Protein Supplementation for the Prevention and Management of Sarcopenia in the Elderly

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Abstract: Sarcopenia is common in patients with many physiological or pathological conditions, especially in aging people. Nutrition plays an important role in the prevention and treatment of sarcopenia. Sarcopenia is often related to insufficient protein intake in the elderly. Muscle protein synthesis occurs mainly through mTORC1 pathway, and degradation occurs by ubiquitination-mediated pathways. This review summarizes the growing body of evidence, including substantial clinical trials, which increasing the protein intake can serve as the basis for preventing and managing muscle loss in patients with sarcopenia. Supplementation of essential amino acids (EAA), branched chain amino acids (BCAA), and especially leucine-rich whey protein may promote muscle protein synthesis by activating the mTORC1 signaling pathway, and may inhibit protein degradation by decreasing ubiquitin-mediated degradation. Taking in sufficient energy and protein and engaging in active exercise are the main methods of stimulating muscle protein synthesis and preventing or managing sarcopenia. Therefore, it is necessary to strengthen research on the use of protein supplements for not only elderly patients, but also those with tumor cachexia and other diseases related to sarcopenia.

Key words: Sarcopenia; Muscle mass; Protein synthesis; mTORC1 pathway; Essential amino acids; Leucine; Whey protein

Introduction

Skeletal muscle loss, sarcopenia, occurs in patients with a variety of physiological and pathological conditions, such as chronic heart failure (CHF), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), acquired immunodeficiency syndrome (AIDS), malignancy and so on, as well as during the natural aging process [1,2]. Sarcopenia mainly manifests as a reduced skeletal muscle mass, decreased muscle strength, and decreased quality of life [3]. Research has shown that the muscle mass, strength and physical function of the elderly are closely related to nutrition, which means that nutrition plays an important role in the prevention and treatment of sarcopenia. However, it has been estimated that 15% to 38% of older men and 27% to 41% of older women do not reach the recommended protein intake [4]. Taking in sufficient energy and protein, combined with active exercise, are effective methods for preventing and managing muscle loss [5,6]. The main purpose of the present article is to discuss the key role of protein supplementation for the prevention and management of sarcopenia, especially in the elderly.

Protein Synthesis and Degradation Signaling in Patients with Sarcopenia

Skeletal muscle accounts for approximately 40% of the body weight, and 50%-75% of the total body protein is present in skeletal muscle. Approximately 1%-2% of the bodily protein is turned over every day, requiring extensive protein synthesis and degradation. Nutrient intake is the most important anabolic stimulus for skeletal muscle. Specifically, the amino acid leucine and meal-induced insulin both independently stimulate muscle protein synthesis [7].When protein synthesis is greater than protein degradation (e.g., after intaking nutrients), there is a positive protein balance. A negative balance occurs when protein degradation is greater than protein synthesis (e.g., during fasting). Although muscle protein synthesis occurs later than the synthesis of other proteins, such as plasma and digestive proteins, new muscle can still be detected within a few hours after interventions promoting muscle protein synthesis.

The Involvement of the mTORC1 Pathway in Muscle Protein Synthesis

The process of skeletal muscle protein synthesis is complex, involving a tightly-regulated balance of gene transcription (including modifications of transcription), protein translation, and protein degradation processes. The mammalian target of rapamycin (mTOR) pathway is the main signaling pathway that regulates muscle protein synthesis [8].

The molecular weight of mTOR is 289kDa, and it mainly forms two protein complexes: mTORC1 and mTORC2. mTORC1 is made up of G protein β-subunit-

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like protein (GβL) and regulatory associated protein of mTOR (raptor), while mTORC2 is composed of GβL, mSin, and rapamycin-insensitive companion of mTOR (rictor). Muscle contraction, insulin, essential amino acids, the intake of energy, and other stimulating factors can promote protein synthesis through the mTORC1 signaling pathway [8]. In addition to serving as a substrate for protein synthesis, glucose and amino acids (especially leucine) can also stimulate the mTOR1 signaling pathway directly to promote the translation of muscle proteins, consequently promoting muscle protein synthesis [9]. The main three ways of stimulating the mTORC1 pathway are [10]: (1) glucose activates adenosine 5`-monophosphate (AMP)-activated protein kinase (AMPK) through the insulin pathway; (2) amino acids (especially leucine) activate mTORC1 through human vacuolar protein sorting-34 (hVps34), mitogen-activated protein kinase kinase kinase kinase-3 (MAP4K3), and Rag guanosine triphosphatases (GTPases); (3) growth factors activate mTORC1 through Akt and the tuberous sclerosis complex (TSC1/2complexes). Nutrients can directly or indirectly affect these three ways to activate the mTORC1 pathway, consequently promoting muscle protein synthesis.

