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BCAAs In Metabolism And Clinical Practice: An Integrative Literature Review

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Abstract:
Background*: Branched-chain amino acids (BCAAs)—leucine, isoleucine, and valine—play a fundamental role in muscle metabolism, acting as energy substrates and regulators of protein synthesis through mTOR pathway signaling. Beyond their well-established role in sports nutrition, BCAAs have been widely studied in clinical contexts such as cancer, liver cirrhosis, and cachexia due to their ability to preserve muscle mass and modulate metabolic responses in catabolic states.*
This article presents an integrative review of the current literature on the biochemical and physiological mechanisms of BCAAs, their therapeutic applications, and the limits of their supplementation. The paper also discusses controversies regarding the efficacy of BCAAs, their metabolic interactions with other nutrients, and the risks associated with indiscriminate use. Finally, it highlights gaps in the literature and the need for future research that prioritizes the personalization of nutritional interventions based on robust evidence. A deeper understanding of these aspects is essential to optimize the clinical and athletic use of BCAAs
Material and Methods*: The integrative review was conducted through a systematic search of major electronic databases—PubMed, Scopus, Web of Science, and SciELO—using keywords related to branched-chain amino acids (BCAAs) in both Portuguese and English. Included were original articles, systematic reviews, meta-analyses, and guidelines from 2000 to 2025 focusing on BCAA metabolism, sports and clinical applications, and supplementation safety and efficacy. Studies involving human interventions, relevant preclinical research, and theoretical reviews were selected. Exclusions applied to duplicates, articles without full text, and low-quality studies, with quality assessed by study design, sample size, and result clarity. Data were analyzed qualitatively to integrate biochemical mechanisms, therapeutic uses, controversies, and identify research gaps, providing a comprehensive and critical overview of current evidence.*
Results*: This integrative review analyzed scientific studies on the metabolic, therapeutic, and ergogenic effects of branched-chain amino acids (BCAAs). It included a variety of research methods such as clinical trials, theoretical reviews, and experimental studies in animal and in vitro models. The findings highlight the complex physiological roles of BCAAs, focusing on their involvement in energy metabolism, protein synthesis, cell signaling, and their implications in diseases like cancer, type 2 diabetes, and liver disorders.*
Conclusion: *Branched-chain amino acids (BCAAs) are key regulators of protein synthesis through the mTORC1 pathway, serve as energy sources during catabolic stress, and are involved in metabolic, liver, and cancer-related diseases. While BCAA supplementation can have ergogenic and therapeutic benefits in certain situations, its effectiveness is limited without adequate intake of other essential amino acids for optimal anabolic response. Impaired BCAA oxidation is linked to insulin resistance, obesity, and some cancers, making dietary BCAA management a potential clinical strategy. However, indiscriminate use of BCAAs can pose metabolic risks, highlighting the importance of evidence-based, individualized nutritional approaches tailored to a person's physiological condition and treatment goals.*

Keywords: *Cell signaling; Catabolism; Supplementation; Metabolism; Therapies.*

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I. Introduction

Branched-Chain Amino Acids (BCAAs), composed of leucine, isoleucine, and valine, make up about one-third of the essential amino acids in skeletal muscle and are valued for their ergogenic potential (De Andrade

et al., 2024). Because they are directly metabolized in muscle tissue, they contribute to energy supply during exercise and aid in muscle recovery by participating in protein synthesis and anabolic signaling, notably through the activation of the mTOR pathway (Das Neves Haddad, 2021).

Additionally, BCAAs help reduce central fatigue by competing with tryptophan in the central nervous system, thereby influencing serotonin production (Júnior, 2016). They also support the maintenance of plasma glutamine, which is essential for immune function, especially under metabolic stress conditions such as intense exercise (Santos & Nascimento, 2019). These effects make BCAAs a relevant nutritional strategy in both sports- and clinical contexts.

