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Branched-Chain Amino Acids (BCAAs): Revisiting Their Role in Sport and Health

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Abstract

Branched-chain amino acids (BCAAs), particularly leucine, are essential amino acids recognized for their significant roles in muscle protein synthesis, reducing muscle catabolism, and supporting metabolic health. This review explores the biochemistry, metabolism, and signaling pathways of BCAAs, emphasizing their potential therapeutic applications in conditions like sarcopenia, liver cirrhosis, and cachexia. BCAA metabolism primarily occurs in skeletal muscle and liver, with leucine activating key signaling pathways like mTORC1, promoting muscle growth and reducing protein breakdown. Clinical studies demonstrate the potential benefits of BCAA supplementation, particularly when combined with resistance exercise, in improving muscle quality and functional outcomes. However, effects on broader physical performance markers, insulin sensitivity, and metabolic profiles remain inconsistent. Safety data indicates leucine is well-tolerated at dosages up to 0.53 g/kg/day, but optimal dosages and timing require further study. Despite promising findings, the efficacy of BCAA supplementation is context-dependent, highlighting the need for longer trials and research targeting specific populations, including the elderly and those with chronic illnesses. Future research should focus on personalized protocols, the safety of long-term use, and combining

BCAA supplementation with other interventions to maximize therapeutic potential. This article aims to revisit the biochemistry, therapeutic applications, and safety of BCAA supplementation, highlighting its potential in muscle preservation and metabolic health while identifying gaps for future research.

Keywords: branched chain amino acids; leucine; supplementation; muscle protein synthesis; sarcopenia; frailty syndrome; cachexia

1. Introduction

Amino acids are organic acid derivatives where at least one hydrogen atom is replaced by an amino group. Recognized as some of the earliest and most extensively studied biomolecules, they are present in living organisms both in free form and as integral components of peptides and proteins. The amino acids found in proteins, with the exceptions of proline and hydroxyproline, feature an amino group bonded to the α-carbon, which is also attached to a distinctive side chain (R group) that defines their specific characteristics. While over 300 amino acids have been identified, only 22 are consistently incorporated into proteins. Leucine, isoleucine, and valine are branched amino acids with aliphatic, nonpolar, hydrophobic side chains. These side chains lack functional groups that participate in proton exchange, ionic bonding, or hydrogen bonding, resulting in their water-repelling nature (1). They belong to the group of nine essential aminoacids which must be included in the dietary intake of mammals, as due to their specific structrular features, cannot be produced endogenously. The remaining aminoacids can be produced within the body (2). Amino acids serve as the fundamental components of muscle proteins. Skeletal muscle contains 60-75% of the total protein in the body, and approximately 35% of the essential amino acids present in muscle proteins are BCAAs (3). Leucine is recognized for regulating certain proteins through post-translational modifications, such as phosphorylation, to promote protein synthesis and indirectly reduce muscle degradation. Additionally, they can influence the proteolytic systems to help minimize muscle catabolism (4). The metabolism and function of amino acids in skeletal muscle have been widely studied by numerous research groups, with a focus on both their ergogenic and therapeutic benefits. Some studies investigating nutritional strategies to enhance athletic performance, such as muscle strength, or to treat conditions with muscles atrophy, such as cancer, sarcopenia, or muscle disuse have shown that these benefits can be safely attained without the use of pharmacological agents (3). Given their potential to reduce muscle catabolism, BCAAs are widely used as supplements, particularly among training athletes.

However, there is extensive research exploring their potential applications in various therapeutic contexts. This article seeks to review the current understanding of BCAA supplementation and highlight opportunities for future research and advancements in this area.

2. Materials and methods

To write this article, databases such as ScienceDirect, PubMed, Google Scholar were searched using the following terms: branched chain amino acids, leucine supplementation, muscle protein synthesis, muscle mass increase, sarcopenia, frailty syndrome, cachexia in various combination and in the review context.

