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Review

Branched-chain amino acids in obesity and diabetes: Implications and insights

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Abstract

Branched-chain amino acids (BCAAs), such as leucine, isoleucine, and valine, are vital in metabolic processes and in regulating energy equilibrium. In obesity and diabetes, BCAAs have been implicated in various metabolic dysfunctions, such as insulin resistance and altered glucose metabolism. Elevated BCAA levels are often observed in individuals with these conditions, suggesting a potential link between BCAA metabolism and the etiology of obesity and diabetes. Understanding the implications of BCAAs in these disorders could provide insights into novel therapeutic strategies to improve metabolic health and manage these chronic diseases. Previous reviews on BCAAs in the context of obesity and diabetes have often lacked a comprehensive analysis of their dual role in metabolic pathways. These reviews have focused solely on their positive effects, such as muscle protein synthesis, or potential negative impacts, like insulin resistance. Considering recent research findings and clinical studies, a thorough evaluation of the nuanced effects of BCAAs is necessary. This review seeks to fill these gaps by offering an impartial viewpoint on the metabolic consequences of BCAAs in individuals with obesity and diabetes, highlighting areas for future research and covering the metabolic role of BCAAs, their impact on feed intake patterns, and biochemical insights into BCAA metabolism. The review also delves into leucine's role in diabetes, examining its therapeutic potential and clinical implications. It also investigates mechanisms linking BCAAs to insulin resistance and BCAAs' relationship to mitochondrial dysfunction in obesity, providing a comprehensive understanding of BCAAs' metabolic effects. Given the rising prevalence of obesity and diabetes, this review is crucial for informing therapeutic strategies and identifying areas for future research.

Keywords: Branched-chain amino acids (BCAAs), diabetes, insulin resistance, metabolic dysfunction, obesity, therapeutic strategies

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Although branched-chain amino acids (BCAAs) were initially identified and thoroughly examined in the late 1800s, it is only within the last two decades that their significance in several areas of health and illnesses has become evident. Scientists have begun to reveal the functions of BCAAs that go beyond the processes of protein synthesis and breakdown. Leucine, isoleucine, and valine are examples of BCAAs. Mammals cannot synthesize BCAAs endogenously and rely on obtaining them from their

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nutritional intake. Compelling evidence indicates that bacteria found in the human microbiome can produce BCAAs [1]. These amino acids act as biomarkers for several disorders and conditions, including type 2 diabetes (T2D), obesity (OB), cardiovascular diseases (CVD), and some forms of cancer. Their metabolites can regulate gene expression and the epigenome [2].

BCAAs are essential to a comprehensive and balanced diet. Leucine is the main component of protein. Isoleucine and valine provide carbon atoms for the process of glucose synthesis. The catabolism of BCAAs provides the necessary fuel for the tricarboxylic acid cycle, thereby supplying cells with energy. Leucine, an intracellular amino acid, stimulates the rapamycin complex 1 (mTORC1) activation [3]. This intricate structure performs a pivotal function in regulating cellular growth and metabolism. The organism detects signals from nutrient and energy sources and stimulates cellular development when sufficient resources are present. However, it also stimulates catabolism in the absence of food.

Primarily, the liver is responsible for the breakdown of amino acids via a process known as degradation [4]. However, the liver cannot synthesize the branched-chain aminotransferase (BCAT) enzyme, which is essential for the transamination process of BCAAs [5]. As a result, BCAAs are absorbed directly from the gastrointestinal tract into the bloodstream. This partially explains the rapid fluctuation in blood levels of BCAAs, which depends on diet and the pace of protein synthesis or breakdown. BCAA concentration significantly impacts several physiological processes, including the creation of new mitochondria, energy production, inflammation, and glycolysis [6].

BCAAs, particularly leucine, stimulate protein synthesis initiation and rely on the activation of the mTOR signaling pathway [7]. Consequently, there has been an increase in the use of BCAAs as supplementary substances to augment performance and stimulate muscle development among bodybuilders and those striving to boost their physical fitness. The precise impacts of BCAAs when consumed in isolation or in the presence of other crucial amino acids or hormones still need to be understood [8]. BCAAs are essential for preserving the structural integrity and functionality of proteins and muscles. The favorable effects of BCAA supplementation on protein turnover and the prevention of muscle loss can be demonstrated in individuals with cirrhosis, renal failure, hepatic malignancies, and sepsis. Moreover, BCAAs are crucial as dietary cues and metabolic regulators alongside their anabolic response (Fig. 1).

