its impacts also needed IGF-I and insulin, respectively. This proposes that ursolic acid either facilitates hormone-mediated receptor autophosphorylation or suppress receptor dephosphorylation. The latter possibility is supported by previous in vitro data showing that ursolic acid directly suppresses protein tyrosine phosphatase 1B, a tyrosine phosphatase that dephosphorylates and thereby inactivates the IGF-I and insulin receptors. More research is required to clarify the impact of supplementation with ursolic acid in skeletal muscle in the attenuation of muscle atrophy.

3 Caloric Restriction (CR)

CR typically involves consuming 20–40% fewer calories than normal intake as a means of maintaining mitochondrial health and attenuating sarcopenia. CR is recognized as the most important intervention that delays primary (natural age-associated deterioration) and secondary (related to disease and negative lifestyle behaviors) aging, thereby increasing lifespan in many species. Studies in rodents have consistently indicated that CR extends maximum lifespan by up to 50% and decreases the occurrence of many age-related diseases. These protective impacts are attributable to the ability of CR to decrease the incidence of mitochondrial abnormalities and also decrease oxidative stress. In rodents, CR seems to alter mitochondrial efficiency, content and function via reduced proton leakage which, in turn, is enabled by a shift to a less oxidative milieu. With regards of mitochondrial content and function, CR does not influence gene expression, protein level, or activity of citrate synthase [108]. Lanza et al. [109] indicated that CR maintains mitochondrial function by protecting the integrity and function of existing cellular components rather than by elevating mitochondrial biogenesis. Moreover, CR appears to combat the age-associated increases in pro-apoptotic signaling in skeletal muscle [110]. Importantly, CR has been demonstrated to modulate the majority of the apoptotic

pathways involved in age-related skeletal muscle loss, such as mitochondrial-, cytokine/receptor-, and Ca^{2+}/ER-stress-mediated signaling [110]. Therefore, CR notably inhibits increases in several mediators of the TNF-mediated pathway of apoptosis (TNF-α, TNF-receptor 1, cleaved caspase-3 and -8), possibly by elevating production of a muscle-derived anabolic cytokine, IL-15, which competes with TNF-mediated signaling. Furthermore, the combination of CR with exercise training has been suggested to combat the apoptosis related to sarcopenia more effectively.

It is interesting that Baker et al. indicated a significant increase in PGC-1α in gastrocnemius muscle of rats after a 40% CR diet beginning at 16 weeks of age [111]. It has become apparent that PGC-1α binds to and co-activates many transcription factors in addition to PPARγ, including most nuclear factors. Therefore, PGC-1α has various roles, such as in fatty acid oxidation, myokine secretion, activation of autophagy, and neuromuscular junction (NMJ) gene induction, as well as up-regulation of mitochondrial biogenesis [112]. Valdez et al. [113] indicated that lifelong CR significantly reduced the incidence of pre- and postsynaptic abnormalities in 24- month-old mice as well as the age-associated loss of motor neurons, likely due to PGC-1α induction. Since the level of basal autophagy in the skeletal muscle has been shown to be decreased with age [5, 114], normal function of autophagy by CR may weaken the atrophy of muscle fibers during aging. However, CR in mice did not modulate the level of several autophagy-linked molecules (Beclin-1, Atg9, LC3) at the protein level, except for Atg7 in sarcopenic muscles of rats [5]. However, one study [115] demonstrated that CR has no useful effect on health and survival in rhesus monkeys in contrast to many other reports from studies using the same species [116, 117]. More studies are required to evaluate whether CR is effective in counteracting the age-associated loss of muscle in human subjects and to what extent dietary intervention can be applied in human populations. Because excessive CR (over 50%) may have side effects, milder CR conditions should be applied in the elderly population.