3. Biochemistry and Physiology of BCAAs

3.1 Metabolism of BCAAs

BCAAs play three key roles - they are used for protein synthesis after eating, they act as signals to stimulate protein production, and, as other amino acids, they might be broken down for energy during fasting. Their level in the blood increases with dietary protein intake and is carefully regulated during fasting by degradation pathways. The typical ratio of BCAAs (Val:Leu:Ile) in the dietary intake is about 1.6:2.2:1.0, reflecting their linked synthesis and metabolism. Because they are usually consumed and metabolized together, they are often studied as a single groups, which may lead to wrong conclusions (5,6). On the other hand, studies have shown that leucine-only supplementation has not shown enough significant improvements in markers as part of the treatment of sarcopenia enough to be considered in the nutritional strategy for the treatment of the disease (7).

BCAA metabolism primarily occurs in two key tissues: skeletal muscle and liver. It involves two main steps: transamination and oxidative decarboxylation. (3,6)

Transamination

This reversible reaction is catalyzed by the enzyme branched-chain aminotransferase (BCAT), which exists in two forms: cytosolic (BCATc) and mitochondrial (BCATm). Unlike most amino acids, which are initially metabolized in the liver, the first step in BCAA degradation takes place in skeletal muscle. Here, BCAT facilitates the transamination of BCAAs, producing branched-chain keto acids (BCKAs): α-ketoisocaproate (KIC, from leucine), α-keto-β-methylvalerate (KMV, from isoleucine), and α-ketoisovalerate (KIV, from valine). These BCKAs can be used in the muscle and be released into the bloodstream, along with glutamine and alanine, which may indicate increased BCAA breakdown (3,5). The amino group released from transamination can be used to produce glutamate, which is subsequently involved in

synthesizing other amino acids (e.g., alanine, aspartate, and glutamine) that are essential for various metabolic functions, such as protein synthesis and muscle remodeling. Transamination of BCAAs, especially leucine, also has a significant impact on activating pathways that stimulate muscle protein synthesis (like the mTOR pathway), which is key for muscle hypertrophy and growth. Thus, transamination is linked to muscle remodeling and anabolic processes, contributing to maintaining and building muscle mass (3,6). However, protein synthesis requires the sufficient availability of all essential amino acids that serve as the building blocks for protein production. Therefore, BCAA supplements alone cannot enhance protein synthesis if other necessary amino acids are lacking. (8,9)

Oxidative Decarboxylation

The liver is the primary site for BCAA oxidation due to high levels of the branched-chain α-keto acid dehydrogenase complex (BCKDH) in its mitochondria. This step involves the irreversible (due to losing carbon skeletons of BCAA) oxidative decarboxylation of BCKAs, producing acyl-CoA (or succinyl-CoA) and NADH. Leucine is a ketogenic amino acid, and its keto acid (α-KIC) generates acetoacetyl-CoA. Valine is gluconeogenic, while isoleucine is both ketogenic and gluconeogenic. Their keto acids (α-KIV and α-KMV) transmute into succinyl-CoA, which enters the TCA cycle for energy production (5,6).

The branched-chain α-keto acid dehydrogenase (BCKDH) complex consists of three key enzymes: E1 (branched-chain α-keto acid decarboxylase), E2 (dihydrolipoyl transacylase), and E3 (dihydrolipoyl decarboxylase). The activity of BCKDH is primarily regulated through post-translational modifications involving phosphorylation and dephosphorylation. BCKDH kinase (BDK) inactivates the complex by phosphorylation, while BCKDH phosphatase (BDP) reactivates it by removing the phosphate group. In basal condition, the BCKDH complex in humans remains in its active, dephosphorylated state (3).

There are several factors influencing the balance between active and inactive state of BCKDH. Conditions like low-protein diets and reduced protein breakdown enhance BDK activity, which inactivates BCKDH and conserves BCAA levels. Conversely, catabolic states such as high-protein diets, fasting, diabetes, and inflammation increase BDP activity, activating BCKDH and promoting BCAA breakdown. BCKDH regulation is closely tied to BCAA availability: low BCAA levels and phosphorylation inhibit the complex, while high BCAA levels and dephosphorylation activate it (3,5,6).

BCKDH serves as the rate-limiting step in BCAA metabolism and plays a key role in regulating fasting BCAA levels. This regulation ensures a balance between protein preservation and

energy production during various physiological and pathological conditions. During short-term fasting or starvation, BCAA and BCKA levels initially rise as muscle proteins are broken down for energy. However, as muscle protein stores are depleted, BCAA levels eventually decline. Insulin also lowers BCAA levels, but in insulin-resistant states like type 2 diabetes and obesity, both BCAA and BCKA levels remain elevated. In addition to insulin, other hormones and factors regulate BCKDH activity and BCAA metabolism - anabolic factors such as IGF-1 and growth hormone (GH) promote BCAA utilization, and catabolic factors like TNF-α, cortisol, catecholamines, glucagon, and inflammatory cytokines stimulate protein breakdown and BCAA degradation (3,5,6).