The major effectors of mTOR1 include p70 ribosomal S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E binding protein 1 (4E-BP1) [11]. S6K1 is a positive regulator of mTOR1/protein synthesis [12], while 4E-BP1 is a negative regulator of mTOR1/protein synthesis [13]. S6K1 stimulates protein synthesis by promoting the formation of translational complexes, thus promoting protein translation. The mTOR pathway may be associated with an increase in muscle mass, and rapamycin treatment has been demonstrated to impair load-induced myocardial hypertrophy in mice [14]. A study by Bolster DR et al. found that resistance training could induce rapid activation of the mTOR pathway in rat skeletal muscle cells by increasing the rapid phosphorylation of S6K1 [15].The increase in muscle tissue after resistance training is also related to the phosphorylation of S6K1in human type II muscle fibers [16]. Dreyer HC et al. also found that resistance training could promote human skeletal muscle protein synthesis by increasing the activity of AMPK and decreasing the phosphorylation of 4E-BP1 [17].

Ubiquitination-Mediated Degradation of Muscle Protein

Muscle degradation can be induced by inflammatory reactions, oxidative stress, impaired mitochondrial function, insufficient energy and nutrient intake, etc. [18]. Intracellular proteins are degraded mainly through the ubiquitin-proteasome pathway (UPP). Unwanted or damaged proteins are degraded by the proteasome, a protein complex composed of 20S core particles, 19S regulatory particles and 11S regulatory particles, which break peptide bonds. The ubiquitin-mediated degradation of protein is the main mechanism underlying the skeletal muscle protein loss during sarcopenia [18].

Many factors (such as fasting) may activate the UPP to promote protein degradation to release energy. Long-term bedridden patients, and those with CHF, CKD, and COPD may all have increased proteasome activity, resulting in increased degradation of body protein, especially muscle protein [19]. In contrast, other factors (such as insulin) may inhibit protein degradation by reducing the proteasome activity [20]. In addition, amino acid or protein imbalances may also inhibit the degradation of body proteins by affecting the proteasome activity [21]. The ubiquitin-proteasome system (UPS) is the main system implicated in tumor cachexia-associated protein degradation [22], which occurs before the loss of muscle tissue [23,24]. Ventrucci G et al. [25] found that leucine inhibited the expression of 20S, 19S, and 11S of the muscle proteasome in tumor-bearing mice, inhibited the ubiquitin-mediated degradation of proteins, and promoted myosin synthesis, and thus was beneficial in reducing muscle wasting. The target protein must be ubiquitinated by specific ubiquitylating enzymes before it can be degraded by the proteasome. Atrogin-1 and MuRF-1 are the major ubiquitylating enzymes involved in skeletal muscle degeneration [26]. Transforming growth factor-β (TGF-β) can stimulate the transcription of Atrogin-1 and MuRF-1 mRNA, thus promoting the degradation of protein, especially skeletal muscle proteins [26]. Maki T et al. [27] found that branched chain amino acids (BCAA) decreased the expression of Atrogin-1 and MuRF-1 in rats with hind limb suspension-induced muscle atrophy (HSIMA), and this inhibited muscle protein degradation and contributed to preventing muscle loss.

Calcium-dependent Proteolytic System

The calcium-dependent proteolytic system has been implicated in different types of muscle atrophy [28]. It has been suggested that the apoptosis associated with sarcopenia could involve calpain-dependent proteolysis rather than caspase-dependent mechanisms [29]. Strengthening this idea, m-calpain is expressed in the mitochondria, and several calpain substrates have recently been identified among components of the respiratory chain [30-32]. Apoptosis-inducing factor(AIF) and endonuclease G (Endo G) are pro-apoptotic factors released from the mitochondria by calpain activity, both of which are up-regulated in sarcopenic muscle [29,33]. Furthermore, caspase 12, known to be activated by m-calpain cleavage, was found to be more active in aged muscle [29].