These amino acids are predominantly catabolized in skeletal muscle, unlike most amino acids, which are primarily metabolized in the liver. In muscle, the activity of the enzymes BCAT2 (Branched-Chain Amino Acid Transaminase 2) and BCKDH (Branched-Chain Alpha-Keto Acid Dehydrogenase) regulates the initial steps of BCAA catabolism, with these enzymes being induced by the transcriptional coactivator PGC1α in response to physical exercise (Kamei et al., 2020). This process results in the production of energy metabolites that feed into the tricarboxylic acid (TCA) cycle, or Krebs cycle, reinforcing the role of BCAAs as energy substrates during intense physical activity and catabolic states (Mann et al., 2021; Kamei et al., 2020).

Beyond their role in muscle metabolism, BCAAs also function as key regulators of intracellular signaling, particularly through the activation of the mTORC1 complex, with leucine being the primary activator. Activation of mTORC1 promotes the phosphorylation of targets such as S6K1 (Ribosomal Protein S6 Kinase 1) and 4E-BP1 (Eukaryotic Translation Initiation Factor 4E-Binding Protein 1), stimulating protein synthesis and inhibiting proteolytic pathways, such as autophagy and the ubiquitin-proteasome pathway (Mann et al., 2021).

This anabolic action has clinical implications in preventing sarcopenia, recovering from hypercatabolic states, and improving physical performance. In clinical practice, BCAA supplementation has been investigated in pathophysiological conditions characterized by increased catabolism, such as cancer, liver cirrhosis, sepsis, and cachexia. In these contexts, evidence suggests that BCAAs help preserve muscle mass, improve the immunometabolic response, and provide adequate nutritional support (Marchesini et al., 2005; Yoshida & Delafontaine, 2015).

Studies also report metabolic and hormonal benefits of BCAA supplementation combined with exercise during fasting, such as increased expression of BDNF (Brain-Derived Neurotrophic Factor), activation of the Akt-mTOR pathway, and elevated tissue levels of the T3 hormone, indicating positive effects on both peripheral and central tissues (Giacco et al., 2022).

On the other hand, recent literature points out that chronic plasma accumulation of BCAAs is associated with metabolic disorders such as insulin resistance and type 2 diabetes. Dysfunction in BCAA catabolism may lead to chronic activation of the mTOR pathway, contributing to disruptions in energy and inflammatory homeostasis, especially in individuals with obesity (Vanweert, Schrauwen & Phielix, 2022).

Although the effects of BCAAs on central fatigue remain controversial, evidence from meta-analyses suggests that their supplementation promotes favorable metabolic adaptations during exercise. Even if not directly modulating central circuits related to exhaustion, BCAAs have been shown to significantly reduce classical markers of physiological stress, such as lactate, ammonia, and creatine kinase (CK), in addition to supporting the maintenance of blood glucose. These effects suggest a supportive role for BCAAs in protecting against micro muscle damage and enhancing metabolic efficiency during intense or prolonged physical activities. Thus, when properly targeted, their use may represent a promising nutritional strategy to mitigate muscle wear and sustain athletic performance under high physiological demand (Hormoznejad, Javid & Mansoori, 2019).

Research also highlights emerging roles for BCAAs in hematopoietic and immune processes, such as megakaryocytic differentiation and platelet production through activation of the mTOR pathway, suggesting therapeutic applications beyond the traditional muscular and nutritional scope (Jiang et al., 2023).

In light of this, the present article aims to conduct an integrative literature review, critically addressing the main biochemical and physiological mechanisms of BCAAs, their therapeutic and athletic applications, as well as the limitations and controversies surrounding their supplementation. By gathering updated scientific evidence, it intends to contribute to a more in-depth and well-founded understanding of the use of BCAAs in contemporary clinical and nutritional practice.

II. Material And Methods

To carry out the integrative review, a systematic survey of the scientific literature available in the main electronic databases was conducted, including PubMed, Scopus, Web of Science, and SciELO. The descriptors “branched-chain amino acids,” “BCAAs,” “muscle metabolism,” “clinical applications,” “supplementation,” “mTOR signaling,” and “pathologies”, among other related terms in both Portuguese and English, were used to ensure a comprehensive search.

Inclusion criteria encompassed original articles, systematic reviews, meta-analyses, and guidelines published between 2000 and July 2025 focusing on the metabolic mechanisms of BCAAs, their applications in

sports and clinical contexts, and aspects related to the safety and efficacy of supplementation. Studies involving human interventions, relevant preclinical studies, and theoretical reviews were considered.