BCAA

BCAAs enhance insulin production by modulating proteins and transcription in pancreatic β-cells [9]. In addition, they can regulate fatty tissue metabolism [10] and maintain glucose homeostasis [11]. They also enhance the growth and well-being of the intestines, boost milk supply from the mammary gland, support immunological function, and alter the composition and activities of gut microorganisms. The comprehensive examination of the metabolic and health benefits of consuming BCAAs has been explored in earlier research articles [12].

Preliminary research has shown that, unlike other amino acids, BCAAs can circumvent the liver and reach the bloodstream directly. The liver lacks the enzyme BCAT (branched-chain aminotransferase), which is responsible for breaking down BCAAs [13]. Conversely, the enzyme BCAT converts amino acids into branched-chain keto acids (BCKAs) in organs such as skeletal muscle, kidneys, heart, and adipose tissue. These BCKAs are then released into the circulation and mostly absorbed by the liver for oxidation. The enzyme complex known as branched-chain α-keto acid dehydrogenase (BCKDH) is essential for facilitating the oxidation process. Following synthesis, acyl-coenzyme A (acyl-CoA) undergoes oxidation via a sequence of enzymes, forming succinyl-CoA or acyl-CoA. These molecules enter the tricarboxylic acid cycle to produce adenosine triphosphate (ATP) [14].

McGarrah [15] recently reported research employing *in vivo* isotopic tracing to demonstrate that several peripheral or-

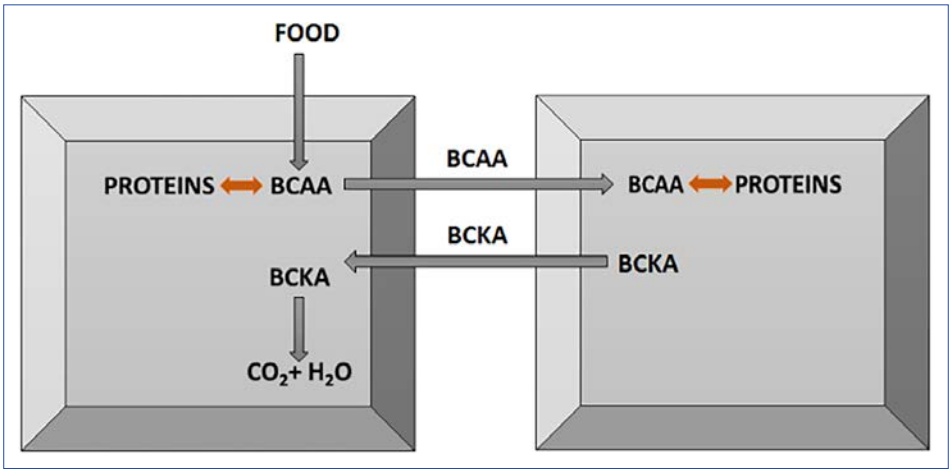

Figure 1. Pathways of BCAA catabolism.

BCAA: Branched-chain amino acid; BCKA: Branched-chain keto acid.

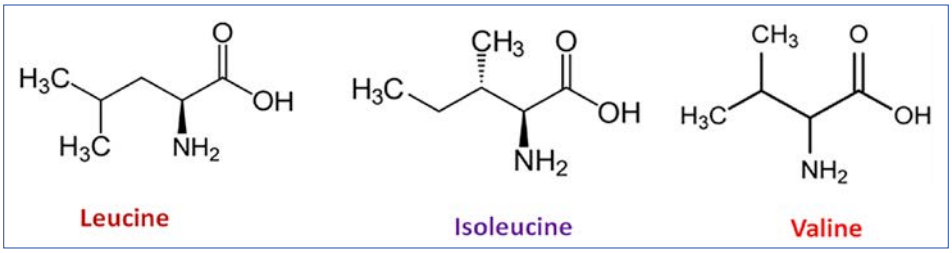

Figure 2. Branched chain amino acids.

gans have the potential to metabolize BCAAs. These findings suggest that organs other than the liver may significantly influence BCAA metabolism.