In the light of these data and our personal experience, we believe that the calcium-dependent proteolytic

system plays a pivotal role in the sarcopenic phenotype. However, which intracellular calpain-dependent pathway(s) is affected during muscle aging remains to be elucidated.

Autophagy-lysosomes System

Autophagy is a process by which a flat membrane cistern envelops a portion of the cytoplasm, eventually forming a closed double-membrane vesicle called the autophagosome, which fuses with the lysosome where its cargo is degraded [34]. The induction of autophagy in the muscles of young mice leads to myofiber atrophy, muscle mass loss, and a proportional decrease in muscle strength [35].

Among the signaling pathways that regulate autophagy, transcription factors of the forkhead box O (FoxO) family increase autophagic degradation in muscle by promoting the expression of autophagy-related genes [36,37]. For example, it was found that muscle-specific overexpression of wild-type FoxO and of constitutively active 4E-BP preserves the basal level of autophagy and muscle function during aging [38]. Moreover, the levels of chaperone proteins Hsp27 and a B-crystallin, and of poly-ubiquitylated proteins, are increased in the detergent-insoluble fractions of muscles in old humans and mice [39,40]. This suggests that protein aggregates develop in aged muscles. The muscle-specific knockout of the key autophagy genes Atg5 and Atg7 leads to defective autophagy, the accumulation of p62-poly-ubiquitin protein inclusions, abnormal mitochondria, and sarcomeric defects that presumably explain the decreased muscle strength observed in these mice [41]. Furthermore, sustained activation of mTORC1 signaling in mouse skeletal muscle leads to inhibition of autophagy and to a severe myopathy characterized by the accumulation of p62-containing protein aggregates and dysfunctional mitochondria [42]. Similarly, muscle-specific loss of AMPK (an inducer of autophagy) results in premature age-related muscle weakness and mitochondrial dysfunction [43], which is a hallmark of sarcopenia. The same phenotype is also seen in mice with muscle ablation of mitofusin 2 (Mfn2), which leads to inhibition of mitophagy and the accumulation of dysfunctional mitochondria [44].

Overall, the above studies highlight the important roles of autophagy in regulating several aspects of skeletal muscle homeostasis during aging. Moreover, changes in skeletal muscle autophagy also have important systemic effects.

Effects of Protein and Amino Acid Supplementation on Sarcopenia

Supplementation of essential amino acids (EAA)

Sarcopenia is frequently related to insufficient protein intake [45], especially in the elderly [46]. Morley JE et al. reported that 32%-41% of females and 22%-38% of males ≥ 50 years old consume less protein per day than the recommended intake (0.8g/kg·d) [4]. EAA are a major factor that stimulates muscle protein synthesis [47]. Although earlier studies indicated that the intake of nutrients or amino acids affects 30%-100% of protein synthesis, later research showed that the effects were mainly due to EAA. In both healthy people and insulin-resistant patients, amino acids are essential for the protein synthesis regulated by insulin-induced mTOR/S6K1 signaling pathways.

Some studies showed that EAA treatment could promote muscle synthesis in elderly patients with sarcopenia. Solerte SB et al. [48] designed a study where elderly people (aged 66-84) with sarcopenia were treated with 8g of EAA per day for 18 months (formula including: 2.5g L-leucine, 1.3g L-lysine, 1.25g L-isoleucine, 1.25g L-proline, 0.7g L-threonine, 0.3g L-cysteine, 0.3g L-histidine, 0.2g L-phenylalanine, 0.1g L-methionine, 0.06g L-tyrosine and 0.04g L-tryptophan), and found that EAA treatment decreased the serum tumor necrosis factor-alpha (TNF-α) level and increased the serum insulin-like growth factor-1 (IGF-1) level significantly. EAA treatment also increased the insulin sensitivity and skeletal muscle mass.

Some researchers have suggested that combining EAA and resistance training may be more effective to improve skeletal muscle protein synthesis than EAA alone. Drummond MJ et al. [8] found that combining EAA with resistance training promoted muscle protein synthesis by stimulating the mTORC1 pathway. The stimulation of protein synthesis by combined resistance training and EAA was delayed in older people compared to adult controls, which provides an additional explanation for the skeletal muscle loss in the elderly [49].

