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Amino Acids: Metabolism, Functions, and Their Role in Health and Disease Management

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Abstract. *Amino acids are indispensable components of human metabolism, playing essential roles in protein synthesis, energy production, and cellular regulation. Branched-chain amino acids (BCAAs)-leucine, isoleucine, and valine—are particularly significant due to their involvement in muscle repair, metabolic signaling, and insulin sensitivity. While BCAAs are vital under normal physiological conditions, multiple studies have shown that elevated plasma BCAA levels are linked to insulin resistance, obesity, and type 2 diabetes. This association has led researchers to investigate whether these elevations are a cause or consequence of metabolic dysfunction. Recent findings have revealed that impaired BCAA catabolism in tissues such as adipose and liver contributes to their accumulation in circulation. If skeletal muscle becomes insulin resistant, it may shift BCAA metabolism further, exacerbating the imbalance. Moreover, the modulation of specific enzymes and transporters has been proposed as a therapeutic avenue to mimic the beneficial effects of dietary protein restriction. Although several mechanisms have been proposed, including mTOR activation, fatty acid oxidation interference, and altered neurotransmitter synthesis, no single pathway fully explains BCAA-induced metabolic disturbances. Therefore, a comprehensive understanding of amino acid metabolism is crucial, particularly if dietary and pharmacological interventions are to be optimized for preventing or treating age-related and metabolic diseases.*

Keywords: *Amino Acids; Branched-Chain Amino Acids; Cancer Treatment; Diseases; Insulin Resistance; Metabolic Health.*

1. INTRODUCTION

Amino acids are chemical compounds that form proteins essential to many biological functions. Amino acids are critical to human health due to their metabolism, functions, and nutritional value. Beyond protein synthesis, they regulate metabolic pathways, maintain cellular activities, and support critical physiological processes. Amino acids support energy generation, neurotransmitter synthesis, immune system modulation, and homeostasis. They also synthesize hormones, nucleotides, and enzymes. Despite their importance, food, genetics, and physiology affect the body's amino acid use. Thus, knowing amino acid metabolism, functions, and nutrition is crucial for scientific study and health, and disease treatment (Alagawany et al., 2021).

Protein is recognized as one of the three essential macronutrients, playing a pivotal role in maintaining physiological vitality. Unlike carbohydrates and lipids, which are stored in the body as glycogen and adipose tissue respectively, protein lacks a dedicated storage depot. Consequently, when dietary protein is limited, the body must rely on alternative mechanisms to maintain amino acid homeostasis. Notably, proteins are metabolized into amino acids and short peptides, both of which exert diverse and significant physiological effects. Since amino

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acids serve as the building blocks of proteins and protein complexes, they are central to the structure and function of biological systems. Moreover, they act as precursors to numerous critical metabolites, such as purines, pyrimidines, and neurotransmitters, which arise through cellular amino acid metabolism. Because of the absence of a storage form, the body has evolved dynamic mechanisms to recycle amino acids and regulate protein utilization. For instance, autophagy and lysosomal protein degradation ensure a continuous internal supply of amino acids. At the same time, cellular processes adapt by reducing protein synthesis in inactive tissues and decreasing cellular turnover in those that consume high levels of amino acids. If dietary protein intake becomes insufficient, these adaptations are upregulated, and ureagenesis is downregulated in response to reduced substrate availability. Recent studies have highlighted how these tightly regulated mechanisms contribute to metabolic flexibility and nitrogen conservation under varying nutritional conditions. Therefore, the regulation of protein metabolism remains a critical factor in overall homeostasis, particularly under stress or nutrient-limited environments (Tan, Nawaz, & Buckow, 2023).

However, some critical metabolic processes need the removal of the amino group from amino acids, resulting in an essential depletion of amino acids that must be replenished by dietary intake. Consequently, a sufficient protein diet is essential to provide these vital amino acids. The "Amino Acid Nutrition and Metabolism in Health and Disease" special issue covers the latest research and key topics in this nutritional sector. Dietary protein limitation may improve metabolic health in preclinical trials (Kitada et al., 2018).

This review discusses the amino acids roles, especially BCAAs, in synthesis of protein, metabolic health, and disease prevention. It links BCAA metabolism abnormalities to obesity, insulin resistance, and neurodegenerative illnesses. The review emphasizes balanced amino acid consumption for insulin sensitivity, muscle repair, and disease progression. Dietary therapies and supplements may improve health, particularly in metabolic diseases.

- **Branched-chain amino Acids (BCAAS) and Their Role in Metabolic Health, Insulin Resistance, and Exercise Physiology**

  BCAAS make up about 20% of the protein amino acids and are vital to mammalian existence. Leucine, isoleucine, and valine must be eaten. Fungi, bacteria, and plants create BCAAS. Few BCAA shortages occur because of their abundance. Mammals have plenty of BCAAS in muscle protein. Since excess protein does not build muscle protein; hence, it is constantly catabolized, unlike carbohydrates and lipids, which may be stored

as glycogen and adipose tissue. The BCAA catabolism pathway is now tightly regulated (Gannaban, 2023).

As illustrated in Figure 1, the initial two stages of branched-chain amino acid (BCAA) catabolism, namely transamination followed by decarboxylation and dehydrogenation, are conserved across all three BCAAs: valine, leucine, and isoleucine. Although the first two catabolic steps are shared, the degradation pathways diverge thereafter. Valine is catabolized into propionyl-CoA, which subsequently enters the tricarboxylic acid (TCA) cycle and may serve as a gluconeogenic precursor. In contrast, leucine is exclusively ketogenic, yielding acetyl-CoA. Isoleucine contributes to both pathways by producing both propionyl-CoA and acetyl-CoA. Consequently, the metabolic fate of each BCAA distinctly influences energy homeostasis and substrate availability.