The liver and muscles primarily store glucose and fatty acids, which are used in substantial amounts as glycogen. Conversely, white adipose tissue stores them in the form of triglycerides. Amino acids, including BCAAs, are not converted into protein for subsequent use. Therefore, the only method of controlling excessive BCAAs is through their catabolic route [16]. The importance of BCAA catabolism is evident in people with inherited metabolic deficiencies, such as those with maple syrup urine disease [17]. This rare genetic disorder occurs when mutations in the BCKDH enzyme complex are inherited in an autosomal recessive manner. The human body cannot digest BCAAs, resulting in abnormally high amounts of BCAAs and BCKAs in the bloodstream. Consequently, these individuals suffer from hypotonia and ketoacidosis, along with severe neurological problems such as developmental delay, hallucinations, seizures, and coma [18].

Type 2 diabetes (T2D) is a very common global condition that is closely linked to the widespread problem of obesity. Obesity may lead to T2D, which occurs when pancreatic β-cells do not produce enough insulin to compensate for the decreased insulin sensitivity often associated with obesity.

In recent years, there has been a growing recognition of the significance of BCAA breakdown in the development of insulin resistance in individuals with obesity and T2D [19]. BCAA concentrations are markedly elevated in the plasma and tissues of these individuals. Furthermore, a significant association exists between elevated levels of BCAAs in the circulatory system and the development of insulin resistance in people with obesity and T2D [20]. The reasons for these high levels of BCAAs and their association with insulin resistance remain unclear. However, a dysfunctional breakdown of BCAAs might be a contributing factor.

Multiple studies have investigated the circulation levels of BCAAs in persons with obesity and T2D. However, more research is needed on the importance of dietary BCAAs for metabolic diseases and their impact on circulating BCAA levels [21]. Circulating BCAAs may increase negative feedback signaling by activating mammalian target of rapamycin (mTOR), which leads to insulin resistance and poor glucose metabolism [22].

Furthermore, epidemiological studies conducted on several demographic groups have shown a negative correlation between increased BCAA consumption and the risk of obesity. This review seeks to understand the processes behind elevated BCAA levels in obese individuals with T2D. It is important to consider their role in the development of insulin resistance. Moreover, this review examines pharmacological and alternative lifestyle intervention options to reduce plasma BCAA levels and their impact on metabolic health.

Metabolic Significance of BCAAs

BCAAs, the amino acids leucine, isoleucine, and valine, are important in several metabolic processes. The human body cannot produce these crucial amino acids, so they must be acquired via diet. BCAAs are distinct from other amino acids as they are mostly broken down in the muscle rather than the liver [23]. This highlights their important function in muscle protein synthesis and energy generation. Leucine has a vital role in regulating the mechanistic target of the rapamycin (mTOR) pathway, which is essential for the synthesis of muscle proteins. Leucine is vital in promoting muscle tissue development and repair by activating mTOR [24], making it essential for athletes and individuals involved in resistance training.

Furthermore, BCAAs are essential for extended physical activity, particularly when glycogen reserves are exhausted. This function aids in preserving muscle mass and alleviating muscular fatigue. In addition to their role in muscle metabolism, BCAAs impact glucose metabolism and insulin sensitivity. Studies have shown that they can regulate insulin released by pancreatic beta cells, which is essential in controlling blood glucose levels [25]. Increased concentrations of BCAAs have been linked to insulin resistance, a condition frequently seen in individuals with obesity and T2D. This paradox implies that while BCAAs are essential for regular metabolic functioning, their imbalance may lead to metabolic diseases.

BCAAs also have a role in the production of neurotransmitters by traversing the blood-brain barrier and impacting brain activity [26]. They compete with aromatic amino acids, such as tryptophan, for transportation into the brain, which may influence the production of neurotransmitters like serotonin. This interaction could affect mood and cognitive function.