Figure 1. Is showing the general metabolism of BCAA depending on the location.

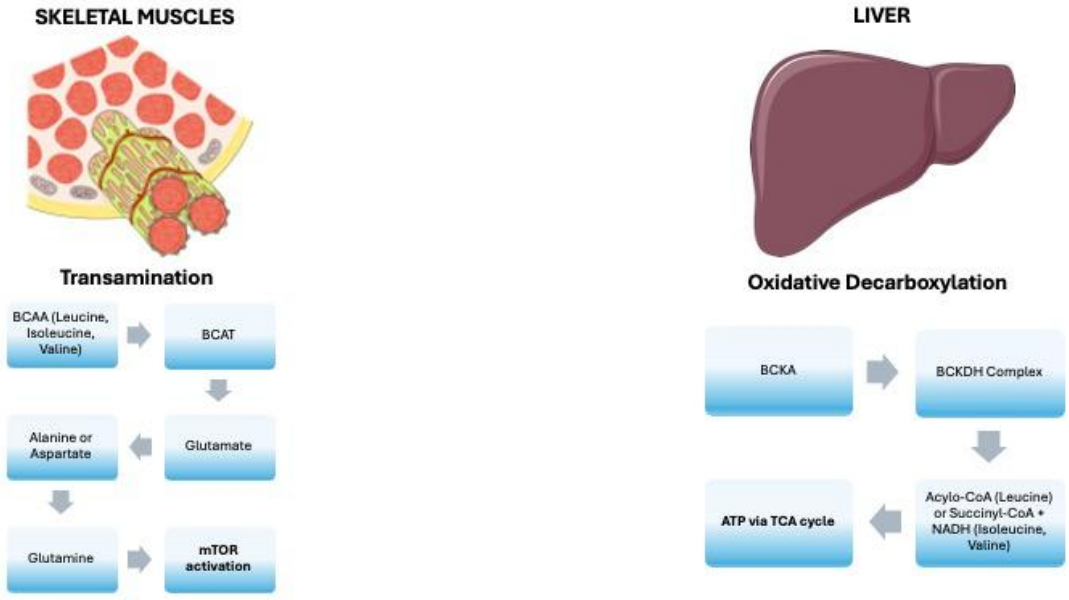

Figure 1. While in skeletal muscles the enzymes ratio promotes mainly transamination needed for muscle protein synthesis, in the liver branched chained amino acids (BCAA) are mostly used as energetic resources during oxidative decarboxylation. Abbreviations: BCAT – Branched-Chain Aminotransferase, mTOR – mammalian target of rapamycin,
BCKA – Branched-Chain Keto Acids, BCKDH Complex - branched-chain α-keto acid dehydrogenase complex. This figure is created using Servier Medical Art, licensed under Creative Commons Attribution 4.0 Unported License, https://creativecommons.org/licenses/by/4.0/, (accessed December 2024)

3.2 **Signaling pathways of BCAA**

MTOR, glutamate dehydrogenase, valine catabolites

The mammalian (or sometimes referred as mechanistic) target of rapamycin (mTOR) pathway plays a central role in regulating cellular growth, protein synthesis, and autophagy. Leucine is a key activator of this pathway, particularly the mTORC1 complex. In the absence of leucine, Sestrin2 binds to GATOR2, a positive regulator of mTORC1, and inhibits its activity. However, when leucine becomes available, it directly binds to Sestrin2, causing the release of GATOR2 and enabling full mTORC1 activation. Additionally, leucine activates mTORC1 through loaded leucyl-tRNA synthetase (LeuRS), providing an alternative mechanism to enhance its activity. Once activated, mTORC1 phosphorylates key proteins such as S6K and 4E-BP1, which promote protein synthesis, while also suppressing autophagy by acting on Ulk1 and TFEB. This dual action stimulates protein production while preventing protein breakdown, which is essential for muscle growth and maintenance, particularly in the postprandial state.