The determinant of muscle strength and muscle quality is not just the total amount of protein taken in, but also the quality of the protein and the timing of the intake. Some studies have implied that the distribution pattern of protein intake affects skeletal muscle protein synthesis. Mamerow MM et al. [50] compared the effects of a protein supply divided roughly evenly among three daily meals (breakfast: 31.5 ± 1.3g, lunch:29.9 ± 1.6g, dinner:32.7 ± 1.6g protein) with a protein supply provided mainly at dinner (breakfast:10.7 ± 0.8g, lunch:16.0 ± 0.5g, dinner: 63.4 ± 3.7g) during a 7-day experimental period. The results showed that the even protein distribution group had more skeletal muscle protein synthesis during a 24h period than the imbalanced group. However, a recent study reported different results. In that study, fourteen older subjects were randomly divided into either an EVEN or UNEVEN group. The UNEVEN group consumed the majority of their dietary protein with dinner (UNEVEN, 15%/20%/65%; breakfast, lunch,

dinner), while the EVEN group consumed dietary protein evenly throughout the day (EVEN: 33%/33%/33%).The results of that study showed no significant differences in lean body mass, muscle strength, protein synthesis and breakdown, or other functional outcomes between the EVEN and UNEVEN groups before and after an 8-week intervention [51].

With regard to the timing of protein consumption in combination with resistance training, Drummond MJ et al. [8] designed an experiment involving 4 groups: a resistance exercise group, an EAA group, an EAA intake before resistance exercise, and a group immediately provided EAA after resistance training. The results showed that the muscle protein synthesis rate was highest in the group immediately provided EAA after resistance exercise group, followed by the EAA group, and the EAA intake before resistance exercise group. The group treated with resistance exercise alone had the lowest muscle protein synthesis rate. This study indicates that EAA should be given immediately after resistance training to promote muscle protein synthesis.

Supplementation of BCAA

BCAAs includes leucine, isoleucine and valine, which all are EAAs. The catabolism of BCAAs mainly occurs in skeletal muscle [52]. Beginning in the 1980s, BCAAs supplementation was used for patients with liver diseases. The long-term application of BCAAs increased the albumin levels and improved the quality of life in liver cancer patients with chemotherapy-induced drug embolization [53]. The BCAAs are also considered to have anti-anorexia and anti-cachexia properties. Recent studies have confirmed that BCAAs play a role in stimulating food intake and preventing muscle loss in people with anorexia and weight loss [54]. As noted earlier, BCAA also promote muscle synthesis though the mTOR pathway [55].

When the body is inactive or immobile, the catabolism of skeletal muscle protein increases. Paddon-Jones D et al. [47] studied 13 healthy male volunteers who were subjected to prolonged (28-day) bedrest. The normal meal energy ratio was 50% carbohydrates, 29% fat, and 14% protein. However, the experimental group was given BCAA-enriched EAA and carbohydrates, at 16.5g EAA + 30g sucrose, which were administered three times per day at 11:00 am, 16:00 pm, and 21:00 pm. After 28 days, dual-energy X-ray detection showed that the lean leg mass was maintained throughout bedrest in the experimental group (+0.2 ± 0.3kg), but decreased in the control group (-0.4 ± 0.1kg). In addition, the leg extension strength test showed that the strength loss was more pronounced in the control group (control, -17.8 ± 4.4kg; experimental, -8.8 ± 1.4kg), and the fractional synthetic rate (FSR) was higher in the experimental group (experimental, 0.093 ± 0.006%/h; control, 0.075 ± 0.005%/h). This study indicates that supplementation of BCAA-enriched EAA combined with carbohydrates may represent a viable intervention for individuals at risk of sarcopenia due to immobility or prolonged bedrest.

HSIMA is a common rat model of muscle atrophy that has been used to study immobility-induced muscle loss. Maki T et al. [27] found that the expression levels of the ubiquitinating enzymes (Atrogin-1 and MuRF1) in the HSIMA rat model were decreased by BCAA treatment, and that the ubiquitination-mediated degradation of muscle protein in rats with sarcopenia was inhibited, contributing to preventing muscle loss.