Moreover, BCAAs regulate lipid metabolism. They can affect the expression of genes involved in lipid production and breakdown, impacting overall metabolic health. BCAAs are crucial in dietary strategies for managing obesity and metabolic diseases (Fig. 2). Understanding their complex meta-

bolic processes is essential for developing effective dietary and pharmacological therapies. Elevated amounts of BCAAs, tyrosine, and phenylalanine, accompanied by decreased levels of glycine, have been linked to insulin resistance (IR) in individuals with obesity [27].

A study examining blood samples from individuals with obesity and insulin resistance, as opposed to those who are lean and have insulin sensitivity, has shown a significant association between elevated levels of BCAAs and IR [28]. Studies have also shown that fatty acids and their byproducts contribute to the onset of IR and T2D [29]. Studies on mice have demonstrated that the addition of BCAAs to a standard chow (SC) diet does not affect insulin levels. However, adding BCAAs to a high-fat diet (HFD) causes obesity and IR to develop [30]. These studies indicate that the presence of both BCAAs and lipids is required for the development of insulin resistance.

Research on an animal model of obesity found that the buildup of acyl-carnitine and acyl-CoA in muscles is caused by the incomplete breakdown of fatty acids and an excessive burden on the mitochondria [31]. An abundance of BCAAs leads to increased mitochondrial activity, altering lipid metabolism. Based on current understanding, a diet lacking in BCAAs may enhance the body's capacity to metabolize fats [32]. This process entails activating the general control nonderepressible 2 (GCN2) gene, which inhibits the expression of genes linked to fat creation and protein synthesis. Moreover, it restores glycine levels in the muscle to their initial condition and promotes acyl-glycine production. Excreting acyl-glycine helps decrease acyl-CoA concentrations.

The skeletal muscle of animal models with insulin resistance exhibits incompletely esterified lipids, namely acyl-carnitine and diacylglycerol [33]. IR may be caused by an overabundance of catabolic byproducts of BCAAs and the buildup of partially esterified lipids in the muscle [34]. Lipotoxicity occurs when lipids accumulate, leading to glucose intolerance, IR, and, ultimately, the onset of T2D. Metabolomics has also shown that elevated levels of BCAAs in the bloodstream may serve as an early indicator of the onset of T2D. Bariatric surgery results in a rapid reduction in BCAAs and aromatic amino acids (AAAs) [35]. Conversely, elevated amounts of BCAAs, AAAs, and their byproducts in pregnant women affect the amount of fat in the fetus [36]. Mendelian randomization research determined that BCAAs are causally linked to insulin resistance (IR) [37].

A hypothesis has been proposed suggesting that hypothalamic IR negatively affects BCAA metabolism in patients with T2D and obesity. These findings indicate that increased plasma BCAAs are a sign of insulin resistance in the hypothalamus rather than the primary source of insulin resistance in peripheral tissues [38]. Two comprehensive human studies have shown that consuming a large amount of BCAAs is associated with a higher likelihood of developing T2D [39]. The variations in results may be explained by the fact that some research examined the combined effects of all three BCAAs, while others specifically investigated the impact of leucine alone.

A recent study has shown that each BCAA has unique effects on metabolism. The three BCAAs activate mTORC1, an essential metabolic regulator, via separate mechanisms. After translation, they also modify various proteins, generating diverse intermediates and ultimate catabolic products [40]. Studies on leucine and isoleucine have shown that they enhance insulin sensitivity and facilitate the transformation of white adipose tissue (WAT) into brown adipose tissue in obese mice [41]. Leucine supplementation in obese individuals promotes weight reduction, decreases inflammation in WAT, and enhances mitochondrial function.

Currently, there is significant attention being given to the use of leucine supplementation as a potential therapy for T2D and obesity. A comprehensive investigation in this area [42] found that although the administration of leucine directly into the central nervous system reduces food consumption, this outcome is not consistently replicated. Ongoing research is focused on developing methods to more effectively analyze the many variables (such as nutrition, gut flora, and physical activity) that impact BCAA metabolism [43]. Therefore, it is reasonable to expect that leucine may soon be used for medicinal purposes.