Duplicate articles, publications without full-text availability, and studies with low methodological quality were excluded. Methodological quality was assessed based on criteria such as study design, sample size, and clarity of results.

Data analysis was conducted qualitatively, aiming to integrate information on biochemical mechanisms, therapeutic applications, and existing controversies, as well as to identify gaps for future research. This approach provided a broad and critical view of the topic, consolidating current evidence to support the article's discussion and conclusions.

III. Results

This integrative review identified and analyzed a set of scientific studies addressing the metabolic, therapeutic, and ergogenic effects of branched-chain amino acids (BCAAs). Through systematic screening of relevant databases, studies with diverse methodological approaches were selected, including clinical trials, theoretical reviews, and experimental investigations in animal models or in vitro systems, presented in Frame 1, which provides the authors, objectives, and conclusions on the topic. The findings highlight the complexity of the physiological effects of BCAAs, with emphasis on their roles in energy metabolism, protein synthesis, cell signaling, and their implications in pathologies such as cancer, type 2 diabetes, and liver diseases.

Table 1: Main Articles Used in the Integrative Review.

ARTICLE TITLE - YEAR	AUTHORS	OBJECTIVE	CONCLUSION
The adverse metabolic effects of branched-chain amino acids are mediated by isoleucine and valine. (2021)	Baur, J. A.; Malecki, K. C.; Lamming, D. W.	Investigate adverse metabolic effects of BCAAs, especially isoleucine and valine.	Isoleucine and valine are primarily responsible for BCAAs' adverse metabolic effects.
Maple syrup urine disease: mechanisms and management. (2017)	Blackburn, P. R. et al.	Review mechanisms and management of maple syrup urine disease.	Emphasizes the importance of early diagnosis and dietary interventions.
Efectos de los suplementos de proteína y aminoácidos de cadena ramificada. (2024)	Blanco, J. R.; Linares, I. P.	Analyze effects of protein and BCAA supplementation.	Supplements may improve performance, but adverse effects must be considered.
Revisão das rotas metabólicas dos aminoácidos essenciais: individuais, sinérgicos, BCAAs e sulfurados. (2024)	De Andrade, T. N. et al.	Review metabolic pathways of essential amino acids.	Highlights interactions between amino acid pathways, including BCAAs, with metabolic implications.
Exploiting pancreatic cancer metabolism: challenges and opportunities. (2023)	De Santis, M. C. et al.	Explore pancreatic cancer metabolism and therapeutic opportunities.	Altered BCAA metabolism offers potential targets for pancreatic cancer therapy.
Quantitative determination of branched-chain amino acids in dried blood spot samples by LC–MS/MS. (2021)	Fuenzalida, K. et al.	Quantify BCAAs in dried blood spot samples via LC–MS/MS.	Reliable and sensitive method for BCAA quantification in clinical/laboratory contexts.
A branched chain amino acid metabolite drives vascular transport of fat and causes insulin resistance. (2016)	Jang, C. et al.	Investigate how BCAA metabolites affect fat transport and insulin resistance.	A BCAA metabolite promotes fat transport and insulin resistance.
Defective BCAA catabolism disrupts glucose metabolism and sensitizes the heart to ischemia-reperfusion injury. (2017)	Li, T. et al.	Analyze how defective BCAA catabolism impacts glucose metabolism and heart function.	Impaired BCAA catabolism increases cardiac vulnerability and disrupts glucose metabolism.
Branched chain amino acids. (2019)	Neinast, M.; Murashige, D.; Arany, Z.	Review the role of BCAAs in human physiology.	BCAAs are involved in complex processes beyond energy metabolism.
Branched chain amino acids beyond nutrition metabolism in cancer. (2020)	Nie, C. et al.	Explore BCAAs' functions beyond nutritional metabolism.	BCAAs participate in cell signaling, immunity, and disease.
Multifaceted role of BCAA metabolism in cancer. (2014)	Peng, H.; Wang, Y.; Luo, W.	Explore the multifaceted role of BCAA metabolism in cancer.	BCAA metabolism directly influences cancer growth and progression.
Efectos de los aminoácidos ramificados en deportes de larga duración: revisión bibliográfica. [Effects of branched-chain amino acids on endurance sports: a bibliographic review]. (2014)	Salinas-García, M. E. et al.	Review effects of BCAAs in endurance sports.	BCAAs help reduce fatigue and improve performance in long-duration activities.
Efeitos da ingestão dos aminoácidos de cadeia ramificada na fadiga central. [Effects of branched-chain amino acid intake on central fatigue]. (2005)	Silva, P. A.	Investigate effects of BCAAs on central fatigue.	BCAA supplementation may reduce central fatigue during prolonged exercise.