The decrease in the serum concentration of BCAA and the increase in the concentration of aromatic amino acid (AAA) in patients with advanced cirrhosis are believed to be major causes of hepatic encephalopathy (HE), sarcopenia and liver cancer. Sarcopenia in patients with liver disease may be due to a decrease in muscle protein synthesis, and a lack of EAA, including BCAAs. Hiraoka A et al. [56] found that in patients with cirrhosis who were given BCAAs and prescribed walking exercise, their BCAA/tyrosine ratio increased after 3 months of intervention, and their muscle mass, leg strength and handgrip strength also increased. BCAAs supplementation to treat sarcopenia in patients with cirrhosis should thus be combined with appropriate exercise [57].

Takeuchi I et al. [58] performed a multicenter randomized controlled trial in sarcopenic older adults undergoing in-hospital rehabilitation who had low muscle strength (handgrip strength) and low muscle mass (based on the calf circumference) according to the cut-off values for older Asians. The intervention group was given BCAA and vitamin D, while the control group was not, and both groups participated in low-intensity resistance training in addition to the post-acute rehabilitation program. The results of the 8-week intervention showed that the muscle strength, muscle mass, BMI, and serum albumin level were all significantly improved compared with the control group. This suggests that nutritional supplements could stimulate muscle protein synthesis in older adults to counteract or prevent muscle loss.

Supplementation of Leucine-enriched EAA and Leucine Metabolite, beta-hydroxy-beta-methylbutyrate (HMB)

In addition to being a substrate for the synthesis of peptide chains, amino acids have many other functions, such as regulating transcription and translation during protein synthesis. Leucine, one of the BCAAs, regulates the initiation of mRNA translation and also regulates protein turnover (cycling) through the mTOR-dependent pathway via 4E-BP1 and p70 (s6k) [59]. Due to its ability to stimulate muscle protein synthesis, leucine has been receiving a lot of attention. Studies have shown that only

leucine, not other essential amino acids, could activate the mTORC1 signaling pathway during muscle protein synthesis [60]. However, the unique mechanism(s) involving leucine still needed to be elucidated.

It is known that leucine inhibits the ubiquitin-mediated degradation of muscle proteins [25], and it also promoted muscle synthesis in mice with cachexia. Peters SJ et al. [61] used a C26 tumor-bearing cachectic mouse model to assess the effects of dietary supplementation with leucine on muscle weight. Male mice were subcutaneously inoculated with tumor cells (tumor-bearing mice; TB) or a sham injection (control, C). The mice were fed a standard diet or a diet supplemented with leucine; the TB +C group received 8.7% leucine/g protein, the TB1Leu group received 9.6% leucine/g protein and the TB2Leu group received 14.6% leucine/g protein. After 21 days, the mass of the gastrocnemius (mG), tibialis anterior (mTA), extensor digitorum longus (mEDL) and soleus (mS) muscles were determined. The results showed that higher leucine supplementation (TB2Leu) reduced muscle wasting and promoted protein synthesis in the cancer cachectic mice.

Leucine is also a muscle-specific amino acid in humans. The supplementation of leucine-enriched EAA in combination with resistance training could stimulate skeletal muscle protein synthesis. Drummond MJ et al. [8,62] found that the induction of muscle protein synthesis by leucine via the mTOR pathway may help to prevent muscle loss in patients with cachexia. Interestingly, Katsanos C et al. [63] observed the effects of a high leucine diet on muscle protein synthesis in the elderly. The leucine ratios were 26% and 41%, respectively, and 41% leucine was found to significantly stimulate protein synthesis in the elderly compared with younger people.

Devries MC et al. [64] studied the effects of twice-daily consumption of either a 15 g milk protein beverage containing 4.2 g leucine or a 15g mixed protein (milk and soy) beverage containing 1.3 g leucine on the acute and integrative myofibrillar synthesis in healthy elderly women, and found that high leucine levels were associated with an increase in the acute myofibrillar synthesis. Increasing the leucine-rich protein intake strengthens the synthesis of muscle protein in elderly women to help maintain muscle mass and function.