Individuals diagnosed with T2D have increased skeletal muscle amounts of BCAAs and enhanced activation of the mTORC1/S6K1 pathway [44]. These patients exhibit defective insulin signaling through reduced activity of PI3K/Akt, resulting in insulin resistance [45]. The inadequate nourishment of muscle fibers may account for this behavior, as glucose absorption is suppressed due to the presence of leucine. Consequently, this impedes the insulin signaling pathway by inducing an elevation in S6K1 phosphorylation.

Furthermore, KIC, which results from the breakdown of leucine, has similar activity, suggesting that the suppression of insulin function is linked to an elevation in S6K1 phosphorylation [46]. The impact of this metabolite, known as KIC, is diminished in cells with a decreased abundance of BCAT2. The metabolite undergoes an additional conversion into leucine, which allows it to consistently hinder the entry of glucose into cells. Confirming these findings, skeletal muscles that lack the BCKDH enzyme exhibit decreased glucose absorption, whereas the phosphorylation status of S6K1 remains unchanged [47]. This suggests an alternative mechanism for impeding the activity of insulin [48].

The findings suggest that increased levels of the metabolite 3-hydroxybutyrate, produced when valine is broken down, play a role in insulin resistance by causing an abnormal buildup of fatty acids in skeletal muscles. Based on this discovery, limiting the intake of BCAAs in Zucker rats enhances insulin efficiency in skeletal muscle and simultaneously promotes the degradation of fatty acids [49]. While elevated levels of BCAAs have been associated with IR, athletes who follow diets abundant in BCAAs do not exhibit indications of IR [50]. This apparent paradox may be explained by the fact that athletes consume a significant amount of BCAAs via their diet, preventing the accumulation of BCAAs in their bodies.

BCAA on Dietary Intake Patterns

Multiple studies have shown the inhibitory impact of intravenous leucine infusion on feed consumption [51]. The mTOR signaling pathway is crucial in the brain for detecting nutritional availability and controlling energy balance. Yao et al. [52] experimented on rats and demonstrated that mTOR signaling in some areas of the hypothalamus is regulated by energy levels. They also found that mTOR signaling is present in the same locations as neurons in the arcuate nucleus, including neuropeptide Y and proopiomelanocortin [53].

However, the effect of leucine on food consumption varies depending on whether it is administered through the diet. Multiple experiments have shown that augmenting the diet with more leucine does not lead to increased feed consumption in animals. The varying outcomes observed when comparing oral and central leucine supplementation may be attributed to leucine's capacity to infiltrate the blood-brain barrier and access the central nervous system [54]. While additional BCAA supplementation in the diet did not increase feed consumption, it is important to acknowledge the role of a BCAA-deficient diet in reducing feed intake.

Biochemical Pathways into BCAA Metabolism

The link between BCAAs and obesity has recently been reaffirmed and confirmed by many studies using high-throughput metabolomics analysis [55]. Following the rise in the popularity of BCAAs, it was shown that plasma BCAAs and their derived intermediates, BCKAs, are not only elevated in individuals with insulin resistance or T2D, but they also act as dependable indicators for future susceptibility to these conditions, regardless of age and ethnicity [56].

Recent findings suggest that BCAAs or BCKAs are linked to the excessive stimulation of mTOR signaling, the production of oxidative stress, compromised mitochondrial function, apoptosis, and, importantly, the development of insulin resistance and poor glucose metabolism. These components are essential for the onset of diabetes. These findings are corroborated by the observation that including BCAAs in a high-fat diet (HFD) or inhibiting BCAA oxidation by eliminating methylmalonyl-CoA mutase in mice results in IR and decreased glucose tolerance. In a recent study, Nilsen et al. [57] showed that individuals with diabetes had higher amounts of 3-hydroxybutyrate, a valine catabolic precursor. This compound was found to enhance the transit of fatty acids in the blood vessels of muscles, resulting in reduced glucose tolerance in mice.

Ketoisocaproic acid, a byproduct of leucine metabolism, hinders the transportation of glucose triggered by insulin in L6 myotubes [58]. On the other hand, if BCAAs are removed from the regular chow diet or HFD in mice, or if a diet with lower amounts of all three BCAAs is provided to genetically diabetic Zucker fatty rats, insulin sensitivity improves and blood sugar levels are better regulated [59].