Leucine and its metabolite KIC also stimulate insulin secretion from pancreatic β-cells via activation of glutamate dehydrogenase (GDH). Insulin further enhances mTORC1 activity, amplifying protein synthesis and supporting muscle growth. Together, leucine, insulin, and other growth factors like IGF-1 coordinate the activation of mTORC1 to optimize protein synthesis (10).

BCAA metabolites also play roles beyond protein synthesis. For example, valine catabolites such as beta-amino-isobutyric acid (BAIBA) and 3-hydroxyisobutyrate (3-HIB) are released by skeletal muscle and contribute to systemic energy regulation. BAIBA enhances fatty acid oxidation in the liver, promotes thermogenesis in adipocytes, and supports osteocyte survival, while 3-HIB facilitates fatty acid transport into skeletal muscle to support energy metabolism. Leucine also has indirect effects on mTORC2, which regulates insulin and IGF-1 receptor activities as well as cytoskeletal organization. This ensures that leucine, in synergy with insulin and growth factors, effectively promotes muscle protein synthesis and energy balance. While BCAAs, particularly leucine and isoleucine, have insulin-stimulating effects during the postprandial phase, they serve a gluconeogenic role during fasting, with valine and isoleucine contributing modestly to the production of endogenous glucose. However, prolonged exposure to elevated leucine levels may indirectly cause insulin resistance by affecting insulin receptor substrate-1 (IRS-1) through downstream signaling of the mTOR pathway. Overall, leucine-mediated activation of mTORC1, combined with its influence on insulin signaling and the production of metabolites, highlights its multifaceted role in supporting muscle growth, suppressing protein breakdown, and maintaining energy homeostasis (6,8).

3.3 **Potential impact of imbalance in BCAA supplementation**

It is well-documented that leucine supplementation reduces plasma levels of the other branched-chain amino acids, valine and isoleucine (11). However, the clinical relevance of this finding is still a matter of discussion. Contrary to common belief, some studies indicate that leucine supplementation alone in healthy individuals or patients with type 2 diabetes is not an effective nutritional strategy for improving muscle mass, strength, or glycemic control (10, 11). The underlying mechanism may involve the effect on the BDK/BCKDH ratio and activity. Supplementing leucine in isolation increases the production of its keto acid (α-KIC), which inhibits BDK and activates BCKDH. This activation enhances the oxidation of other BCAAs, namely isoleucine and valine, reducing their availability for protein synthesis (3, 12). This imbalance caused by the elevated oxidation of isoleucine and valine can negatively affect protein balance in skeletal muscle, potentially impairing muscle protein synthesis and promoting muscle catabolism. However, it is important to note that these studies did not observe any measurable decrease in muscle mass or strength in the groups of patients evaluated (11–13). Many studies on the overall effect of leucine supplementation often find positive anabolic outcomes, particularly in terms of stimulating mTOR signaling and protein synthesis. The idea that isolated leucine supplementation may impair muscle protein synthesis through competitive oxidation is more nuanced, and this effect may be context-dependent, occurring under conditions of prolonged supplementation without balancing the intake of other amino acids and overall protein dietary intake (12,14).

3.4 **Significance of altered BCAA metabolism**

Changes in BCAA metabolism have been associated with several pathological conditions, such as Type 2 diabetes (T2D), Maple Syrup Urine Disease and other genetic conditions, liver or kidneys diseases, and cancer (10). BCAA enriched diets are believed to support metabolic health, primarily due to their anabolic effects. However, further research is required to better understand the connection between elevated BCAA levels and various pathological conditions. It is established that BCAA can trigger excitotoxicity, hyperexcitability, inflammation, and oxidative stress, potentially playing a role in the onset of neurodegenerative diseases, mainly by alteration of neurotransmitter levels in the central nervous system, leading to imbalances in neurotrophic factor regulation. Disruptions in BCAA levels and their metabolic pathways may contribute to the development of major neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) (15). In addition,

impaired BCAA catabolism has been associated with the development and progression of common diseases. (16,17).