Leucine could also change the initial rate of synthesis of globular proteins and specific proteins by activating specific signaling pathways. For example, Fujita S et al. [65] confirmed that leucine-enriched EAA could stimulate skeletal muscle synthesis through the mTOR signaling pathway in humans. Of note, after providing leucine-enriched EAA, leucine and phenylalanine were increased in muscle tissue, and the level of phosphorylated AMPK was decreased, leading to activation of the mTOR signaling pathway. This led to a subsequent increase in the FSR%, stimulating skeletal muscle synthesis.

The upper limit (UL) of leucine (with regard to safe supplementation) has been identified in young men, but the UL value of leucine in older men is unclear. Rasmussen B et al. [66] investigated the safety of leucine supplementation for healthy elderly men, and found that the UL for leucine is not different between young men and elderly men, and suggested the leucine UL can be set at 500mg/kg/day.

Oktaviana J et al. [67] explored the effects of HMB on muscle mass, strength and function in older people (> 60 years) with sarcopenia and frailty, where the main outcomes were the lean body mass, handgrip strength, leg press strength, and Short Physical Performance Battery (SPPB) score. The results showed that HMB supplementation could increase the lean body mass and preserve muscle strength and function in older people with sarcopenia or frailty.

Another study [68] highlighted the potential relationship between HMB dietary supplements and parameters related to the maintenance of muscle mass and strength in the elderly. Their findings suggest that HMB can prevent muscle atrophy or improve muscle mass while increasing muscle strength/function and physical performance in elderly people with a reduced lean body mass. The European Society of Clinical Nutrition and Metabolism guidelines on nutritional support for polymorbid internal medicine patients suggest that in malnourished inpatients (or in those at high risk of malnutrition), nutrient-specific supplementation (with HMB) should be administered, as such treatment may maintain muscle mass, reduce mortality and improve quality of life in these patients [69].

The Role of Whey Protein

Increasing the plasma free amino acid concentration is a key factor in promoting skeletal muscle protein synthesis in the elderly [70], and supplementing whey protein is an effective way to achieve this goal. EAA and whey protein may have different effects on stimulating muscle protein synthesis in the elderly. Studies have found that whey protein intake promoted more muscle protein synthesis in the elderly than pure EAA or non-essential amino acids (NEAA) [71]. Katsanos CS et al. randomly divided 15 older people into 3 groups: a whey protein group, EAA group, and NEAA group. The whey protein group was given 15g whey protein, the EAA group was just given 6.17g EAA (exactly contained in 15g whey protein), and the NEAA group was just given 7.57g NEAA (exactly contained in 15g whey protein). After 3.5h, the muscle phenylalanine balance (reflecting positive nitrogen balance) and insulin response were measured. It was found that both of these were higher in the whey protein group than that in the EAA and NEAA

groups, indicating that EAA or NEAA alone could not effectively promote positive a nitrogen balance, but whey protein with EAA and NEAA contributed to maintaining a positive nitrogen balance and increased muscle strength during resistance training [71].

There have been reports about whether EAA or whey protein is the better supplement. Paddon-Jones D et al. [72] found that both EAA and whey protein stimulated muscle protein synthesis, while EAA seemed to be more effective. In that study, researchers observed muscle protein synthesis in healthy elderly individuals following the ingestion of an isocaloric whey protein (n = 8) or essential amino acid (n = 7) supplement. The phenylalanine uptake and mixed muscle FSR were calculated during the post-absorptive period and for 3.5h following the ingestion of 15g EAA or 15g whey protein. The results showed that the phenylalanine uptake and the FSR% in the whey protein group were lower than those in the EAA group.

In contrast, Borack MC et al. [73] gave older men a soy-dairy protein blend (PB, soybean and whey proteins mixed) or whey protein isolate (WPI) after exercise. The data showed that both groups had increased amino acid concentrations and mTORC1 signaling after protein ingestion. There were no significant differences in the changes in the plasma amino acid concentration, mTORC1 signaling, FSR%, fractional breakdown rate (FBR%), or net protein balance between groups, suggesting that both PB and WPI ingestion after exercise by older men could cause similar responses.

Pennings B et al. [74] studied the stimulatory effects of whey protein, casein protein and casein hydrolysate on postprandial muscle protein in elderly men, and demonstrated that whey stimulates postprandial muscle protein accretion more effectively than casein or casein hydrolysate. They attributed this effect to whey's more rapid digestion and absorption kinetics and to its higher leucine content.