Moreover, the entire catabolic process occurs within the mitochondrial matrix, with the BCKDH complex specifically anchored to the inner face of the inner mitochondrial membrane. This localization ensures direct access to mitochondrial coenzymes and substrates, thereby facilitating efficient metabolic flux. Recent studies have emphasized the importance of this compartmentalization in coordinating mitochondrial energy metabolism and have revealed novel insights into how dysregulation of BCAA catabolism contributes to metabolic disorders. Thus, understanding the regulation and fate of BCAA metabolism remains essential for elucidating its broader physiological and pathological roles (Fabi, 2024).

Do Increases in BCAAs Induce Insulin Resistance?

Since the 1960s, both diabetes and obesity have been linked to BCAA increases in blood levels. Recent impartial metabolomics profiling of obese insulin-resistant adults compared with leaner insulin-sensitive people found that elevated BCAA levels were most closely connected to a lack of insulin (Vanweert, Schrauwen, & Phielix, 2022).

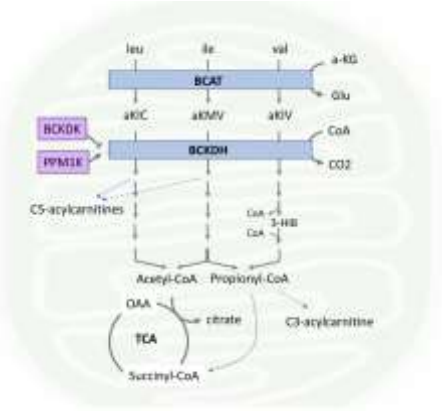

Figure 1. Biochemical mechanisms of branched-chain amino acid catabolism (Vanweert et al., 2022).

- Human BCAA treatments severely reduce sensitivity to insulin, as generally assessed by hyperinsulinemic-euglycemic clamps. Likewise, the co-administration of BCAAS with a high-fat diet (HFD) in mice often exacerbates the resulting insulin resistance. In contrast, low-BCAA diets increase resistance to insulin. In any animal designs, lipids or a high-fat diet (HFD) were necessary, but BCAAS alone exhibited little or no effect, strongly suggesting that BCAAs mechanistically interact with lipids to enable insulin resistance. In insulin resistance or diabetes animal models, incompletely esterified or oxidized lipid molecules accumulate in skeletal muscle. These kinds of compounds contain acyl-carnitines, acyl-CoAs, and diacylglycerols (DAG); however, which species largely triggers insulin resistance is still debated (Shah, 2023).
- Elevated plasma BCAA levels may be identified in individuals over a decade prior to the onset of diabetes (Shah, 2023).
- An unbiased metabolomics study compared preserved blood samples from 189 Framingham Heart Study participants who developed diabetes to 189 controls who did not acquire the illness. BCAAs were the most important indicator for diabetes onset in this study. No subjects had diabetes or insulin resistance at the initial blood test. Independent research found similar findings, while a tertiary study did not. A genetic Mendelian randomization study found a region proximal to PPM1K that was highly connected with genome-wide BCAA levels and diabetes incidence, strongly indicating a causative association. Other genetic studies found similar connections, although they suggested an inverse causal relationship. Genetic variants affect all tissues. However, BCAA oxidation may affect different tissues differently, which may hinder genetic studies (Chevli et al., 2021).
- Pharmaceutically activating BCKDH accelerates BCAA oxidative breakdown and reduces BCAA increases in the Zucker rat model of obesity and diabetes, increased resistance to insulin (White et al., 2021).

  This study does not prove causality, but it strongly suggests that sustained BCAA rises in people and rodent models promote insulin resistance and diabetes. Insulin resistance may increase BCAA levels by not regulating protein breakdown, creating a negative cycle. The rising evidence that high BCAA levels cause resistance to

insulin has encouraged various labs to study the processes (Mansoori, Ho, Ng, & Cheng, 2025). Two key questions arise: Plasma BCAAs rise how? Can high BCAA levels cause insulin resistance?

What Causes Increases in BCAAs?

The most convincing evidence so far has supported the inhibition of BCAA catabolism in specific tissues. Nevertheless, the precise identification of tissues primarily involved in BCAA catabolism under physiological conditions remains surprisingly debated. Up to this point, investigations have relied predominantly on ex vivo analyses of BCAA metabolism using tissue slices or extracts. However, these techniques overlook several critical in vivo regulatory factors, including the physiological availability of substrates, the inhibitory effects of metabolic products such as NADH and acetyl-CoA, and the subcellular localization and compartmentalization of key enzymatic components (Choi, Hyun, & Koo, 2024).

Recent definitive studies that have employed heavy isotope steady-state infusion in conscious mice have revealed that most tissues actively absorb branched-chain amino acids (BCAAs); nonetheless, skeletal muscle and liver appear to contribute most significantly. Although no comparable studies have yet been conducted in humans, it is widely assumed that similar mechanisms may operate. Moreover, if BCAA concentrations rise systemically, it is likely due to dysregulated metabolism in specific tissues. In this context, both adipose tissue and the liver have been identified as the principal contributors to elevated circulating BCAA levels, as illustrated in Figure 2 (Arany & Neinast, 2018).