Influence of BCAA ingestion on creatine kinase post-exercise on recovery: a systematic review and meta-analysis. (2024)	Wang, S.	Evaluate BCAAs' effects on recovery after eccentric exercise.	BCAA intake aids recovery by reducing creatine kinase levels and muscle soreness.
Branched-chain amino acids in disease. (2019)	White, P. J.; Newgard, C. B.	Discuss the role of BCAAs in various diseases.	BCAAs are linked to metabolic diseases like obesity and type 2 diabetes.
BCAAs and muscle protein synthesis in humans: myth or reality? (2017)	Wolfe, R. R.	Investigate the relationship between BCAAs and muscle protein synthesis in humans.	Muscle protein synthesis depends on all essential amino acids; BCAAs alone are not sufficient.
BCAA catabolism breaks glutamine addiction to sustain hepatocellular carcinoma progression. (2022)	Yang, D. et al.	Assess how BCAA catabolism affects hepatocellular carcinoma progression.	BCAA breakdown reduces glutamine dependence, promoting tumor growth.
Gut-Microbial Metabolites, Probiotics and Their Roles in Type 2 Diabetes. (2022)	Zhai, L. et al.	Explore the role of microbial metabolites and probiotics in type 2 diabetes.	BCAA-derived metabolites affect gut microbiota and are linked to insulin resistance.
BCAAs in Liver Diseases: Complexity and Controversy. (2024)	Zhang, Y.; Zhan, L.; Zhang, L.; Shi, Q.; Li, L.	Review the role of BCAAs in liver diseases.	The role of BCAAs in liver function is complex and varies by disease type and stage.

IV. Discussion

The Dynamics of BCAAs in the Muscular Environment Under Physiological Demand

Branched-chain amino acids (BCAAs)—leucine, isoleucine, and valine—stand out for being predominantly metabolized in skeletal muscle, unlike most amino acids that are catabolized in the liver. This is due to the high activity of mitochondrial branched-chain aminotransferase (BCAT2), almost absent in hepatic tissue. Their catabolism starts with transamination by BCAT, producing keto acids that are oxidized by the branched-chain α-keto acid dehydrogenase (BCKDH) complex, whose activity depends on cellular energy status. This metabolic particularity places muscle as the main site of BCAA regulation, directly linking them to protein anabolism and energy homeostasis under conditions of increased physiological demand (Neinast et al., 2019; Holeček, 2013; Mann et al., 2021; Trillos-Almanza et al., 2024).

BCAA catabolism begins with transamination catalyzed by BCAT2, resulting in the formation of the corresponding keto acids (BCKAs), which are then irreversibly degraded by the branched-chain α-keto acid dehydrogenase (BCKDH) enzyme complex. This process is highly regulated by post-translational modifications and the cell's energy availability, standing out as a rapid response pathway in contexts of metabolic stress, such as physical exercise or prolonged fasting (Kaspy et al., 2023; Kamei et al., 2020).

During intense or prolonged physical exercise, BCAAs are recruited as alternative energy substrates, especially under conditions of glycogen depletion. Leucine, in particular, exerts a regulatory function by activating the mTORC1 complex, promoting protein synthesis and inhibiting proteolysis by suppressing autophagic and ubiquitin-proteasome pathways. This activation contributes to maintaining the structural and functional integrity of skeletal muscle in the face of catabolic aggression (Mann et al., 2021; Kamei et al., 2020).

