POSSIBILITIES OF USING BRANCHED-CHAIN AMINO ACIDS FOR THE TREATMENT AND PREVENTION OF SARCOPENIA IN ELDERLY AND OLD PATIENTS (LITERATURE REVIEW)

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ABSTRACT

Due to the high prevalence of sarcopenia among elderly and old patients, early prevention and treatment of sarcopenia and its complications are relevant. Protein supplements can be used to maintain muscle strength and mass during aging. The possibility of using branched-chain amino acids (BCAAs) in the treatment and prevention of sarcopenia in geriatric patients is of scientific interest. BCAAs promote the synthesis and inhibit the degradation of muscle tissue proteins, are involved in the regulation of tissue sensitivity to insulin, ammonia utilization, the tricarboxylic acid cycle, etc.

Search strategy. *The search for scientific articles for literature review was carried out in the PubMed and PubMed Central databases. The selection criterion was scientific articles published up to December 2022. We used the following search keywords: "branched-chain amino acids", "BCAA", "body composition", "sarcopenia", "aging". The 2019 European Working Group on Sarcopenia in Older People 2 (EWGSOP2) Consensus was included in the list of articles.*

Conclusions. *The possibility of using BCAAs in elderly and old patients for the prevention and treatment of sarcopenia is a relevant topic that continues to be actively studied. The effectiveness of BCAA supplementation in the diet is debatable as long as sufficient protein is consumed daily. On the other hand, BCAA supplementation may be justified in cases where it is not possible to consume enough high-quality protein in the diet. More research is needed on this topic.*

Key words: *branched-chain amino acids, BCAA, gerontology, body composition, sarcopenia, aging, metabolism*

Received: 30.01.2023
Accepted: 31.05.2023
Published: 11.07.2023

For citation: Kurmayev D.P., Bulgakova S.V., Treneva E.V., Chetverikova I.S., Kosareva O.V., Sharonova L.A., Dolgikh Yu.A. Possibilities of using branched-chain amino acids for the treatment and prevention of sarcopenia in elderly and old patients (literature review). *Acta biomedica scientifica*. 2023; 8(3): 106-114. doi: 10.29413/ABS.2023-8.3.11

ВОЗМОЖНОСТИ ПРИМЕНЕНИЯ АМИНОКИСЛОТ С РАЗВЕТВЛЁННЫМИ БОКОВЫМИ ЦЕПЯМИ (ВСАА) ДЛЯ ЛЕЧЕНИЯ И ПРОФИЛАКТИКИ САРКОПЕНИИ У ПАЦИЕНТОВ ПОЖИЛОГО И СТАРЧЕСКОГО ВОЗРАСТА (ОБЗОР ЛИТЕРАТУРЫ)

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РЕЗЮМЕ

В связи с высокой распространённостью саркопении среди пациентов пожилого и старческого возраста актуальными являются ранняя своевременная профилактика и лечение саркопении и её осложнений. Для сохранения мышечной силы и массы при старении могут применяться пищевые добавки белков. Представляет научный интерес возможность применения аминокислот с разветвлённой цепью (BCAA, branched-chain amino acids) в лечении и профилактике саркопении у гериатрических пациентов. BCAA способствуют синтезу и замедляют деградацию белков мышечной ткани, участвуют в процессах регуляции чувствительности тканей к инсулину, утилизации аммиака, цикле трикарбоновых кислот и т. д.

Стратегия поиска. *Поиск научных статей для обзора литературы производился в базах «PubMed» и «PubMed Central». Критерием выбора являлись научные статьи, опубликованные в период до декабря 2022 г. включительно. Ключевые слова для поиска: «branched-chain amino acids», «BCAA», «body composition», «sarcopenia», «aging». В список статей был включён Консенсус Европейской рабочей группы по саркопении второго пересмотра (European Working Group on Sarcopenia in Older People 2, EWGSOP2) 2019 г.*

Выводы. *Возможность применения BCAA у пожилых и старых пациентов для профилактики и лечения саркопении является актуальной темой, которая продолжает активно изучаться. Эффективность добавок BCAA в рацион питания является спорной при условии ежедневного потребления достаточного количества белка. С другой стороны, добавление BCAA может быть оправдано в тех случаях, когда невозможно потреблять достаточное количество высококачественного белка с пищей. Необходимы дополнительные исследования по этой теме.*

Ключевые слова: *аминокислоты с разветвлённой цепью, BCAA, геронтология, композиционный состав тела, саркопения, старение, метаболизм*

Статья поступила: 30.01.2023
Статья принята: 31.05.2023
Статья опубликована: 11.07.2023