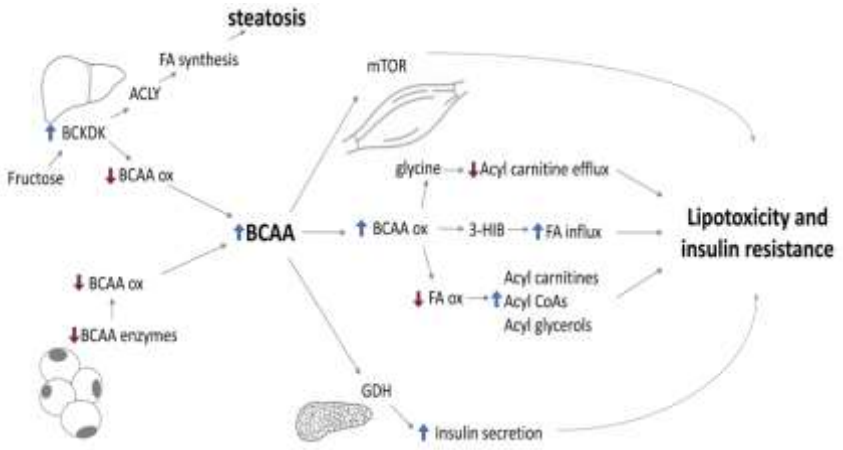

Figure 2. Integration of hypothesized mechanistic hypotheses for branched-chain amino acid-induced insulin resistance. Refer to the text for more information (Arany & Neinast, 2018).

- Adipose tissue: Mice Glut4 expression in adipose tissue caused systemic insulin resistance, reduced BCAA catabolic gene mRNA expression, and increased circulating BCAA levels. Many obesity and insulin resistance models and people with diabetes have downregulated BCAA catabolic genes in adipose tissue. Bariatric surgery reduces plasma BCAA and increases adipose BCAT and BCKDH expression in humans. A coordinated suppression of BCAA catabolism in adipose tissue may cause systemic BCAA elevations. Endoplasmic reticulum stress, inflammation, and tissue hypoxia may cause this suppression, while insulin sensitizer thiazolidinediones alleviate it in rats and humans. Nonetheless, a significant shortcoming of these models is that adipose tissue oxidizes only negligible amounts of BCAAS, possibly less than 5% of total body oxidation, even in obese subjects, indicating that the elevation in circulating BCAA levels must have other contributing factors (De Bandt, Coumoul, & Barouki, 2022).
- Hepatic tissue: The activity of BCKDH is reduced in the liver of obese and diabetic mice. However, the underlying mechanism varies from that in adipose tissue: BCKDK expression is elevated, resulting in enhanced inhibitory phosphorylation of BCKDH. The expression of BCKDK is partially regulated by ChREBP-beta. This carbohydrate-responsive transcription factor is particularly sensitive to dietary carbohydrate intake, especially fructose, hence possibly associating contemporary high-fructose diets with increased plasma BCAAs. Adiponectin and other hormones may also regulate liver BCKDH activity, as well as neural pathways in response to brain insulin (Bollinger et al., 2022).
- Skeletal Muscle: Although skeletal muscle serves as the primary reservoir for glucose after a glucose load and represents a major site of insulin resistance, none of the aforementioned studies have reported alterations in mRNA or protein expression, nor have they shown significant changes in BCAT or BCKDH phosphorylation within muscle tissue. Conversely, evidence from diabetic rat models has indicated elevated levels of C3 and C5 carnitines in skeletal muscle, implying that insulin resistance may enhance BCAA catabolism in this tissue. Moreover, recent investigations utilizing heavy isotope steady-state infusion in db/db mice have

strongly supported this hypothesis, suggesting that BCAA catabolism may shift away from adipose and hepatic tissues toward skeletal muscle under insulin-resistant conditions. Additionally, a recent study has demonstrated that insulin-resistant skeletal muscle downregulates genes involved in BCAA catabolism, thereby reinforcing the notion that metabolic adaptations in muscle play a pivotal role in systemic BCAA regulation (Mauvais-Jarvis, 2024).

How Do High BCAA Levels Cause Insulin Resistance?

Many significant concerns remain unsolved about this problem, such as: Do increasing BCAAs cause insulin resistance, or is it due to increased BCAA catabolism?

Which tissue bed promotes insulin resistance in response to high BCAA levels? Is one BCAA primarily accountable? Our discussion below covers possible processes and their consequences for these topics (Fig. 2).

- mTOR: The lysosome-associated mTORC1 complex boosts development and responds well to metabolic cues like amino acids in most cells. Leucine, which directly binds to the GATOR complex modulator Sestrin2, activates mTORC1 best. BCAA supplementation in rats stimulates mTOR and downstream targets, whereas human AA infusions impair muscle and liver insulin sensitivity and activate mTOR. Rapamycin, a mTOR inhibitor, partially reversed insulin resistance in rats fed BCAAs on HFD. However, some results dispute leucine-activated mTOR's main role in insulin resistance. Leucine-only diets enhance insulin sensitivity, but BCAA-supplemented diets reduce insulin resistance. Leucine supplementation activates BCKDH, lowering the other BCAAs. If so, isoleucine or valine may produce insulin resistance rather than leucine, which activates mTOR. Release insulin. Beta cell failure, peripheral insulin signaling pressure, and compensatory desensitization may develop insulin resistance and diabetes in chronic hyperinsulinemia. In insulin resistance, post-prandial insulin levels rise before glucose changes (Melnik, 2021).
- BCAAs, particularly leucine, are powerful insulin secretagogues, especially at normal or low glucose. Hence, high BCAA levels may cause prolonged hyperinsulinemia and induce insulin resistance. Similar to the mTOR theory, the model predicts leucine as a stronger insulin resistance driver than the other BCAAs despite contrary experimental results (Melnik, 2021).