4. Application of BCAA Suplementation

3.1 Evaluation in exercise and physical activity context

The current evidence on BCAAs supplementation, usually in combination with resistance exercise, is primarily derived from short studies in which f.e. the phosphorylation of proteins involved in skeletal muscle protein synthesis is measured. Most of the studies are limited, maximally a few months interventions. A systematic review on the effects of leucine supplementation, either alone or as part of a supplement, with or without physical exercise in older adults with sarcopenia identified only one study that lasted longer than a year. (18) Therefore, the common belief that chronic effects of supplementation and exercise might result from the cumulative impact of repeated acute responses is valid in those circumstances but might be only constructed based on limitations of the studies duration.

One study showed that resistance exercise, combined with BCAA supplementation (45% leucine, 30% valine, 25% isoleucine) significantly increased the phosphorylation of proteins like $p70^{S6k}$ at Thr^{389} during recovery, which was more pronounced in the supplemented group (19). This protein has a significant role in the signaling networks controlling protein synthesis. A follow-up study showed that BCAA supplementation increased $p70^{S6k}$ phosphorylation 11- to 30-fold immediately and 1 hour post-exercise, with unexpected increases also observed in the non-exercised leg (a 5- and 16-fold increase), possibly due to a neural cross-education effect (20). In conclusion, BCAA consumption during and after resistance exercise, or without exercise, might activate signal transduction pathways involving $p70^{S6k}$ in skeletal muscle, theoretically effecting in increase muscle mass after exercising.

Exercises and overall physical activity are a significant part of a lifestyle that should be carried out be older people with frailty syndrome, that might reduce the connected risks and symptoms. It is proven that even small amounts of physical exercises might reduce the risk of frailty (21). A study conducted on 35 participants of residential care homes (RCH) in a duration of 40 weeks demonstrated that long-term exercise programs effectively improved functional capacity and slowed or prevented the progression of frailty in older adults living in RCH compared to a non-exercising control group. BCAA supplementation alone did not enhance functional fitness, but over a short duration (16 weeks) contributed to reducing frailty. When combined with exercise,

BCAA supplementation showed potential in mitigating the decline in functional capacity during a detraining period. Exercise alone also significantly improved functional capacity and prevented the worsening of frailty observed in the control group, where frailty scores increased over time ($p < 0.01$). While BCAA supplementation had no impact on functional fitness, its short-term use helped reduce frailty. The combination of exercise and BCAA supplementation may further counteract functional declines during periods without training (22)

A report of the International Sarcopenia Initiative, which was a systematic review, suggested that supervised resistance exercise is recommended for individuals with sarcopenia, and essential amino acids supplementation (including leucine) may improve muscle outcomes (23). However, a double-blinded randomized clinical trial studying the use of a specific BCAA supplement combined with regular resistance exercise in adults aged 50 years and older showed that intervention did not lead to a significant increase in skeletal muscle mass. Sub-group analysis using MRI revealed improvements in the mid-thigh cross-sectional area, but no significant differences were found in muscle strength or physical performance between the intervention and control groups (14)

Moreover, a systematic review, which included 12 randomized controlled trials examining the effects of BCAA supplementation in humans on physical performance, muscle damage, and body composition showed no significant impact on body composition, blood parameters, or performance. The studies primarily involved physically active or untrained males, with intervention periods ranging from 1 day to 8 weeks and an average BCAA dose of 19.5 g/day. However, some studies reported reduced subjective muscle pain with supplementation of BCAA (24).

Table 1. is summarizing the studies discussed above, concentrating on the study design, intervention and results

Study	**Design**	**Intervention**	**Results**
Resistance Exercise + BCAA (19)	Single study measuring protein	BCAA supplementation (45% leucine, 30%	Significant increase in p70S6k phosphorylation during recovery, more

	phosphorylation post-exercise	valine, 25% isoleucine) combined with resistance exercise	pronounced in the BCAA group.
Follow-up Study (20)	Follow-up study measuring protein phosphorylation	BCAA supplementation with resistance exercise	p70S6k phosphorylation increased 11-30 fold post-exercise in the exercised leg; unexpected increase (5-16 fold) observed in the non-exercised leg, possibly due to neural cross-education effect.
Frailty in Older Adults (22)	RCT; 40-week exercise program in residential care homes	Exercise alone, BCAA supplementation alone, or BCAA + exercise	Exercise improved functional capacity and prevented frailty progression. BCAA alone reduced frailty short-term (16 weeks). Combined BCAA + exercise mitigated functional decline during detraining.
Sarcopenia Review (23)	Systematic review	Supervised resistance exercise with or without leucine supplementation	Resistance exercise is recommended; essential amino acids, including leucine, may improve muscle outcomes.
BCAA + Resistance Exercise in Adults (14)	Double-blind RCT; adults ≥50 years	BCAA supplementation combined with resistance exercise	No significant increase in muscle mass. Sub-group MRI analysis showed improvement in mid-thigh CSA; no