Для цитирования: Курмаев Д.П., Булгакова С.В., Тренева Е.В., Четверикова И.С., Косарева О.В., Шаронова Л.А., Долгих Ю.А. Возможности применения аминокислот с разветвлёнными боковыми цепями (ВСАА) для лечения и профилактики саркопении у пациентов пожилого и старческого возраста (обзор литературы). *Acta biomedica scientifica*. 2023; 8(3): 106-114. doi: 10.29413/ABS.2023-8.3.11

INTRODUCTION

Due to the high prevalence of sarcopenia among elderly and old patients, early prevention and treatment of sarcopenia and its complications are relevant [1]. Nutrition, along with physical exercise and treatment of chronic non-communicable diseases, plays a significant role in the comprehensive prevention and treatment of sarcopenia. To increase the strength and mass of skeletal muscles, nutrition should fully compensate not only for the energy requirements of Basal Metabolic Rate (BMR), but also for the additional calorie expenditure and metabolites during exercise [2]. Protein supplements can be used to maintain muscle strength and mass during aging. In addition, it is of interest to add branched-chain amino acids (BCAAs) to the diet, which promote the synthesis of muscle tissue proteins, slow down the degradation of muscle tissue proteins, participate in the processes of regulation of tissue sensitivity to insulin, ammonia utilization, tricarboxylic acid cycle, etc. [3].

BCAAs (valine, leucine and isoleucine) are common amino acids in humans and animals, making up approximately 35 % of the essential amino acids in most mammals. The functional R-groups of all three BCAAs are branched (hence their name), small and hydrophobic, making them essential components of most proteins. Collectively, BCAAs account for about 18 % of all amino acids and 63 % of the hydrophobic amino acids in protein. The molar relative abundance of BCAAs to each other is nearly always approximately 1.6:2.2:1.0 (Val:Leu:Ile), reflecting the linked nature of their synthesis and oxidation [4]. BCAAs are not only used for protein synthesis by the body, but also play an important role in signaling pathways [5]. BCAAs induce an anabolic response of muscle protein synthesis and stimulate muscle mass growth [6]. Along with skeletal muscles, white adipose tissue is also involved in BCAA metabolism [7].

Overall, BCAAs play several important metabolic and physiological roles besides substrates for protein synthesis.

For example, S. Gancheva et al. (2018) suggest that BCAAs play a key role in interorgan metabolic interactions, and dysregulation of BCAA catabolism may play a significant role in a number of metabolic diseases [8].

F. Vanweert et al. (2022) showed in a literature review that impaired BCAA catabolism plays a major role in the development of insulin resistance in obese people with type 2 diabetes mellitus (T2DM). Among these patients, BCAA levels are significantly elevated in plasma and tissues [9].

Much of the evidence for the effects of BCAAs has come from rodent studies. Some foreign studies have shown that BCAAs in rats can limit the skeletal muscle protein degradation rate, and thus, adding BCAAs to the diet can promote hypertrophy of rat musculature [10, 11]. O.V. Turtikova et al. (2014) performed experimental work on laboratory rats. The effect of BCAA administration on *m. gastrocnemius medialis* of rats was investigated during a 30-day recovery period after 16-week alcohol intoxication. BCAA usage promoted more efficient recovery of fast muscle fiber size, resulted in complete restoration of phosphorylated p90RSK content and did not significantly affect overall proliferative processes and myonuclear number in the rat medial musculus gastrocnemius [12]. However, according to R.R. Wolfe (2017), the results of rodent studies have questionable generalizability to humans. In particular, rats have a much lower percentage of skeletal muscle mass compared to humans. In addition, the processes involved in regulating muscle protein synthesis and myoprotein degradation differ from those in humans at both the initiation and translation stages [13].

When evaluating the effectiveness of BCAA supplementation for increasing muscle mass and strength in humans, it is important to consider the various factors against which BCAA intake occurs. There is a number of aspects that can affect the results, including nutrition (total macronutrient and energy intake), presence or absence of strength training, timing of BCAA intake, consumption of other amino acids, demographics, measurement protocols, etc. [3].

Of interest is the possibility of using BCAAs in the treatment and prevention of sarcopenia in geriatric patients.