- FAO fatty acid oxidation competition. BCAA indications are often related to higher C3 and C5 acylcarnitines and incompletely oxidized BCAA catabolism products such as propionyl CoA, according to epidemiological research. TCA cycling BCAA catabolism enhanced or misbalanced with carnitine combustion may occur in insulin resistance. Excess BCAA catabolism may compete with fatty acid beta-oxidation for carbon entry into the TCA cycle, producing incomplete lipid intermediate oxidation and mitochondrial stress that causes muscle and liver insulin resistance. Even under normal physiological conditions, BCAAs contribute little to muscle and liver TCA carbons, making this hypothesis difficult to reconcile. The model predicts acetyl-CoA increases, which insulin-resistant situations have not shown (Pabla, 2021).
- Glycine: Obese Zucker rats' muscle insulin resistance was reversed by BCAA reduction. BCAA restriction decreased muscle even chain-length acyl-CoAs and restored glycine in ZF rats at many metabolomics screens. Human investigations of insulin resistance have shown low plasma glycine levels, which correlate with increased BCAA levels. Glycine may transport incompletely oxidized fatty acids as acyl glycine, which were shown to be lower in the urine of ZF rats. The authors hypothesized that decreased glycine in skeletal muscle increases acyl-CoA accumulation due to competition between BCAA and fatty acid oxidation, making it harder for stored acyl-CoAs to leave as acyl-glycines. The model assumes that BCAA oxidation competes with FAO to induce acyl-CoA buildup (Ježek, 2025).
- 3-HIB: After BCKDH, all BCAA catabolic products are covalently linked to CoA and held in mitochondria, except for 3-HIB (Fig. 2). Thus, mitochondria may release 3-HIB, presumably in proportion to active BCAA catabolism flux. Secreted 3-HIB increases fatty acid flow to skeletal muscle by stimulating transendothelial fatty acid transport in capillary endothelial cells (Choi et al., 2024). Elevated plasma BCAAs may stimulate muscle BCAA catabolism, promoting 3-HIB production and trans-endothelial fatty acid transport, resulting in muscle lipid buildup and insulin resistance. In rats, 3-HIB administration leads to muscle diacyl glycerol buildup and insulin resistance. Elevated levels of 3-HIB in plasma and urine are linked to current and future insulin resistance. Valine produces 3-HIB. This model supports the hypothesis that BCAA catabolism, not levels, causes insulin resistance. The concept aligns with evidence that leucine alone does not cause insulin resistance, but all three BCAAs combined do (Choi et al., 2024).

- Indirect consequences: A recent study reveals liver BCKDK modulates BCKDH and directly activates ATP citrate lyase (ACLY), a rate-limiting enzyme for fatty acid synthesis. PPM1K reverses ACLY phosphorylation like BCKDH. BCKDK levels in the liver may affect fatty acid synthesis, causing steatosis and insulin resistance, independent of BCAA catabolism. How these findings relate to greater BCAAs is unknown. BCKAs, especially leucine-derived aKIC, allosterically block BCKDK on BCKDH. As anticipated, elevated BCKAs may reduce insulin resistance and steatosis by decreasing BCKDK action on ACLY (Gannaban, 2023).
- Several mechanisms have been suggested to demonstrate how BCAA increases cause insulin resistance, but none have been verified. Note that various processes may operate concurrently in Curr Diab Rep (2018) 18:76, thereby explaining the apparent discrepancies. To revisit the three questions from the beginning: Current data suggests that increased catabolism, particularly in skeletal muscle, maybe the primary cause of BCAA-related insulin resistance and diabetes risk, though this is inconclusive. Tissue-specific BCAA catabolism genetic alteration in skeletal muscle is needed for proof (Wang et al., 2021).

- **Amino Acid Transport and Restriction: Implications for Metabolic Health, Aging, and Exercise Physiology**

Javed and Bröer have found that mice missing a key protein responsible for moving certain building blocks of protein through the body have shown blood profiles similar to those of mice eating a diet low in protein. This specific protein normally helps absorb these nutrients from food in the gut and reabsorb them in the kidneys. Because of this, blocking its function could potentially copy the positive effects of eating less protein. Since eating less protein has already been linked to better health as animals age, stopping this protein's action might be a promising way to improve long-term health and prevent age-related diseases (Javed & Bröer, 2019).

Branched-chain amino acids (BCAA) are considered a significant factor in the influence of dietary protein intake on metabolic health (Arany & Neinast, 2018). Ribeiro *et al*. (Ribeiro et al., 2019), Examined and compared circulating BCAA, body composition, and consumption in older mice and men. Protein intake correlated with circulating BCAA levels in mice and humans, but body weight and fat correlated positively. David *et al*. (David, Dardevet, Mosoni, Savary-Auzeloux, & Polakof, 2019)

In insulin-resistant rats fed high-fructose diets, they examined circulation BCAA levels, body composition, and tissue BCAA catabolism. This paradigm showed that insulin-resistant rats' increased BCAA levels were connected to skeletal muscle BCAA catabolic capabilities, not body composition.

The limitation of sulfur-containing amino acids (SCAA), namely L-methionine and L-cysteine, provides health advantages for age-related diseases. Jonsson *et al*. (Jonsson, Margolies, & Anthony, 2019) Conducted a comprehensive analysis of the regulation and function of signaling pathways, with a special focus on the integrated stress response.