4 Dietary Patterns

The eating habits of elderly individuals are affected by several factors, including food preferences that have been formed throughout life, physiological alterations related to aging, socioeconomic conditions, being institutionalized or not, physical disability, and living with a spouse or alone. Food insecurity and hunger are issues of concern for many elderly individuals, especially for those having low socioeconomic status or from minority ethnic groups [118, 119]. Energy requirements decrease with advancing age, and elevated physical activity or exercise may be important to combat this trend. In addition, with higher energy intake by those with increased energy requirements, it is easier to provide the amount of food necessary to meet the nutritional recommendations, especially for micronutrients [120]. The modern Western-type diet is rich in animal products and limited in fruits and vegetables [121], which leads to a net acid production, in contrast with diets abundant in potassium that possess an alkalinizing effect [121]. Moreover, a sufficient

potassium intake and an alkaline diet may favor lean tissue mass in elderly people [122], while acidosis [121] can intensify the reduction in muscle mass. This is also particularly important considering that the normal reduction in kidney function related to age may also favor acidosis [121]. In addition to being important for potassium intake, consumption of fruit and vegetables is negatively related to inflammation in the elderly population [75], and ensuring sufficient intake of these foods is also important to achieve sufficient ingestion of anti-oxidants, including carotenoids [123], polyphenols, tocopherols, ascorbate and selenium [124].

Many of the components previously indicated as having beneficial effects of inflammation and redox status, especially n-3 LCPUFAs and dietary anti-oxidants, are natural constituents of the Mediterranean diet, considering its high content of vegetables, legumes, fruit, nuts, seeds, whole grain cereals, olive oil, fish and herbal infusions [125]. Hence, nutritional strategies are required to limit muscle atrophy and to combat decreases in muscle mass and function. When evaluating relationships between grip strength and empirically healthy dietary patterns such as the prudent dietary pattern, grip strength was positively associated with prudent diet score in community-dwelling elderly population [126]. This diet is generally characterized by high consumption of vegetables, fruit, fatty fish and whole grains, and a low consumption of white bread, chips, sugar and full-fat dairy products. Looking for nutrients and foods using a whole dietary pattern approach may present several advantages over a "single nutrient approach", considering the high number of interactions and synergies that may exist between food components, and future studies are required to investigate this in detail.

5 Exercise Training

Resistance exercise can promote muscle protein synthesis within 1 h of training, which can last for up to 72 h after exercise. Resistance training has been shown to be the most promising among interventions aimed at reducing the impacts of sarcopenia, since it elevates strength, power and mobility function, and induces different degrees of skeletal muscle hypertrophy [127]. For example, 12 weeks of whole-body resistance training led to an increase in type II muscle fiber area in men aged 64–86 years and 65–72 years. A 2-year longitudinal trial of resistance training reported increases in leg press (32%) and military press (90%), single-repetition maximum weight lifted and knee extensor muscle cross-sectional area (9%) in elderly people aged 60–80 years [128]. The functional advantages of resistance training have been investigated in a large trial of 72–98-year-olds and frail nursing home residents, with resistance training elevating muscle strength (113%), stair-climbing power (28%), gait velocity (12%), and spontaneous physical activity [129]. In the elderly, resistance training induces the muscle levels of IGF-I, myogenic regulatory agents, and IL-6, which lead to muscular hypertrophy by regulating the activation, proliferation, and differentiation of satellite cells. However, several studies using humans and rodents demonstrated a lower degree of activation

in mitogen-activated protein kinase (MAPK) and Akt-mTOR pathways after muscle contraction or mechanical overload than occurs in young adults [114]. However, Mayhew et al. [130] reported that resistance exercise induced a similar extent of activation in translational signaling (Akt, p70S6K, ribosomal protein S6, and 4E-BP1) between young and old participants. It might appear surprising that physical activity can influence muscle inflammation. The evidence indicates that chronic resistance physical training leads to the control of locally-derived inflammation via adaptations to repeated and acute elevations in pro-inflammatory mRNA within muscle. Several studies [131] have indicated that the addition of intensive strength training for the elderly reduces the effective gain of muscle strength and mass especially in women. Hence, careful attention should be paid when estimating the amount and intensity of resistance training in this advanced age group.