Hays NP et al. [75] compared the nitrogen balance of two protein supplements (whey protein or hydrolyzed collagen) using a crossover study design for 15 days. The results showed that the nitrogen balance and weight in the hydrolyzed collagen group were superior to those in the whey protein group. The roles of whey protein and hydrolyzed collagen need to be further studied in larger groups of patients.

Supplementation of Protein Combined with Exercise, Vitamin D and Other Treatments

Sarcopenia and osteoporosis are two related diseases affecting the elderly, and postmenopausal women are more likely to develop both of these conditions. Nutrition and lifestyle have a positive impact on the quality and function of muscles and bones [76]. Protein, vitamin D and calcium supplements, combined with specially designed exercise training regimens, may be a good way to prevent both sarcopenia and osteoporosis [77].

A randomized, controlled, double-blind study by Chanet A et al. [78] investigated the acute effects of supplementing breakfast with vitamin D and leucine-rich whey on the postprandial muscle protein synthesis, as well as the long-term muscle quality in healthy elderly men. The study was conducted in 24 healthy older men, and all participants received a medical nutrition drink (test group: 21g leucine-enriched whey protein, 9g carbohydrates, 3g fat, 800IU cholecalciferol (vitamin D3), and 628kJ) or a noncaloric placebo (control group) before breakfast for 6 weeks. The study showed that supplementing breakfast with a vitamin D- and leucine-enriched whey protein nutrition drink stimulated postprandial muscle protein synthesis and increased the muscle mass after 6 weeks of intervention in healthy older men and may therefore be a way to support muscle preservation in older people.

Another multicenter, randomized, controlled, double-blind, 2 parallel-group trial by Bauer JM et al. studied the effects of a vitamin D- and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in 380 sarcopenic primarily independent-living older adults with Short Physical Performance Battery (SPPB;0-12) scores between 4 and 9 and a low skeletal muscle mass index. The active group received a vitamin D and leucine-enriched whey protein nutritional supplement to consume twice daily for 13 weeks. The control group received an iso-caloric control product to consume twice daily for 13 weeks. The results showed that the 13-week intervention using the vitamin D- and leucine-enriched whey protein oral nutritional supplement improved the muscle mass and lower-extremity function among sarcopenic older adults [79].

Bo Y et al. examined the effects of a nutritional supplement containing whey protein, vitamin D and vitamin E on measures of sarcopenia in a total of 60 sarcopenic older adult subjects as part of a randomized, double-blind, placebo-controlled (iso-caloric control product) trial for 6 months. They measured the muscle mass [relative skeletal mass index (RSMI) measured by bioimpedance analysis (BIA)], muscle strength (handgrip strength), physical function (6-m gait speed, chair stand test, and timed-up-and-go test, TUG)], quality of life (measured by the Short-Form 36-Item Health Survey, SF-36), and blood biochemical indices before and after the 6-month intervention. The combined supplementation of whey protein, vitamin D and vitamin E significantly improved the RSMI, muscle strength, and anabolic markers such as IGF-1 and IL-2 in older adults with sarcopenia [80].

van de Bool C et al. [81] launched a study of 81 COPD patients with poor muscle mass who were admitted for outpatient pulmonary rehabilitation.

The patients were randomly given either oral specific nutritional supplements (enriched with leucine, vitamin D and omega-3 fatty acids) or PLACEBO during four months of high intensity exercise training. The study found that specific nutritional supplementation had beneficial effects on the nutritional status, inspiratory muscle strength, and physical activity compared with placebo, while the daily steps decreased in the control group.

The European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) working group issued a statement on the importance of adequate nutrition for the prevention and treatment of sarcopenia in elderly people, with a special emphasis on ensuring adequate intake of protein, vitamin D, antioxidants, and long-chain polyunsaturated fatty acids at the same time [82].

Protein Recommendations for Prevention and Treatment of Sarcopenia

Mitchell CJ et al. [83] reported that a twice the RDA (2RDA) protein diet had beneficial effects on the skeletal muscle mass and physical function in elderly men. The participants were provided with a complete diet containing either 0.8 (RDA) or 1.6 (2RDA) g protein/kg/d aimed to balance the energy needs, and dual-energy X-ray absorptiometry was used to measure the whole-body and appendicular lean mass before treatment and after 10 weeks of intervention. The results showed that the whole-body lean mass increased in the 2RDA group in comparison with the RDA group, and the appendicular lean mass decreased in the RDA group compared with the 2RDA group. Another study demonstrated that patients with sarcopenia need serum 25(OH)D concentrations exceeding 50nmol/L and dietary protein intake (> 1g/kg/d) in long-term nutritional interventions, so protein and vitamin D supplementation can have beneficial effects and can help lead to significant muscle mass gain [84].