They distinguish adaptive responses to SCAA restriction from standard comprehensive response to stress activation. This special issue includes two unique biochemistry studies concerning function of SCAA. Olsen et al. (Olsen et al., 2018), The pilot-randomized research experiment examined the feasibility of SCAA reduction and high unsaturated FA consumption with various amino acid indicators, while Lee *et al*. (Lee et al., 2018) Studied the relationship between acute and chronic exercise, insulin sensitivity, and plasma amino acids. Additional contributions of clinical investigations examined specific amino acid supplements on characteristics. Tsuda *et al*. (Tsuda, Yamaguchi, Noma, Okaya, & Itoh, 2019) investigated the impact of combined different amino acids supplements on exercise-induced fatigue in normal individuals: a randomized, double-masked, placebo-controlled crossover study. Their findings indicated that amino acid combination administration reduced the sensation of weariness after physical exertion. It will be intriguing to see if these findings influence real exercise performance in further investigations.

- **Functions of Amino Acids in the Human Body**

Human physiological activities depend on amino acids, the building blocks of proteins. Organic molecules are classed as essential or non-essential amino acids. Non-essential amino acids may be generated internally, while necessary amino acids must be eaten. They support several metabolic processes essential for growth, repair, and health. Creating polypeptides that build and maintain tissues, enzymes, hormones, and immunological components is one of amino acids' key tasks. The body needs amino acids, specifically BCAAs, to repair and grow muscle tissue after physical exertion or muscle injury. Leucine, isoleucine, and valine branched-chain amino acids are necessary for energy synthesis and muscle metabolism. Since these amino acids are mostly digested in muscle tissue, they are essential for exercise performance and recuperation

and may boost muscle protein synthesis (Malik, Narayanasamy, Pratyusha, Thakur, & Sinha, 2023). Deficits in these amino acids may hinder muscle repair and recovery, causing muscular atrophy and fatigue. BCAAs increase insulin sensitivity and pancreatic release, regulating blood sugar. Insulin-resistant and diabetic persons may benefit from BCAA ingestion, according to research. An increased BCAA level, especially in a high-protein or high-fat diet, may produce insulin resistance, highlighting the need for amino acid metabolism balance. BCAA changes may cause insulin resistance and type 2 diabetes, particularly in the setting of metabolic stressors like obesity or a high-fat diet. Amino acids support neurotransmitter production. Serotonin, which controls mood, sleep, and appetite, comes from tryptophan (Kondaveeti, Naseem, Hemalatha, & Marwaha, 2024).

The stress response and cognitive neurotransmitters dopamine, norepinephrine, and epinephrine start with tyrosine. Insufficient amino acids may cause emotional and cognitive difficulties. Glutathione, an antioxidant that protects cells from oxidative damage, requires amino acids. Glutathione requirement increases cysteine and glycine demands due to oxidative stress. Depletion of these amino acids may impair oxidative damage defense. Balanced amino acid intake is essential for health. Additionally, amino acids are metabolic intermediates. They generate glucose, fatty acids, and the energy-producing TCA cycle. During prolonged fasting or low-carbohydrate ingestion, gluconeogenesis converts amino acids like alanine and glutamine into glucose, fueling brain cells. This system supplies substrates for metabolic stress and homeostasis when carbohydrates are low. Finally, amino acids, especially BCAAs, are essential for metabolic health, muscle maintenance, neurotransmitter production, and physiological function. Thus, a balanced amino acid diet is necessary to meet the body's structural and functional needs, prevent deficiencies, and lower metabolic disease risks, including insulin resistance and diabetes. Nutritional or illness-related amino acid imbalances may have major health repercussions. Thus, they must be recognized and balanced (Salyha, 2023).

In fasting or malnutrition, oxidative phosphorylation or gluconeogenesis may generate energy from these intermediates. Glutamine may be converted into energy-producing alpha-ketoglutarate, a citric acid cycle intermediate. Amino acids also transaminate a reversible process that transfers an amino group to a keto acid to form new amino acids. Transamination produces non-essential amino acids from metabolic pathway intermediates. Transamination of oxaloacetate produces aspartate, which is

essential to protein synthesis and cellular metabolism. Additionally, amino acids are needed to synthesize proteins for structural and functional biological functions during anabolism. Translation, directed by mRNA coding for protein amino acids, produces proteins. This sequence is governed by DNA genetics. During translation, cytoplasmic ribosomes process mRNA to connect amino acids in a precise sequence. Some signaling mechanisms influence protein synthesis, including the mTOR pathway, which is triggered by leucine. The mTOR pathway stimulates muscle repair and development after exercise, and leucine is essential for muscle protein synthesis (Srivastava et al., 2025).

The synthesis of neurotransmitters, hormones, and nucleotides requires amino acids. Serotonin regulates mood, whereas tyrosine produces dopamine, norepinephrine, and epinephrine, which are needed for stress response and cognitive function. Learning and memory are affected by glutamate, the brain's principal excitatory neurotransmitter, produced from glutamine. The physiological-amino acid metabolism link is significant. During fasting, muscle protein is broken down to release amino acids for gluconeogenesis, guaranteeing adequate glucose for vital organs, including the brain. Protein catabolism increases in response to sickness or injury to provide immunological and tissue repair amino acids. This adaptability mechanism helps the body manage more physiological demands. Liver disease may impede amino acid metabolism, causing toxic byproducts or amino acid shortages that affect protein synthesis and metabolic homeostasis. Genetic anomalies in amino acid metabolism may cause diseases like phenylketonuria (PKU) that prevent the breakdown of amino acids like phenylalanine, causing nervous system damage (Srivastava et al., 2025).