In a subsequent investigation, White et al. [22] confirmed these results by demonstrating an 80% reduction in glucose intolerance and insulin resistance when rats were exposed to BCAAs in a Western diet for four weeks. Studies have shown that drinking water with BCAA metabolites may decrease the active form of AKT (pAKT), which indicates insulin signaling in muscle [60]. Zhou et al. [61] demonstrated that supplementing an HFD with BCAAs leads to a decrease in pAKT levels and an increase in mTOR signaling activation in skeletal muscle compared to combining BCAAs with a conventional diet or HFD alone. Consequently, this results in a decline in the body's capacity to efficiently metabolize glucose.

Corroborating these findings, the absence of BCAAs in mice leads to elevated levels of pAKT in the liver and improved insulin sensitivity. This study provides evidence supporting the idea that BCAAs are not only associated with but also have a causative impact on the advancement of fat buildup, insulin resistance, and diabetes. The inhibition of the AKT signaling pathway in insulin-sensitive tissues may explain this behavior. The metabolic profiles derived from targeted and untargeted metabolomics approaches used to characterize obesity and insulin resistance indicate decreased BCKD activity in humans.

Cysteine is produced during the breakdown of cystathionine, which is formed from methionine/homocysteine by the action of cystathionase [62]. α-KB may also be generated from threonine through the activity of threonine hydratase. The liver BCKD, after partial purification, effectively catalyzes the oxidation of α-KB, resulting in propionyl-CoA production. This process is almost equivalent to the oxidation of BCAA-derived BCKA by the liver BCKD. α-KB can competitively inhibit the oxidation of BCKA by rat liver mitochondria and vice versa.

PDH similarly affects α-KB, while BCKD seems to have greater importance [63]. This is because, unlike pyruvate, the degradation of an α-ketobutyrate precursor known as α-aminobutyrate was not observed in fibroblasts derived from individuals with PDH deficiency [64]. The binding affinity of α-KB for partially purified PDH is four to five times lower than that of BCKD [65]. Thus, BCKD functions as the primary α-KB dehydrogenase.

This hypothesis is supported by the discovery that α-KB is one of the organic acids that acts as an indicator for maple syrup urine disease, a disorder caused by a defective BCKD complex, diagnosed by detecting increased levels of BCAAs in the blood or urine. Individuals with obesity and insulin resistance may have elevated levels of α-KB and its derivative, α-HB, due to reduced activity of BCKD (which is formed when LDH acts on α-KB), along with increased concentrations of BCAAs in the bloodstream. Theoretically, a biochemical obstruction at BCKD would lead to higher levels of methionine and cysteine-cystine upstream, resulting in greater concentrations of these compounds in the blood or tissues.