The influence of BCAAs is not limited to protein synthesis. Studies indicate that their oxidation in muscle provides intermediates for the TCA, reinforcing their role in ATP generation during prolonged efforts. Furthermore, leucine and its derivatives, such as HMB (β-hydroxy β-methylbutyrate), modulate the expression of anabolic genes and mitochondrial biogenesis, promoting morphofunctional adaptations to muscular overload (Kaspy et al., 2023; Bryan; Myles, 2024).

In addition to their function as energy substrates and regulators of protein anabolism, BCAAs play a relevant role in modulating glycemic homeostasis and lipid metabolism in muscle tissue. During exercise, these amino acids favor glucose transport into the muscle cell through the activation of the PI3K/Akt pathway, promoting the translocation of GLUT4 transporters to the plasma membrane. This mechanism contributes not only to maintaining blood glucose under metabolic stress but also to optimizing glycogen resynthesis during the recovery period. Additionally, there is evidence that BCAAs, especially leucine, participate in mitochondrial biogenesis and the increase in muscle oxidative capacity, effects mediated by the co-activation of PGC-1α—a critical factor in physical training adaptation (Trillos-Almanza et al., 2024; Kamei et al., 2020).

However, the effectiveness of BCAA supplementation alone is still a subject of debate. Although studies show a transient increase in protein synthesis and an improvement in markers like creatine kinase and post-exercise ammonia, the absence of other essential amino acids can limit total protein synthesis. This is because the availability of all essential amino acids is necessary for the elongation of peptide chains during translation. Thus, although leucine acts as a trigger for mTORC1 activation, a complete anabolic response depends on the simultaneous presence of a complete protein profile, such as that found in whole food sources or high-quality biological proteins (Kaspy et al., 2023). Therefore, the strategic use of BCAAs may be more effective when

associated with well-structured nutritional and training protocols, respecting the physiological context and individual needs.

Metabolic Responses to BCAAs in Catabolic States: From Pathology to Exertion

Catabolic states, such as trauma, infection, prolonged fasting, and high-intensity exercise, cause intense metabolic changes that affect the body's protein balance. In these contexts, branched-chain amino acids (BCAAs)—leucine, isoleucine, and valine—play a critical role as energetic precursors and anabolic signaling agents, particularly in muscle tissue. During muscle catabolism, there is an increase in the release of BCAAs into the bloodstream and an intensification of their uptake by peripheral tissues, which contributes to maintaining energy homeostasis and reducing protein degradation (Neinast; Murashige; Arany, 2019).

Among the BCAAs, leucine stands out for its ability to activate the mTORC1 (mammalian target of rapamycin complex 1) pathway, stimulating protein synthesis and inhibiting autophagy, especially in situations of post-exercise recovery or tissue trauma. In extreme states, such as fasting or sepsis, this pathway may be compromised, and leucine signaling becomes vital for preserving lean mass and cellular integrity (Nie et al., 2018). Studies demonstrate that BCAA supplementation can attenuate muscle loss under conditions of immobilization and during major surgical interventions (De Andrade et al., 2024).

In addition to their anabolic function, BCAAs also have broad metabolic effects. The catabolism of BCAAs occurs predominantly in skeletal muscles, where enzymes like BCAT and BCKDH act by transforming these amino acids into intermediates that enter the Krebs cycle. In catabolic states, BCKDH expression is negatively regulated, promoting the accumulation of circulating BCAAs, which is associated with pathologies like insulin resistance, type 2 diabetes, and cardiovascular diseases (White; Newgard, 2019).

In patients with chronic metabolic diseases, such as obesity and type 2 diabetes, BCAA oxidation is reduced, leading to a systemic accumulation of these amino acids and their metabolites, such as the branched-chain α-keto acids (BCKAs). This imbalance leads to metabolic overload, oxidative stress, and mitochondrial dysfunction, worsening the pathological condition. Paradoxically, while BCAAs promote anabolism in acute states of physiological stress, their persistent elevation in chronic conditions can be deleterious (Neinast; Murashige; Arany, 2019; White; Newgard, 2019).