Ultimately, the production, breakdown, and regulation of proteins and other molecules depend on amino acid metabolic pathways. Amino acid metabolism influences practically every aspect of cellular function and health, from citric acid cycle energy generation to neurotransmitter and hormone manufacturing. These pathways maintain metabolic flexibility, allowing the body to adapt to fasting, exercise, and disease. Understanding amino acid metabolism's complexity helps nutrition, medicine, and exercise science promote health and prevent sickness via amino acid balance (Mrozek et al., 2023).

- **The Role of Amino Acids in Nutrition and Dietary Sources**

Protein metabolism, tissue growth, repair, and maintenance need amino acids. BCAAs-leucine, isoleucine, and valine are necessary amino acids for a balanced diet and nutrition. These amino acids are essential because the body cannot produce them and must be eaten. BCAAs are unusual because they are digested in muscle tissue, making them critical for muscle protein synthesis, recuperation, and energy generation during exercise. Insufficient BCAA consumption, especially in athletes or those engaging in severe physical activity, may delay muscle repair and cause muscular catabolism, reducing physical performance. Amino acids, especially BCAAs, are primarily found in protein-rich animal and plant meals (Ahmad, Ahmed, Fatma, & Peres, 2021).

Protein from meat, poultry, fish, eggs, and dairy contains all the amino acids the body needs. Because of this, these meals help people satisfy their amino acid demands. However, legumes, nuts, seeds, and certain grains are incomplete proteins because they lack critical amino acids. People can get all the amino acids they need for good health by mixing plant-based diets. Rice and beans supplement essential amino acids like BCAAs. This emphasizes the need for vegetarian and vegan diet variations. BCAAs also regulate glucose metabolism and improve insulin sensitivity. BCAAs enhance insulin sensitivity in metabolic diseases such as obesity and type 2 diabetes. High BCAA consumption, especially in an unbalanced diet, may cause insulin resistance and glucose homeostasis issues. As obese and insulin-resistant people commonly have increased plasma BCAA levels, inadequate BCAA metabolism may contribute to these metabolic disorders (Mann, Mora, Madu, & Adegoke, 2021).

BCAAs may increase insulin resistance and endanger metabolic health if ingested in excess, especially without sufficient calorie intake or macronutrient balance. The diet further affects amino acids, notably BCAAs, and metabolic health. Refined sweets, bad fats, and processed meals may raise blood BCAA levels, causing oxidative stress and mitochondrial dysfunction, which are linked to chronic illnesses, including diabetes and cardiovascular disease. However, diets high in whole foods, fiber, and antioxidants may assist in maintaining amino acid balance, especially BCAAs, by boosting efficient metabolism and reducing amino acid catabolism byproducts from overproduction. Additionally, lifestyle factors like exercise may affect amino acid metabolism. Resistance exercise increases muscle protein synthesis and repair, particularly BCAAs. The effects of BCAA supplementation on sports performance and muscle recovery have been widely studied. Amino acid shortage may cause muscle fatigue, pain, and poor recovery in athletes and regular exercisers (Kim, Singh, Wang, & Applegate, 2022).

During calorie restriction or fasting, the body may synthesize energy from amino acids, notably BCAAs, without carbohydrate storage. These amino acids may be transformed into glucose by gluconeogenesis to sustain blood sugar and critical processes. Amino acids affect health beyond muscle metabolism. Tryptophan, tyrosine, and glutamine help synthesize neurotransmitters that control mood, cognition, and immunity. Tryptophan, a precursor to serotonin, affects mood and sleep, whereas tyrosine produces catecholamines that affect stress response and cognition. Glutamine boosts immunity and intestinal health. Thus, appropriate amino acid consumption is essential for physical performance and mental and emotional health. (Xu, Ji, Jin, & Chen, 2023). In conclusion, amino acids, especially BCAAs, affect muscle metabolism, glucose control, immunological function, and cognitive health. The body can get these amino acids from animal- and plant-based foods. People may satisfy their amino acid needs and stay healthy by eating a balanced diet with a range of protein sources. According to the study, the body's amino acid balance is fragile, and excess BCAAs may harm insulin sensitivity and metabolic health. To obtain their full advantages, amino acids must be used in moderation and within a balanced diet and lifestyle (Rehman, Ali, Zhang, Zafar, & Wang, 2023).

Amino acid needs vary by age, sex, physical activity, and health. Infants, children, and pregnant women require more protein and amino acids for growth, development, and fetal health. Athletes and intense exercisers may need more BCAAS like leucine, isoleucine, and valine for muscle repair and recovery. Due to protein synthesis for immune response and tissue repair, amino acid needs might rise during sickness. These circumstances may need amino acid or protein supplements to satisfy the requirements (Ling et al., 2023).

Despite their significance, amino acids must be balanced for health. Amino acid overload, especially from supplements, may disrupt metabolism. Excess methionine, a methylation amino acid, may raise cardiovascular disease risk. Amino acid imbalances may also impair nutrition absorption or cause toxicity. To avoid health issues, amino acids must be consumed within the prescribed diet. For those with metabolic diseases like phenylketonuria (PKU), which causes harmful amino acid buildups, this equilibrium is crucial (Ling et al., 2023).

- **Essential vs Non-Essential Amino Acids: What You Need to Know**

Lack of these important amino acids in meals may affect development, immunological function, and muscle repair. The body may synthesize non-essential amino acids from other amino acids or metabolic intermediates. Include alanine, asparagine, aspartate, glutamine, serine, and others. Even though the body produces these amino acids are essential to cellular function. For instance, glutamine is necessary for gut and immunological function. The body needs essential amino acids and other nutrients like vitamins and minerals to generate non-essential amino acids, but they do not have to be eaten (Khadka, 2021).