BIOCHEMICAL AND PHYSIOLOGICAL ASPECTS OF BCAAS

Branched-chain amino acids (BCAAs) are leucine, valine, and isoleucine. BCAAs are the most hydrophobic of the amino acids and play a key role in the structure of spheroproteins as well as in the interaction of the transmembrane domains of integral membrane proteins with phospholipid bilayers. The evolutionary occurrence of BCAAs in nature is due to their primary role in protein structure rather than their secondary metabolic role. BCAAs typically make up approximately 20–25 % of most dietary proteins [14]. C. Nie et al. (2018) showed that BCAAs act as signaling molecules that regulate glucose, lipid and protein metabolism [15]. BCAAs are unique in that they largely bypass first-pass metabolism in the liver, and utilization occurs primarily in the mitochondria of skeletal myocytes. The first steps in their catabolism are common to all three amino acids, including BCAA aminotransferase (BCAT) and branched-chain alpha-keto acid dehydrogenase (BCKD). Their further metabolism uses different pathways to produce different end products (glucose and/or ketone bodies) [14]. Unlike other amino acids, BCAAs are primarily metabolized in muscle tissue, where they serve as precursors to other amino acids and as an energy substrate. In the presence of hyperammoniemia, BCAA metabolism in muscle tissue is altered and promotes ammonia detoxification through glutamine formation [16]. Also in brain tissue, BCAAs are used as an alternative pathway for ammonia detoxification [17].

Muscular hypertrophy results from an increase in myofibrillar proteins (actin, myosin, troponin, etc.). The rate of synthesis increases with strength exercise and increased protein intake with food [18].

E.L. Glynn et al. (2010) showed that the beneficial effects of protein supplementation include increased synthesis and/or suppression of muscle protein degradation [19].

Skeletal muscle mass growth occurs as a result of a positive balance of muscle protein, i. e., the predominance of synthesis over degradation [2].

G. Biolo et al. (1997) observed that BCAA supplementation increased anabolism, leading to a positive muscle protein balance with little change in degradation, both at rest and after exercise [20]. According to I. Rieu et al. (2006), of the three BCAAs, leucine is the most prominent key regulator of muscle protein synthesis [21].

Protein synthesis is regulated by a network of intracellular signaling cascades that modulate mRNA translation during initiation and elongation. The target of rapamycin (mTOR) or, more specifically, the mTOR-1 complex, a key regulator of protein synthesis, plays an important role in this regulatory network [4, 22, 23]. Energy and protein intake from food is a major nutritional effector of the mTOR-1 complex, which acts as a "nutrient sensor" and thus increases muscle tissue protein synthesis. BCAAs activate signaling pathways that converge in the mTOR-1 complex [24]. S.R. Kimball and L.S. Jefferson (2006) confirmed that BCAA and, in particular, leucine stimulate mTOR and increase muscle protein synthesis [25].

The important role of strength exercises as a powerful stimulator of mTOR and, as a consequence, an activator of muscle protein synthesis has been noted [26, 27]. Human studies with C^{13}-labeled leucine have shown that BCAA oxidation increases 2–4-fold during exercise [28]. BCAA catabolism in muscles increases and plasma BCAA concentration decreases during physical exercise [26].

In addition to stimulating muscle anabolism, BCAAs are involved in the processes of regulating tissue sensitivity to insulin. For example, M.S. Yoon (2016) showed that BCAAs improve the ability of muscle fibers to absorb glucose from blood plasma and modulate insulin signaling [29]. F. Vanweert et al. (2022) confirmed that rodent studies and to a lesser extent human ones strongly suggest that increased BCAA catabolism improves glucose homeostasis in metabolic disorders such as obesity and DM2 [9]. L. Breen, S.M. Phillips (2012) believe that leucine plays the role of the so-called "leucine trigger". This "leucine trigger" hypothesis is that some minimum, threshold level of dietary leucine intake is required, below which stimulation of muscle protein synthesis does not occur [30]. According to O.C. Witard et al. (2016), the minimum "threshold level" for leucine in the diet is 2–3 g per day [31].

However, excessive dietary leucine intake does not further increase muscle protein synthesis [30]. There is probably an upper threshold of BCAA concentration in plasma, beyond which the action of BCAA can lead to adverse effects [3]. So, D.E. Lackey et al. (2013) believe that elevated blood BCAA levels are associated with insulin resistance and DM2, which may be the result of decreased cellular utilization and/or incomplete oxidation of BCAA [7]. On the other hand, the thresholds for BCAA and leucine among the elderly have not yet been clearly defined.

The question of the need for BCAA supplementation in the diet is an interesting one. According to C. Giezenaar et al. (2016), leucine supplementation can promote skeletal muscle hypertrophy when it is impossible to consume sufficient protein [32]. However, some researchers believe that muscle mass growth depends not only on BCAAs, but also on sufficient amounts of other essential amino acids in the diet. For example, R.W. Morton et al. (2017) showed in a systematic review and meta-analysis that healthy adults should consume at least 1.6 g per kg of body mass per day of complete protein containing all nine essential amino acids in order to improve strength performance and body composition during physical training [33]. T.A. Churchward-Venne et al. (2014) showed that the need for essential amino acids increases in the period after intense physical exercise [34].