6 Malnutrition-Sarcopenia Syndrome

Malnutrition has been explained as a status of an imbalance of energy, protein and other nutrients that result in negative impacts on body composition, physical function and clinical conditions [132]. One vital clinical aspect often not evaluated in nutrition screening or assessment is the loss of lean body or muscle mass. Lean body mass is explained as that portion of the body mass except for the fat and includes water, mineral, muscle and other protein-rich structures (including viscera, enzymes, red cells, and connective tissues) [133]. Skeletal muscle mass constitutes the majority of lean body mass and provides strength, mobility and balance [134]. Muscle mass also plays a vital role in whole-body protein metabolism and affects quality of life in patients with chronic diseases [135]. The balance between muscle protein anabolism and catabolism is critically important for maintaining skeletal muscle mass, especially in elderly people who lose muscle mass as a consequence of aging and/or illness [135, 136]. Sarcopenia has been explained as an age-related loss of muscle mass, combined with loss of strength, functionality or both [137].

Research has demonstrated that reductions in handgrip strength are common in individuals who have sarcopenia as well as in individuals who are malnourished [137, 138]. Many elderly individuals are malnourished or at high risk for malnutrition due to many factors. Reduced appetite and food intake, poor dentition, an increased frequency and severity of acute and chronic medical states, multiple medications, social and economic challenges, and cognitive decrease can all play a role in the etiology of malnutrition among older adults. Advanced age is an independent risk factor for malnutrition and is related to a lower body weight, body mass index, and serum albumin levels [139–141].

In many patients, malnutrition and sarcopenia occur in parallel and manifest clinically through a combination of reduced nutrient intake and reduced body weight, along with a decrease in muscle mass, strength, and/or physical function. This has led to coining of the proposed clinical condition as the Malnutrition-Sarcopenia Syndrome. This is the clinical presentation of both malnutrition and

accelerated age-related loss of lean body mass, strength, and/or physical performance. Malnutrition and sarcopenia are each independently related to negative health outcomes that affect older adults across healthcare settings. Patients with malnutrition and/or sarcopenia are at risk of elevated morbidity and mortality, reduced functioning and quality of life, and increased re-hospitalization, length of hospital stay and higher healthcare costs [142–146].

A prospective observational study of a cohort of older adults indicated that higher lean mass predicted lower mortality with an 85% reduction in the risk, proposing that alterations in lean mass, rather than body mass index, are better predictors of mortality in elderly people [147]. This highlights the role of lean muscle mass loss in defining malnutrition.

Hence, examining both of the patient's nutritional and functional status through screening and evaluation for both malnutrition and sarcopenia will enable healthcare practitioners to better determine the presence of the Malnutrition-Sarcopenia Syndrome in their patients and prescribe interventions tailored to fit individual requirements. In addition, as the world is aging and older adults will utilize healthcare services at an increased rate, this could finally lead to better patient care and outcomes in this unique and expanding patient population.

7 Conclusions

To develop strategies to combat or retard sarcopenia, a better understanding of the lifestyle factors that affect the rate of muscle mass and functional losses in older age is required. Current data demonstrates the importance of sufficient quality and quantity of the diet in this process. The high prevalence of low nutrient intake among elderly population has made this a major concern. In addition, much has demonstrated that regular exercise can minimize the physiological impacts of an otherwise sedentary lifestyle by limiting the development and progression of chronic disease and disabling conditions, but only a limited proportion of older adults are physically active. Hence, older adults should optimize both nutrition and exercise as both are important modifiable factors that elevate muscle strength and mass, and contribute to the maintenance of muscle mass and function and the prevention and treatment of sarcopenia. Because the elderly portion of the population has undergone a steady rise over the last century, future work in this area should be designed in younger as well as in older populations.

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