Conversely, during extreme physical exercise, the body increases the mobilization and oxidation of BCAAs as a source of energy, especially when glycogen reserves are depleted. Valine, for example, generates succinyl-CoA, contributing to gluconeogenesis, while leucine forms acetyl-CoA and acetoacetate, being considered ketogenic. This adaptation is beneficial, promoting improved performance and muscle endurance, provided that the nutritional intake of BCAAs is adequate for the physiological demands (Neinast; Murashige; Arany, 2019).

Therefore, the metabolic responses to BCAAs vary according to the type of stress the body is subjected to. In pathological situations, the deregulation of their oxidation worsens metabolic disorders. In physiological states of extreme exertion, BCAAs act as energy substrates and anabolic signaling agents, being essential for the preservation of muscle function. This demonstrates the importance of an individualized approach in therapeutic and nutritional strategies involving these amino acids (De Andrade et al., 2024; Nie et al., 2018).

What Studies Say About Supplementation: Efficacy, Limits, and Controversies

Supplementation with branched-chain amino acids (BCAAs) has gained increasing interest in both clinical practice and sports, mainly for its supposed ergogenic effects and muscle recovery properties. Studies have shown that BCAAs, composed of leucine, isoleucine, and valine, play a relevant role in protein synthesis and the attenuation of markers of muscle damage, such as creatine kinase (CK), especially after intense eccentric exercise (Wang, 2024). However, the findings are not unanimous, and methodological divergences between studies raise debates about the true effectiveness of these supplements.

One of the main effects attributed to BCAA supplementation is the reduction of delayed-onset muscle soreness (DOMS) and exercise-induced muscle damage (EIMD). A meta-analysis conducted by Wang (2024) revealed that doses above 10 g/day, especially in trained individuals and during anaerobic exercises, are effective in decreasing post-exercise CK levels. In contrast, studies that used smaller doses or supplementation protocols combined with other nutrients did not observe significant benefits, suggesting that the effectiveness of BCAAs depends heavily on the dosage, timing of intake, and type of exercise.

The controversy increases when considering the use of BCAAs in long-duration sports. Although some studies indicate improved endurance and delayed central fatigue by modulating the tryptophan/BCAA ratio in the central nervous system (Silva, 2005), others question the magnitude of these effects. The impact on serotonergic neurotransmission has been proposed as one of the mechanisms by which BCAAs could influence central fatigue, but there are limitations regarding the replicability and consistency of these findings in different populations and sports modalities.

The clinical efficacy of BCAAs is also explored in pathological situations, such as in Maple Syrup Urine Disease (MSUD), where the serum levels of these amino acids need to be strictly controlled. A study conducted by Fuenzalida et al. (2021) demonstrates the importance of precise BCAA quantification through mass spectrometry as a diagnostic and monitoring tool for patients with MSUD. However, the extrapolation of this data to healthy individuals in sports contexts must be done with caution, given the distinct nature of metabolic needs.

In the context of physical performance, a review by Salinas-García et al. (2014) indicates that BCAA supplementation can provide positive effects on performance maintenance during prolonged exercises, especially when combined with carbohydrate consumption. However, the authors highlight that interindividual variability and training adaptation can interfere with the results, which reinforces the need for individualizing nutritional strategies. Furthermore, adverse effects at high doses or the risk of renal overload have been pointed out as possible limitations of the indiscriminate use of these supplements.

Additionally, some authors draw attention to the risk of overvaluing BCAAs, especially to the detriment of more comprehensive dietary strategies. Blanco and Linares (2007) warn that many athletes resort to supplementation without proper professional guidance, which can lead to an unbalanced intake of amino acids and compromise overall protein metabolism. Therefore, while BCAAs may have promising applications, their use must be based on robust scientific evidence and an individualized assessment of needs and goals.

Emerging Therapies and Clinical Perspectives Involving BCAAs

Emerging therapies and clinical perspectives involving branched-chain amino acids (BCAAs) represent a promising area in medical research, especially in metabolic and oncological disorders. A deeper understanding of BCAA metabolism has revealed its multifaceted role in health and disease, paving the way for new therapeutic strategies.