			changes in muscle strength or performance.
Systematic Review of effects of branched-chain amino acids supplementation in physical exercise (24)	Systematic review of 12 RCTs (1 day–8 weeks, 19.5 g/day BCAA dose)	BCAA supplementation in physically active or untrained males	No significant effects on body composition, blood parameters, or performance. Some studies reported reduced subjective muscle pain.

Table 1. BCAA supplementation combined with exercise improves muscle signaling and reduces frailty short-term but shows inconsistent effects on muscle mass, strength, and performance across studies.

3.2 Clinical Population

BCAA supplementation holds therapeutic promise for diseases associated with muscle loss, such as liver cirrhosis, sarcopenia, and cachexia. By enhancing protein synthesis and reducing muscle breakdown, BCAAs may help preserve muscle mass, improve functional capacity, and support overall health in these conditions. Their role in mitigating muscle wasting makes them a potential strategy for managing chronic illnesses.

A randomized, controlled, double-blind study in 25 cancer patients compared the effects of two medical foods on muscle protein synthesis (FSR). The experimental group (n=13) received a medical food containing 40 g of casein and whey protein enriched with 10% free leucine (total leucine 7.8 g, 19%), while the control group (n=12) received 24 g of casein-based protein (total leucine 2 g, 8.5%). Plasma leucine levels peaked at 400 μM with the experimental food, significantly higher than the 200 μM peak in the control group ($p < 0.001$). Muscle protein FSR increased from 0.073 to 0.097 %/h with the experimental food ($p = 0.0269$), whereas the control food showed no improvement (0.073 to 0.065 %/h. It is worth noting that, despite the protein content, the medical food also included other macronutrients, such as carbohydrates and was enriched with particular fats. The results indicate that muscle protein synthesis can still respond to appropriate nutritional interventions in cancer patients with pre-cachexia, emphasizing the need for specifically formulated nutrition to prevent progression to cachexia (25). The protein

enriched food balanced with higher leucine level seems to have impact in this group.

Another RCT evaluated a 12-week multimodal therapy in advanced cancer patients, combining a leucine-rich supplement with nutrition and exercise. The intervention group showed good adherence but no significant improvement in the primary endpoint, physical fitness measured with the short physical performance battery (SPPB), after three or six months compared to the control group. However, handgrip strength significantly improved in the intervention group ($p < 0.001$). Secondary endpoints, including nutritional status, dietary intake, fatigue, quality of life (QoL), and clinical course, showed trends toward improvement, but were not statistically significant. The program demonstrated safety and effectiveness for handgrip strength but failed to achieve broader functional gains (26).

Interventions with BCAA supplementation are also used within patients with liver diseases, considering their tendency to malnutrition, sarcopenia and cachexia. A systematic review and meta-analysis of five RCTs (total 434 patients) assessed the efficacy of BCAA supplementation for sarcopenia in liver cirrhosis (LC). BCAAs significantly reduced the liver frailty index (MD: −0.14, P = 0.03), increased BMI (MD: 0.99, P = 0.02), and improved quality of life (QoL) (SMD: 0.27, P = 0.03). However, no significant effects were observed for handgrip strength, skeletal muscle index, gait speed, or Model for End-Stage Liver Disease (MELD) score. However, these findings were limited by outcome variability and study bias, emphasizing the need for further high-quality RCTs to validate these results.

A RCT evaluated the effectiveness of branched-chain amino acid supplementation and/or exercise on quadriceps muscle quantity and quality in patients with cirrhosis 220 liver cirrhosis patients (Child-Pugh B and C). After 28 days, all intervention groups (BCAA, exercise, or both) showed significant improvements in quadriceps muscle thickness, echo-intensity, muscle strength, performance using SPPB, and nutritional status. Laboratory parameters (hemoglobin, platelets, ALT, AST, bilirubin, creatinine, urea, INR) and MELD scores also improved. In addition to above, ultrasonography was used to assess muscle thickness and quality via echo intensity, and it was proved effective in tracking changes in muscle quality and quantity. The combination of BCAA and exercise yielded the best results, particularly in Child-Pugh B patients, while single interventions still provided benefits in Child-Pugh C patients (27).

