Leucine Supplementation and Sarcopenia

Subjects: Nutrition & Dietetics

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Treating sarcopenia remains a challenge, and nutritional interventions present promising approaches. We summarize the effects of leucine supplementation in treating older individuals with sarcopenia associated with aging or to specific disorders, and we focus on the effect of leucine supplementation on various sarcopenia criteria, e.g., muscular strength, lean mass, and physical performance.

leucine sarcopenia muscular mass muscular strength elderly

1. Introduction

Sarcopenia is defined as a progressive loss of muscle mass, strength, and function [1][2]. From a physiological point view, sarcopenia starts in the fifth decade of life and at a population level, proceeds at a rate of ∼ 0.8% annually. In fact, the decrease in skeletal muscle strength induced by sarcopenia, known as dynapenia, is even more precipitous, occurring at an annual rate of ∼ 2–3% [2][3] and it is estimated that more than 20% of adults aged over 65 years, and over 50% of those aged at least 80 years are sarcopenic [4]. In some pathological conditions such as liver cirrhosis [5], chronic obstructive pulmonary disease [6][7], and diabetes [8], sarcopenia can appear earlier and its progression occurs more quickly. Several studies report that the most sarcopenic individuals are at an increased risk of developing severe sarcopenia-related complications, such as an increased risk of falls [9][10], frailty [11], disability [12], and type-II diabetes [13][14], which all have a negative impact on their quality of life and premature mortality.

Within the framework of the Third National Health and Nutrition Examination Survey, Srikanthan and Karlamangla [12] have demonstrated that muscle mass is a predictor of longevity when taking into account the all-cause mortality in North American adults (aged over 55 or 65 years for men and women, respectively). One of the main ways in which sarcopenia contributes to the disease is that it alters muscular turnover and metabolism [15][16]. Moreover, older adults exhibit a decreased anabolic response to protein feeding [17][18], which is a mechanism underpinning the loss of muscle mass in sarcopenic individuals. Compared to younger adults, those aged over 65 years required ∼ 70% more protein per meal to maximally stimulate muscle protein synthesis [19]. Furthermore, at a global level, only 40% of older adults meet the recommended daily allowance for protein (0.8 g·kg^{-1}·d^{-1}) and 10% of older women do not even meet the estimated average requirement of 0.66 g protein·kg^{-1}·d^{-1} [20][21].

One strategy to increase the muscle protein synthesis that has been investigated is the supplementation of diets with leucine, an essential branched-chain amino acid with important regulatory actions in muscles, which are at least partially mediated by the mammalian target of the rapamycin pathway [22]. Leucine modifies protein turnover in skeletal muscles, by decreasing proteolysis and by increasing protein synthesis. Physiological research reports have shown that leucine can enhance muscle protein-synthesis [23][24][25][26]. Furthermore, leucine can stimulate insulin release by pancreatic cells [27], showing that besides its beneficial effect in enhancing skeletal muscle glucose uptake, it is also an important anabolic signal in skeletal muscle.

Based on the above, administration of leucine-containing supplements is therefore a promising approach for treating sarcopenia. We took a systematic approach to analysing the current scientific evidence in this area, and to ascertaining whether the administration of leucine-containing supplements is effective in the treatment of sarcopenia. We also included interventions that used whey protein as a supplement, because these contain large amounts of leucine (approximately 13 g leucine/100 g protein [28]) and the consumption of whey protein appears to be the most effective at increasing muscle protein synthesis [29].

2. Current Insights on Leucine Supplementation and Sarcopenia

The loss of muscle mass and strength (sarcopenia) and its functional consequences such as reduced walking speed can occur to a varying degree both as a part of physiological changes during aging [30] or in some pathological conditions increasing the amount of time in bed which in itself can result in catabolism and a decrease in muscle mass [31][32] or patients with chronic diseases such as liver cirrhosis [5][33], COPD [6][7], diabetes [34] and post-stroke patients [35]. Severe sarcopenia is associated with an extremely high rate of disability but not necessarily with body-weight loss, and obese sarcopenic patients appear to have even worse outcomes [36][37][38].