D.L. Plotkin et al. (2021) suggest that there is no benefit from additional leucine supplementation in the presence of adequate daily protein intake or with respect to measures of muscular hypertrophy. However, when there is no source of whole protein or sufficient essential amino acids available, a higher dose of leucine or BCAAs may slow the degradation and increase muscle protein synthesis [3]. The anabolic effects of whole food protein depend on a number of factors, such as physical training, nutritional status, body mass and skeletal muscle condition [35]. L.S. Macnaughton et al. (2016) believe that the optimal dose of high-quality protein to stimulate muscle anabolism is between 20 and 40 g [36].

Of interest is the question of whether plasma levels of essential amino acids during protein supplementation differ from those that can be obtained after protein intake with normal food.

In 2014, O. Bouillanne et al. published a randomized controlled trial involving 66 elderly people with malnutrition admitted to a rehabilitation unit. The authors found that a single supplement of concentrated powdered plasma protein enriched with leucine (20 g whey protein and 2.8 g leucine) increased the postprandial plasma concentration of essential amino acids by 50 % more compared to a normal diet [37].

The results of several studies suggest that young and middle-aged people who consume sufficient protein with food do not derive additional benefit from BCAA supplementation [35, 38–40].

A.F. Aguiar et al. (2017) showed that during 8 weeks of weight training, leucine supplementation did not increase muscle mass and strength with adequate protein intake (more than 1.6 g of protein per kg of body mass per day) [38]. C.B. Mobley et al. (2017) reported no differences in muscular hypertrophy between groups of participants supplemented with placebo, or 3 g of leucine alone, or 25 g of whey protein (standardized for leucine content) for 12 weeks of physical training. All study participants reported an intake of ~1.8 g protein per kg body mass per day, so the authors believe that supplementation did not confer any additional benefits for building muscle mass. Interestingly, the group that consumed only whey protein had a higher number of satellite cells, suggesting an increased potential for long-term/sequential muscle mass growth [40]. I.T. de Andrade et al. (2020) showed that supplementation with 10 g of leucine per day did not increase muscle mass or strength gains compared to a control group during 12 weeks of weight training and residual dietary protein intake [39]. Thus, it can be assumed that BCAA supplemention is ineffective in increasing muscle mass during weight training with adequate dietary protein intake.

On the other hand, loss of muscle mass can be minimized by using BCAAs during physical training against a calorie-restricted diet. S. Mettler et al. (2010) believe that increased consumption of protein supplements leads to the maintenance of muscle mass during weight training and calorie-restricted diet [41]. However, this study was conducted with athletes and the results should be interpreted on older adults with caution.

In addition, according to D.L. Plotkin et al. (2021), it is questionable whether BCAA supplementation will enhance muscle growth against energy restriction. Whole high-quality protein is superior to BCAAs in performance, so there is no logical justification for taking BCAAs in place of a more complete protein source, regardless of energy status [3].

BCAAS AND SARCOPENIA IN GERIATRIC PATIENTS

Sarcopenia is often associated with malnutrition whether it is related to low food intake (starvation, inability to eat), reduced nutrient bioavailability (diarrhea, vomiting) or high nutrient requirements (chronic inflammatory disease, oncopathology or organ failure with cachexia) [1]. Therefore, optimal nutrition is essential for geriatric patients with sarcopenia because the availability of the building components necessary for muscle recovery is crucial [42]. To halt and possibly reverse the loss of muscle mass and function with age, several authors recommend weight training, optimizing protein intake, and correcting vitamin D deficiency [1, 43, 44]. Nutritional recommendations for older adults (> 65 years) suggest increasing daily protein intake (1–1.2 g/kg/day; 1.2–1.5 g/kg/day for inflammatory diseases), preferably high-quality protein (e. g. whey protein) high in essential amino acids such as leucine [43, 44].

A number of authors have reported positive effects of BCAA supplementation on preservation of muscle strength, mass, and function in geriatric patients. There is evidence for the potential benefit of BCAAs, particularly leucine, for older adults in the treatment of sarcopenia [45–48].

I.F. Kramer et al. (2017) conducted a study to assess whether muscle tissue protein synthesis differs between elderly men with and without sarcopenia. 15 healthy men (mean age – 69 years) and 15 men with sarcopenia (mean age – 81 years) received a single leucine-enriched whey protein supplement (21 g protein). Basal and postprandial muscle protein concentrations were measured using stable isotopes and collection of blood and muscle biopsy samples. After leucine-enriched whey protein supplementation, muscle protein synthesis increased significantly in both the sarcopenia group and the control group without statistically significant intergroup differences [45].