The potential of reducing muscle catabolism in weight-loss diets has also been a field of research. A RCT was conducted to evaluate the effects of a BCAA-supplemented hypocaloric diet on lean mass preservation and insulin sensitivity in 132 overweight and obese Chinese adults. The participants were block randomly assigned by gender and BMI into 3 hypocaloric

diet (deficit of 500 kcal/d) groups: standard-protein (14%) with placebo (control group) or BCAA supplements at 0.1 $g \cdot kg^{-1}$ body weight $\cdot d^{-1}$, or high-protein (27%) with placebo. After 16 weeks of energy restriction, all groups showed similar reductions in body weight, fat mass, and waist circumference. Lean mass loss in the BCAA group (4.39%) was lower than the control (5.39%) but higher than the high-protein group (3.67%) ($P = 0.06$). Calf muscle volume increased by 3.4% in the BCAA group, and intramyocellular lipids decreased significantly in the BCAA and high-protein groups ($P < 0.05$). During the 8-week weight maintenance phase, lean mass gain was significantly higher in the control group compared to the high-protein group ($P = 0.03$). No significant differences were found in insulin sensitivity or metabolic profiles across the groups. Overall, BCAA supplementation did not preserve lean mass or improve insulin sensitivity, while a high-protein diet showed greater benefits for lean mass preservation (28).

Theoretic potential improvement of respiratory muscle mass in patients with chronic obstructive lung disease (COPD) was studied in another randomized, double-blinded trial. The researchers hypothesized that BCAA supplementation could potentiate the effect of a pulmonary rehabilitation program (PRP) by inducing muscular change. They evaluated the effects of 4-week PRP with or without BCAA supplementation in 60 COPD patients (GOLD 2–3). Both groups showed significant improvements in maximal exercise capacity, functional and muscle performance, quality of life, and dyspnea ($p \leq 0.01$). However, quadriceps muscle oxygenation changes during maximal exercise and recovery period were unaffected in the BCAA group, while recovery kinetics slowed downed in the placebo group. The study concluded that BCAA supplementation provided no additional benefits over PRP alone. However, longer supplementation periods or better patient targeting may be required to observe meaningful effects on muscle recovery and other outcomes (29).

Table 2. is showing the summary of the studies discussed above, underlining the effectiveness of BCAA supplementation intervention.

Study	**Design**	**Intervention**	**Results**
Cancer Patients (Pre-	Randomized, controlled, double-blind trial; 25 cancer patients	Experimental group: medical food with 40 g protein (casein + whey) enriched with 10%	**Effective**: Plasma leucine increased to 400 μM (experimental) vs. 200 μM (control) ($p < 0.001$).

cachexia) (25)		leucine (7.8 g leucine); Control group: 24 g casein protein (2 g leucine).	Muscle protein synthesis (FSR) increased in the experimental group (0.073 to 0.097%/h, *p = 0.0269*) but not in the control group.
Advanced Cancer Patients (26)	RCT; 12-week multimodal therapy; 52 advanced cancer patients	Intervention group: leucine-rich supplement, nutrition counseling, and exercise; Control group: standard care	**Partially Effective**: No significant improvement in SPPB (primary endpoint). Handgrip strength improved significantly in the intervention group ($p < 0.001$). Trends toward improvement in nutritional status, fatigue, and QoL, but not statistically significant.
Liver Cirrhosis Patients (Meta-analysis) (27)	Systematic review/meta-analysis of 5 RCTs; 434 cirrhotic patients	BCAA supplementation for sarcopenia management	**Effective**: BCAAs reduced liver frailty index (MD: -0.14, $p = 0.03$), increased BMI (MD: 0.99, $p = 0.02$) and QoL (SMD: 0.27, $p = 0.03$). Not effective for handgrip strength, skeletal muscle index, MELD score, or gait speed.
Liver Cirrhosis Patients (BCAA + Exercise) (27)	RCT; 220 cirrhotic patients (Child-Pugh B/C); 28-day intervention	Intervention groups: BCAA supplementation, exercise, or both; Control group: standard care	**Effective**: Significant improvement in quadriceps muscle thickness, echo-intensity, muscle strength, SPPB, and nutritional status in all intervention groups. Combined BCAA and exercise showed the best