In disease, stress, or fast development cases, the body may not manufacture enough non-essential amino acids, making food more crucial. A balanced diet, including necessary and non-essential amino acids, is needed for good health (Khadka, 2021).

- **Amino Acids and Muscle Health: Implications for Athletes**

During muscle protein synthesis and post-workout recuperation, BCAAs are absorbed in muscle instead of the liver. Leucine triggers the muscle-growth-regulating mTOR pathway, according to research. This activation speeds up muscle protein synthesis, which is essential for muscle repair and rebuilding following exercise (Elsamman, 2024).

Before and after exercise, athletes should consume enough amino acids, especially BCAAs, to decrease muscle breakdown and speed recovery. Besides muscle regeneration, amino acids give energy during extended activity. Gluconeogenesis converts amino acids into glucose for muscular activity when glycogen levels are low. Amino acids fuel endurance events and extensive training periods. After strenuous exercise, glutamine helps the immune system, which might be impaired (Plotkin et al., 2021).

Too few amino acids may impede muscle recovery, promote atrophy, and increase injury risk. Without amino acids from food or supplementation, athletes may lose performance and muscle mass. Sports performance and muscle integrity depend on amino acid knowledge and a balanced diet and supplement regimen (Ling et al., 2023).

- **Amino Acids in Disease Prevention and Treatment**

Amino acids control metabolism, cellular function, tissue repair, and immunity. Growth, development, disease prevention, and treatment depend on them. Ample supplementation may prevent or mitigate many health disorders caused by amino acid

deficits or imbalances. Know amino acids in sickness prevention and treatment to promote health, notably in protein metabolism, immunological function, and tissue repair (Ling et al., 2023).

Protein synthesis, which regenerates cells and fights infection, needs amino acids. The body requires extra protein when unwell or stressed. Cancer, trauma, burns, and sepsis produce hypermetabolism, where protein breakdown exceeds synthesis, causing muscle loss, immune suppression, and delayed wound healing. These conditions need amino acid intake to restore protein balance and repair tissue. Glutamate, arginine, and BCAAs may improve protein production and reduce issues (Ling et al., 2023).

- **Immune Function and Recovery Amino Acids**

  BCAAs and others boost immunity: Antibodies, cytokines, and proteins are made from amino acids. Leucine, isoleucine, and valine improve immunity under stress, sickness, and exercise. Depletion of amino acids, especially BCAAs, may slow injury and infection recovery. BCAAs may directly affect immune cell development by affecting protein synthesis and growth. Leucine influences immune cell growth and function via activating mTOR. BCAAs after heavy exertion or illness may boost immunity. Glutamine synthesis from amino acids protects the intestinal barrier, the body's main pathogen defense (Aquilani et al., 2021). Glutamate deprivation in severe sickness or stress may harm the immune system. Lack of glutamine may decrease intestinal barrier function and increase infection risk. Under physical stress, glutamine is needed for immunological activation. Nitric oxide from arginine boosts blood flow and reduces inflammation. Nitric oxide is needed for infection-fighting macrophages and T-cells. If arginine levels are low, immune cells may not fight infections. Immune function is more dependent on amino acids, especially BCAAs, following injury or hard exercise (Li & Wu, 2022).

  After hard exercise or injury, the immune system repairs muscle tissue. BCAAs, especially leucine, are needed for muscle protein synthesis and tissue repair. Leucine activates mTOR, which helps immune cells repair and grow muscle. Muscle discomfort and poor recovery may result from BCAA insufficiency. For athletes and wounded persons, optimum amino acid intake may speed healing and prevent infection. Infections and surgeries promote protein catabolism and amino acid depletion. BCAAs and glutamine may boost immunity and recovery. The immune system needs amino acids to make acute-phase proteins and activate immune cells during inflammation. Inflammation and healing may be prolonged by

malnutrition. BCAA supplements boost immunity, prevent muscle atrophy, and expedite surgery and trauma recovery (Qin et al., 2024).

In critical care, amino acid supplementation improves outcomes after major procedures or severe illnesses. Amino acids maintain cell structure, immune function, and healing. For wound healing and tissue regeneration, collagen contains proline and glycine. So amino acids are necessary for immune function and damage healing. Low amino acid levels impede collagen and protein production, reducing healing and increasing infection risk. In conclusion, amino acids, especially BCAAs, affect the immune, tissue repair, and muscle recovery proteins and molecules. Amino acids are essential for immune system function, especially under stress, disease, or injury. Imbalanced amino acids impede healing, increase infection risk, and lower immunity. Immunity and healing need adequate amino acid intake (Baakhtari et al., 2022).

- **Metabolic Disorder Amino Acids**

Amino acids, especially BCAAs, regulate metabolic processes, and their dysregulation is linked to obesity, insulin resistance, type 2 diabetes, and cardiovascular disease. Protein synthesis and energy, glucose, and lipid homeostasis biochemical processes depend on amino acids. BCAAs leucine, isoleucine, and valine help muscles heal, synthesize protein, and provide energy during exercise. However, metabolic diseases change BCAA metabolism, which is concerning (Russin, Nair, Montine, Baker, & Craft, 2021).