In 2010, the Society for Sarcopenia, Cachexia, and Wasting Disease (SCWD) proposed nutritional recommendations for the management of sarcopenia [4]. Senile muscle loss due to aging is associated with decreased metabolic efficiency, which requires a higher protein intake to promote protein synthesis. Among comprehensive measures for preventing senile sarcopenia, it is recommended that patients receive adequate and balanced energy and protein intake. Elderly people are recommended to have a protein intake of 1.0-1.5 g/kg body weight. It is also recommended that elderly people should consume leucine-enriched EAA. Supplementation with whey and other dietary proteins, particularly in association with exercise training, has been proposed to be beneficial for the elderly to help them gain and maintain a lean body mass and improve health parameters. An intake of approximately 0.4 g protein/kg BW per meal (representing 1.2-1.6 g protein/kg BW/day) may be recommended after taking into account potential anabolic resistance [85].

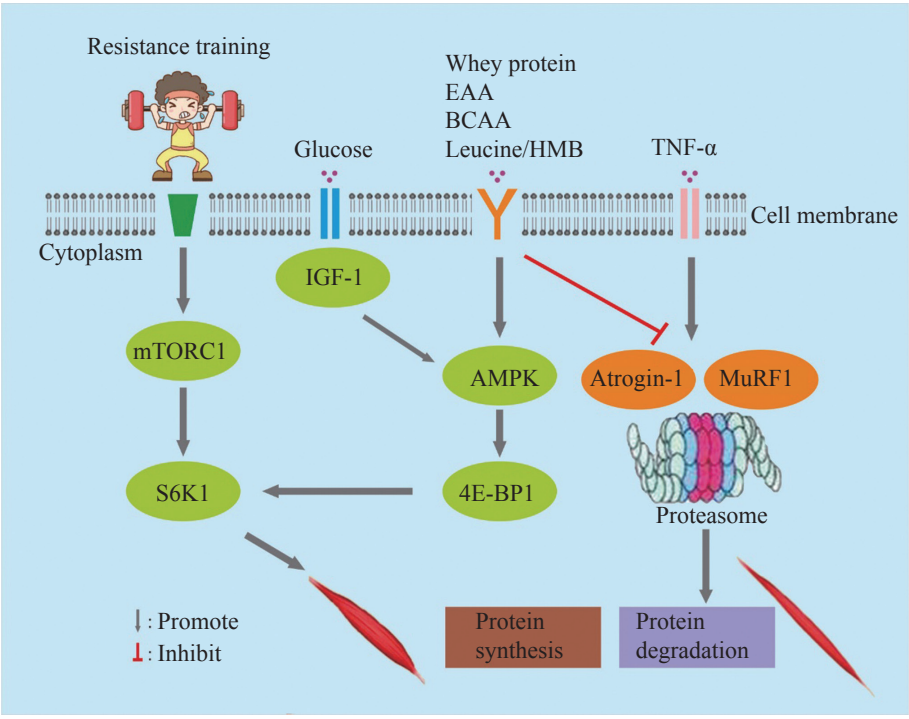

Figure 1 The regulation of muscle protein synthesis and degradation in sarcopenia. EAA: essential amino acids; BCAA: Branched-chain amino acids; HMB: beta-hydroxy-beta-methylbutyrate

Conclusion

An increasing number of studies are showing that the muscle mass, strength and physical function of the elderly are closely related to nutrition. Increasing the protein intake is the basis for preventing and managing muscle loss. Protein therapy for muscle loss requires exercise, in combination with other nutrients (such as vitamin D), to stimulate muscle synthesis. However, the existing research has mainly focused on animal models and elderly patients, and large-scale multicenter random control trials using standardized protocols are needed to provide a more accurate understanding of the human requirements at various ages and stages of disease or disability.

Conflicts of Interests

The authors declare that there are no conflicts of interest.

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