One of the emerging approaches in this area involves the dietary modulation of BCAAs. Studies show that low-protein diets have promoted improvements in metabolic health in both rodents and humans. Specifically, the reduction of dietary isoleucine and valine levels has been shown to rapidly restore metabolic health in diet-induced obese mice, suggesting that isoleucine or valine restriction may represent a new therapeutic strategy to treat and prevent obesity and diabetes (Baur et al., 2021).

In addition to metabolic diseases, BCAAs also play a fundamental role in the oncological context. The metabolism of these amino acids—especially valine, leucine, and isoleucine—has been recognized as a critical axis in tumor progression and resistance to therapy. They act as nitrogen donors for the synthesis of macromolecules, such as nucleotides, which are essential for the growth of human cancer cells (Peng et al., 2020).

This aspect is particularly evident in aggressive cancers, such as pancreatic ductal adenocarcinoma (PDAC). In this condition, an intense metabolic rearrangement is observed, in which glutamine and BCAAs emerge as crucial modulators of both immune function and tumor growth. Clinical trials currently underway seek to explore interventions that target mitochondrial metabolism, the dependence on amino acids like asparagine and glutamine, and the inhibition of autophagy—strategies that may also include the manipulation of BCAA metabolism (Peng et al., 2020; De Santis et al., 2023).

Concurrently, the relationship between BCAAs and insulin resistance constitutes another important focus of therapeutic investigation. Epidemiological and experimental data point to BCAAs as potential contributors to the development of insulin resistance, although the mechanisms are still being elucidated. Recently, 3-hydroxyisobutyrate (3-HIB), a catabolic intermediate of valine, was identified as a paracrine factor that promotes lipid transport to tissues and induces insulin resistance (Jang et al., 2016). This discovery highlights new molecular targets with potential for therapeutic interventions in type 2 diabetes.

In the field of genetic diseases, BCAAs are also directly involved in hereditary metabolic disorders, such as Maple Syrup Urine Disease (MSUD). This is an inborn error of metabolism caused by mutations in the branched-chain α-keto acid dehydrogenase complex, resulting in elevated plasma levels of BCAAs. Treatment traditionally involves a rigorous dietary restriction of these amino acids, combined with continuous metabolic monitoring (Blackburn et al., 2017). Neonatal screening is widely used, allowing for early interventions that prevent irreversible neurological complications.

Additionally, recent studies have highlighted the interactions between BCAAs and the gut microbiota as another relevant regulatory axis in metabolic diseases, especially in type 2 diabetes. Changes in the composition of the microbiota have been observed in diabetic individuals, directly influencing insulin resistance. Products of BCAA metabolism by the gut microbiota can negatively act on insulin sensitivity. In this scenario, probiotic-based strategies are being investigated as a way to indirectly modulate BCAA levels and promote metabolic improvements (Zhai et al., 2021).

In summary, the field of therapies involving BCAAs is constantly evolving, with approaches ranging from specific dietary restriction for obesity and diabetes to oncological strategies and gut microbiota modulation. A deeper understanding of the mechanisms by which BCAAs influence human physiology and pathology is essential for the development of more effective and personalized therapeutic interventions. However, important

challenges remain, such as the metabolic heterogeneity among patients and the need for more clinical trials that validate and optimize these innovative interventions.

Metabolic Interactions with Other Nutrients and Functional Implications

Branched-chain amino acids (BCAAs) – leucine, isoleucine, and valine – have sparked increasing interest in biomedical research and clinical nutrition due to their broad participation in physiological and pathological processes. They are essential amino acids, meaning they cannot be synthesized by the human body and must be obtained through diet, with their main sources being meat, fish, dairy, and eggs. Beyond their function as building blocks of proteins, BCAAs play important roles in cellular energy production, metabolic signaling, and homeostatic regulation.

One of the most significant metabolic interactions of BCAAs occurs with glucose metabolism and insulin sensitivity. Chronically elevated levels of these amino acids in the blood are often observed in people with obesity, insulin resistance, type 2 diabetes, and cardiovascular diseases (White; Newgard, 2019). While the association is well-established, there is still controversy regarding causality: high BCAA levels can be either a contributing factor or a secondary marker of the metabolic disorder. Furthermore, defects in BCAA catabolism can negatively interfere with glucose metabolism and increase cardiac susceptibility to ischemia-reperfusion injury (Li et al., 2017). Metabolically, valine is classified as glucogenic, leucine as ketogenic, and isoleucine has both properties, reflecting their versatility in entering different points of the TCA and contributing to ATP production (Zhang et al., 2024).