This change may raise blood glucose and cause type 2 diabetes. Lipid intermediates, including diacylglycerols and ceramides, which increase insulin resistance, may also accumulate in obesity due to impaired BCAA metabolism. However, lowering BCAA consumption or recovering their metabolism may enhance insulin sensitivity and glucose metabolism, reducing the risk of diabetes and other disorders. BCAA catabolism may be inhibited by enzymes like BCKDH, a therapeutic target for metabolic disorders. Therefore, amino acid equilibrium is essential for metabolic illness prevention and treatment (Cuomo, Capparelli, Iannelli, & Iannelli, 2022).

- **Treatment of Cancer with Amino Acids**

Amino acids, especially BCAAs, affect tumor development, metastasis, and therapeutic response. Essential amino acids leucine, isoleucine, and valine are

important in protein synthesis, energy metabolism, and cellular signaling. Tumorigenesis alters amino acid metabolism, and cancer cells frequently need more amino acids to grow and survive. BCAAs promote the mTOR signaling system, which controls cell growth, proliferation, and survival in cancer. The mTOR pathway is strictly controlled in normal cells but dysregulated in cancer cells, encouraging uncontrollable tumor development (Ling et al., 2023).

BCAA modulation or reduction may inhibit the mTOR pathway, reducing cancer cell growth and boosting cancer therapy effectiveness. BCAA restriction inhibits cancer cell proliferation and improves chemotherapy and radiation treatment. Conversely, high BCAA consumption may stimulate tumor development by activating mTOR signaling, indicating that BCAA balance is essential for cancer control. BCAAs also regulate immunological responses, which is important for cancer therapy. BCAAs may boost immunological activity, helping the body fight malignant cells, especially in immunotherapies. Cancer and chemotherapy may cause muscle atrophy. Thus, amino acid supplements may help. Thus, properly controlling BCAA levels may prevent tumor development and aid recovery following cancer treatment (Xu et al., 2023).

- **Amino Acids for Cardiovascular Health**

  Metabolic illnesses alter BCAA metabolism, which is worrisome. Plasma BCAA levels rise with obesity and insulin resistance, suggesting a link between BCAAs and metabolic diseases (Vanweert et al., 2022). High BCAA levels may alter insulin signaling, increasing insulin resistance and lowering muscle and liver glucose uptake. This alteration may promote type 2 diabetes by raising blood glucose. Obesity may develop insulin-resistant lipid intermediates such as diacylglycerols and ceramides owing to poor BCAA metabolism. Reducing BCAA intake or recovering their metabolism may improve insulin sensitivity and glucose metabolism, decreasing the risk of diabetes and other diseases. BCKDH enzymes may block BCAA catabolism, making them a metabolic disease treatment target. Thus, metabolic disease prevention and therapy need amino acid balance (Cuomo et al., 2022).

- **Neurodegenerative Amino Acids**

  BCAAs impact neurodegenerative disease therapy and development (Fu, Wang, Ren, Guo, & Han, 2024). BCAAs modulate mood, motor function, and

cognition by affecting serotonin and dopamine production and release. BCAA alterations may create neurotransmitter abnormalities, leading to cognitive and motor loss in neurodegenerative illnesses. BCAA metabolism affects mTOR, which may aggravate dementia (Vanweert et al., 2022).

BCAA excess may activate the mTOR pathway, generating neuronal stimulation, oxidative stress, and neurodegeneration. Minimal BCAA and mTOR activation may protect neurons by increasing cellular repair and autophagy, which removes damaged proteins and organelles. BCAAs control the BBB and supply nutrients and metabolites to the brain (Liu, Zhang, & You, 2023). Neurotoxins infiltrate and damage neurons via BBB disruption in neurodegenerative diseases. BCAA metabolism in these illnesses may disrupt the BBB, exacerbating neuroinflammation and toxic protein accumulation, such as amyloid-beta in Alzheimer's and alpha-synuclein in Parkinson's. BCAA supplementation may prevent neurodegeneration by changing neurotransmitter levels, decreasing oxidative stress, and repairing neurons. BDNF production supports neurogenesis and synaptic plasticity, and BCAAs may alter it. Ample BCAA intake may promote BDNF synthesis and prevent neurodegenerative diseases since low BDNF levels are connected to cognitive decline and neuronal death (Terburgh, Coetzer, Lindeque, van der Westhuizen, & Louw, 2021).

In neurodegenerative diseases, amino acids, particularly BCAAs, impact neurotransmitter balance, mTOR signaling, blood-brain barrier integrity, and neuronal repair pathways, making their role convoluted but critical. So, regulating BCAA levels and pathways may provide new methods to reduce neurodegenerative illness and improve quality of life. If handled properly, BCAA metabolism may stop neurodegeneration, alleviate symptoms, and maintain the brain (Ragni et al., 2023).

CONCLUSION

Protein synthesis, metabolism, and immunity rely on amino acids, notably BCAAs. Their roles in muscle regeneration, neurotransmitter synthesis, and energy production are crucial to metabolism. Amino acid metabolism anomalies may induce insulin resistance, obesity, CVD, and neurological diseases. Insulin resistance and type 2 diabetes are linked to high BCAA levels. Amino acid deficiencies or excesses may aggravate Alzheimer's and Parkinson's. Amino acid equilibrium is being studied for health and chronic disease prevention. BCAA catabolism regulation, notably via BCKDH enzymes, may cure metabolic

diseases. However, amino acids may increase exercise recovery, modify immune function, and maintain muscle mass in persons under extreme physical stress or cancer treatment. We will study amino acid metabolism and how targeted diets and supplements may prevent or cure metabolic diseases, aging, and other health difficulties. In conclusion, amino acid intake and metabolism must be balanced for optimal health, and further research is needed to identify their therapeutic significance.

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