The best approaches to treat sarcopenia or delay its progression over time are currently based on physical exercise and nutritional supplementation, with resistance training being the most useful tool for effectively preventing [39][40] and treating sarcopenia [41][42][43]. However, many older people are sedentary and either cannot (social barriers and family support) or do not want to exercise. In these cases, nutritional interventions remain the most promising intervention to delay the appearance of the adverse consequences of sarcopenia such as falls, mobility loss, and a bed-to-sofa lifestyle. Supplementation of the branched-chain amino acid, leucine, or leucine-enriched protein (whey/casein protein) [28][29][44] is one of the most common interventions for treating sarcopenia in older individuals, and several RCTs have been published in the last five years.

Analysis of the trials included in this systematic review showed that these nutritional interventions can improve several aspects of sarcopenia, including muscle strength, lean mass content, and walking speed (although the latter has seldom been investigated) although these effects depend on sarcopenia criteria (ranging from improvement to no effect) and the patients' characteristics. Only one study [45] found a reduction in muscle strength after supplementation with whey protein and casein, although they did not make the reasons for this reduction clear. As possible causes, they cited an insufficient difference in protein intake between groups, a lack of a need for protein-supplementation because of already sufficient dietary protein intake, or the specific characteristics of the patients included in the sample who all had polymyalgia rheumatica. In overall terms, the results of the review suggest that the beneficial effects of leucine-supplementation are more consistent for the improvement in lean mass reported in 63% of the analysed studies, which is consistent with the physiological action of leucine in muscle metabolism.

Interestingly, the majority of interventions that found an improvement in lean mass after leucine supplementation also co-administered vitamin D as a part of the nutritional intervention. Vitamin D is increasingly recognised as playing an important role in normal muscle function, and low vitamin D status is associated with an increased risk of falls and proximal weakness [46] and these effects are more prominent in male individuals [47]. In view of these sex-dependent effects, the differential effects of leucine supplementation with or without vitamin D and the measurement of vitamin D as a biological marker of sarcopenia need further research.

In contrast, the sarcopenia criteria related to muscle strength and physical performance are not only mediated by an efficient and proper lean mass, but also by a central nervous system component which forms a neuro-muscular (motor) unit [3][48]. Improvements in neuromuscular activation precede increases in muscle mass in response to resistance training; neuromuscular activation has therefore been proposed as another measure of muscle quality [48]. The fact that in most studies there were no clear parallelism between a positive effect in lean mass improvement accompanied by a positive effect on muscle strength or physical performance confirms that the central nervous system component is necessary for restoring muscular strength in age- and diseases-related sarcopenia is less sensitive to leucine supplementation than lean mass improvement.

With regards to the effects of leucine supplementation in sarcopenia occurring in individuals with some kind of disease, an improvement in muscle strength was observed in COPD patients [49]. Muscle wasting is common in COPD, particularly among those with the emphysema-type, and associated with a high prevalence of osteoporosis, impaired exercise performance, and higher mortality risk [50]. Further RCT should address the effects of leucine supplementation on physical performance, which may definitely be relevant to patients’ ability to carry out basic activities of daily life and their quality of life.

A beneficial effect of leucine supplementation co-administered with a program of physical exercise was observed in post-stroke patients for both muscular strength and lean mass [35].

Regarding methodological issues, our analysis highlighted that different sarcopenia evaluation methods have often failed to adequately meet the criteria proposed by the international guidelines [1][51][52]. Therefore, future studies should focus on evaluating treatment effects using accepted criteria for defining sarcopenia and to select optimally the features of individuals or patients that could benefit more following an intervention consisting in leucine supplementation [51].

To the best of our knowledge, no published work has investigated the role of comorbidities or polymedication in the effects produced by leucine supplementation and as such further research in this area is clearly warranted. This would enable the selection of patients who could most benefit from supplementation, such as patients with COPD or cirrhosis, because these diseases are classically associated with sarcopenia [49][53][54]. To date, the best available evidence suggests that administration of leucine-enriched proteins such as whey/casein protein or an

EAA mixture, has beneficial effects for sarcopenic individuals, is well-tolerated, and does not have any serious adverse effects.

3. Conclusion

Finally, whenever possible, a multidisciplinary approach to treating sarcopenia must be encouraged. This means that besides leucine supplementation, clinicians should prescribe a balanced diet and physical exercise to treat this condition. Finally, our analysis also provides evidence that leucine or leucine-enriched protein supplementation may also have other beneficial effects, such as improving cognitive function [49][55][53], symptoms of depression [54][56], and quality of life [57][49], which lends further support to the use of this intervention in geriatric populations.

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