A meta-analysis published by B. Komar et al. (2015) studied the effect of leucine supplementation on anthropometric and body composition parameters in elderly and sarcopenia-prone individuals. Leucine supplementation significantly increased body weight gain (1.02 kg; 95% confidence interval (95% CI): 0.19–1.85; $p = 0.02$), lean body mass (0.99 kg; 95% CI: 0.43–1.55; $p = 0.0005$) and body mass index (0.33 kg/m^2; 95% CI: 0.13–0.53; $p = 0.001$) compared to the respective control groups. In terms of total body weight and lean mass, leucine supplementation was more effective in the subgroup of study participants with severe sarcopenia. However, the addition of leucine to the diet did not affect all other body composition parameters investigated. The authors concluded that intake of various protein products containing at least 2 g of leucine per day, regardless of exercise, had a beneficial effect on body composition indices among individuals prone to sarcopenia [46].

M.K. Park et al. (2022) showed a positive effect of BCAA supplementation on the treatment of sarcopenia after stroke. It is known that after stroke, brain damage activates the systemic catabolic pathway and structural changes in muscle lead to a rapid decrease in muscle mass. In addition, hypodynamia due to weakness and poor nutrition caused by dysphagia accelerates the loss of muscle mass. The authors assessed stroke-related functional status using the Korean version of Modified Barthel Index (K-MBI), Berg Balance Scale (BBS), Functional Ambulation Categories (FAC) assessment test, and Manual Function Test (MFT), which are well established in stroke patients.

Swallowing function was assessed using the Functional Dysphagia Scale (FDS) and the Penetration-Aspiration Scale (PAS) based on the results of the Videofluoroscopic Swallow Study (VFSS). As a result, the group of patients with BCAA supplementation in their diet showed an increase in hand grip strength and skeletal muscle mass index. Mobility, activities of daily living and swallowing function improved. The authors suggest that there is a potential benefit of BCAA supplementation in providing functional improvement by increasing skeletal muscle mass index. The results of this study suggest that a comprehensive rehabilitation intervention combined with BCAA supplementation may be a useful option during the critical period of post-stroke neurological recovery [47].

Proper dosage of BCAA supplementation in the dietary intake of geriatric patients is also important. For example, C.S. Katsanos et al. (2006) noted that supplementation of 1.7 g of leucine to the dietary intake of older adults did not result in activation of muscle protein synthesis. However, daily supplementation of 2.8 g leucine has been shown to be sufficient for this purpose [48]. Similar conclusions were reached by L. Breen, S.M. Phillips (2011). The authors believe that due to the effects of age-related anabolic resistance, older adults require higher doses of leucine than younger adults to maximize the muscle protein synthesis response. Moreover, even with aging, anabolic resistance in the elderly may be reduced by exercise and consumption of higher doses of protein and/or leucine [30].

Although the exact etiology of age-related anabolic resistance during aging has not yet been fully elucidated, it is probably the result of the interaction of many factors at the level of muscular, nervous, cardiovascular, and other body systems [1, 49]. Decreases in motoneurons, anabolic hormones, and increased chronic inflammation likely contribute to the decreased sensitivity to anabolic stimuli with aging [3].

Several authors believe that older adults can increase muscle protein synthesis by consuming an additional ~3 g of leucine per day or ~30–35 g of high-quality protein in the diet [44, 50–52].

J.E. Morley et al. (2010) advise that to overcome anabolic resistance of aging muscles and increase skeletal muscle protein synthesis, 25–30 g of high-quality protein and up to 2.8–3 g of leucine (the minimum recommended dose of leucine is 78.5 mg/kg of the body mass per day) should be consumed at each meal and at least twice a day [44]. The recommended daily amount of protein can be effectively achieved by combined supplementation of high-quality protein, BCAA (including leucine) and vitamin D [43]. According to R.W. Morton et al. (2017), if total protein intake requirements are met, there is no apparent benefit of supplemental BCAA intake because muscle mass growth requires the full complement of essential amino acids [33].

CONCLUSIONS

The possibility of using BCAAs in elderly and old patients to prevent and treat sarcopenia is a hot topic that continues to be actively studied. The effectiveness of BCAA supplementation in the diet is debatable as long as sufficient protein is consumed daily. On the other hand, BCAA supplementation may be justified in cases where it is not possible to consume enough high-quality protein in the diet. However, more research is needed on this topic in older and aged adults.

Financing

The study was not sponsored.

Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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