			results in Child-Pugh B patients.
Weight Loss in Overweight Adults (28)	RCT; 132 overweight/obese Chinese adults; 16 weeks hypocaloric diet	Groups: Standard-protein (14%) + placebo, BCAA-supplemented (0.1 g/kg/d), or high-protein (27%) + placebo	**Partially Effective**: Lean mass loss in BCAA group (4.39%) was lower than control (5.39%) but higher than high-protein (3.67%, $p = 0.06$). Calf muscle volume increased (3.4%) in BCAA group. Not effective for insulin sensitivity.
COPD Patients (PRP + BCAA) (29)	RCT; double-blind; 4-week PRP; 60 COPD patients (GOLD 2-3)	Intervention group: PRP + BCAA supplementation; Control group: PRP + placebo	**Not Effective**: Both groups improved in exercise capacity, muscle performance, QoL, and dyspnea ($p \leq 0.01$). No change in muscle oxygenation in BCAA group; recovery kinetics slowed in placebo group. No added benefit of BCAA supplementation.

Table 2. BCAA supplementation shows promise in muscle preservation and functional improvement, particularly when combined with exercise in liver cirrhosis and cancer patients. While benefits were observed in some outcomes like muscle protein synthesis, BMI, and handgrip strength, effects on overall physical performance, skeletal muscle index, and metabolic markers remain inconsistent. Further research with longer durations and targeted patient populations is needed to confirm BCAA's full therapeutic potential.

5. Safety and timing

There is limited data available regarding the effects of BCAA or leucine-only supplementation regarding the upper limits or the timing (pre-, during or post-workout) of intake. Depending on

the source, safe dosage of leucine has been established at an upper limit for safe intake (ULSI) of 0.53 g/kg/day, equivalent to approximately 37 g/day for a 70 kg individual. This level has been shown to be metabolically tolerable in human studies without adverse effects, such as elevated plasma ammonia concentrations. For elderly individuals, a more cautious upper limit of 351 mg/kg/day (around 24.5 g/day for a 70 kg person) has been suggested based on conservative estimates. While leucine intakes as high as 1250 mg/kg/day have not demonstrated serious health consequences, they have resulted in short-term increases in plasma ammonia. The minimum recommended leucine intake for promoting muscle protein synthesis and addressing anabolic resistance is 55 mg/kg/day (approximately 3.85 g/day for a 70 kg individual). Animal studies suggest higher metabolic tolerance, but human scaling aligns with the ULSI of 0.53 g/kg/day. However, these findings are limited by the acute nature of human studies and the focus on healthy male participants. More research is needed to assess chronic safety at high doses and to evaluate the effects in specific populations, such as athletes, females and frail elderly (30,31).

6. Conclusions

The presented review highlights the multifaceted role of branched-chain amino acids (BCAAs), particularly leucine, in enhancing protein synthesis, reducing muscle catabolism, and addressing conditions associated with muscle loss. While promising results were observed in areas such as muscle protein synthesis, quality of life, and functional capacity in clinical populations like cancer and liver cirrhosis patients, the overall effectiveness of BCAA supplementation remains context-dependent. Evidence suggests that combining BCAA supplementation with exercise yields superior outcomes, particularly in improving muscle quality and functional performance. However, the effects on broader physical performance markers and metabolic health, such as insulin sensitivity, are inconsistent. Safety data indicates leucine is well-tolerated at dosages up to 0.53 g/kg/day, but more research is necessary to explore chronic use and its application in specific populations. Overall, BCAA supplementation holds therapeutic potential but requires further long-term studies to optimize its use and establish robust guidelines for diverse populations. Future research on BCAA supplementation should focus on long-term supplementation effects, optimizing dosage and timing, and targeting diverse populations, including elderly and clinical patients. Studies should explore combinations with exercise, molecular mechanisms, and safety and effectiveness at different doses, and the interventions tested out should be longer.

DISCLOSURE

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