In the context of muscle protein synthesis, there is a complex interaction between BCAAs and other essential amino acids (EAAs). Despite the popularization of supplements containing BCAAs with the promise of promoting muscle anabolism, empirical and theoretical evidence indicates that such a benefit, when BCAAs are ingested alone, is overestimated or unfounded (Wolfe, 2017). The synthesis of new proteins requires the simultaneous and adequate presence of all EAAs, in addition to non-essential amino acids (NEAAs). Studies with intravenous infusion of isolated BCAAs have demonstrated a reduction in both muscle protein synthesis and degradation, indicating a decrease in protein turnover. This finding reinforces that an unbalanced supply of amino acids can limit the anabolic response, making the claim that isolated BCAA supplementation significantly stimulates muscle protein synthesis unjustified (Wolfe, 2017).

The liver plays a central role in BCAA metabolism, and the homeostasis of these amino acids is strongly influenced by liver dysfunctions. Due to the low activity of branched-chain aminotransferase (BCAT) in the liver, the initial transamination of BCAAs occurs predominantly in skeletal muscle. However, the branched-chain α-keto acid dehydrogenase (BCKDH) complex, responsible for the irreversible decarboxylation of BCKAs, has higher liver activity, which highlights the cooperation between muscle and liver in processing these amino acids. In liver diseases, the circulating levels of BCAAs can present distinct changes, with the Fischer's Index – the molar ratio between BCAAs and aromatic amino acids – being used as a clinical biomarker to evaluate metabolic imbalances, especially in cases of hepatic encephalopathy. BCAA supplementation in patients with cirrhosis or liver cancer is widely practiced, but its clinical effectiveness remains uncertain due to the heterogeneity of studies and the lack of standardization in assessing the energy and protein needs of these individuals (Zhang et al., 2024).

In addition to metabolic and liver diseases, BCAA catabolism is also relevant in oncological contexts, such as in hepatocellular carcinoma (HCC). Under conditions of glutamine depletion – a fundamental amino acid for cell survival and proliferation – tumor cells activate BCAA catabolism as a compensatory pathway to sustain their energetic and biosynthetic metabolism (Yang et al., 2022). This adaptation highlights the complexity of metabolic interactions between amino acid pathways in the tumor environment and suggests possible therapeutic targets by interrupting the alternative energy supply through BCAAs.

In conclusion, BCAAs have multiple metabolic interactions with broad functional implications that go beyond muscle protein synthesis and involve the regulation of glucose homeostasis, liver function, and tumor metabolism. The isolated supplementation of BCAAs, although widely promoted, does not necessarily result in desirable anabolic effects, especially if the balance between different amino acids is not considered. In pathological contexts, BCAA homeostasis becomes even more complex and dependent on the individual's overall metabolic state. Future research should focus on elucidating the molecular mechanisms of these interactions and on the development of personalized therapeutic strategies, based on a comprehensive assessment of the metabolic profile, to optimize their clinical effectiveness.

V. Conclusion

Branched-chain amino acids (BCAAs) play central roles in human metabolism, standing out as regulators of protein synthesis via the mTORC1 pathway, as energy sources during catabolic stress, and as participants in pathophysiological mechanisms associated with metabolic, hepatic, and oncological diseases. Studies indicate that, although BCAA supplementation may offer ergogenic and therapeutic effects in specific contexts, their

isolated efficacy is limited without adequate intake of other essential amino acids, which compromises the ideal anabolic response.

Moreover, current literature shows that impairments in BCAA oxidation are associated with conditions such as insulin resistance, obesity, and certain types of cancer, suggesting that dietary manipulation of BCAAs may represent a promising avenue for clinical intervention. However, the indiscriminate and context-free use of BCAAs may pose metabolic risks, reinforcing the need for an approach based on robust scientific evidence, individualized assessments, and nutritional strategies that consider the individual's physiological status and specific therapeutic goals.

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