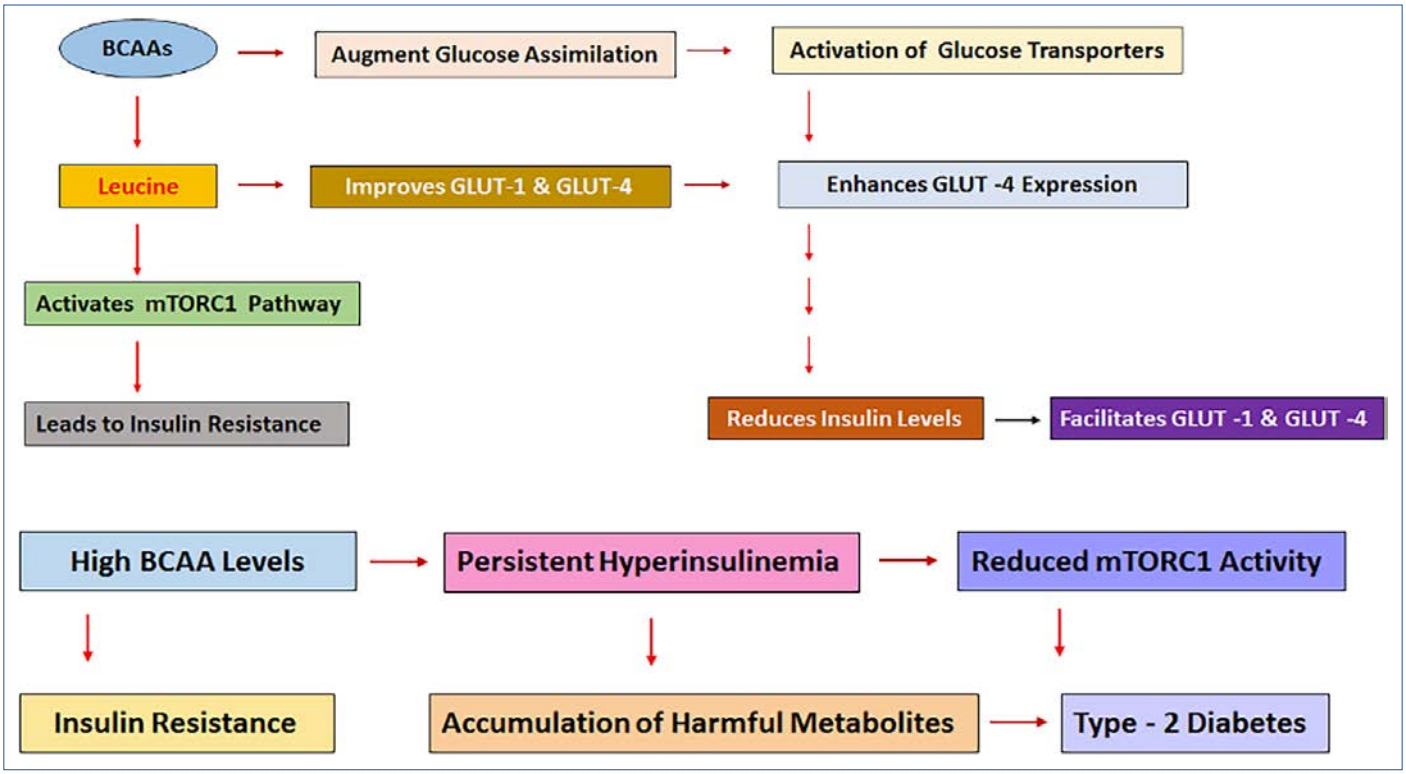

Figure 3. Leucine for diabetes treatment.

BCAAs: Branched-chain amino acids; GLUT: Glucose transporter; mTORC1: Rapamycin complex 1.

Leucine and Its Implications for Diabetes Treatment

Branched-chain amino acids (BCAAs) can augment the absorption and utilization of glucose. Amino acids can enhance glucose assimilation by activating glucose transporters. Leucine improves glucose absorption by facilitating the transportation of glucose transporter 1 (GLUT-1) and glucose transporter 4 (GLUT-4). Leucine may also enhance the expression of GLUT-4 [66]. Two theories explain the correlation between leucine and glucose transporters. One theory suggests that leucine reduces insulin levels and enhances the movement of GLUT-1 and GLUT-4. According to the second theory, leucine enhances glucose absorption in skeletal muscle by activating pathways related to GLUT-4 movement [67].

A strong correlation exists between insulin resistance and elevated levels of BCAAs, as reported in a study examining BCAA concentrations [68]. Studies have demonstrated the efficacy of BCAAs in stimulating insulin release. More specifically, leucine can induce the release of insulin. The presence of high amounts of BCAAs contributes to the onset of persistent hyperinsulinemia by fostering insulin resistance. Cuomo et al. [69] showed that consuming a diet deficient in BCAAs may improve insulin resistance. Similarly, Kim (2023) reported that dietary supplementation with leucine enhances glucose regulation in the body [70].

BCAAs in the blood are linked to insulin receptor substrate-1, which leads to insulin resistance and impaired glucose metabolism [71, 72]. BCAAs can enhance the expression of glucose transporters and stimulate insulin release [73, 74]. Elevated concentrations of these amino acids inside the body activate mechanistic target of rapamycin complex 1 (mTORC1) [75]. Activation of mTORC1 leads to reduced metabolic activity of BCAAs. This decrease is linked to the emergence of insulin resistance and type 2 diabetes, as it results in elevated BCAA levels in the blood and the accumulation of harmful metabolites.

Leucine is the principal amino acid with a branched chain that plays a crucial role in activating the mTORC signaling pathway. Li et al. [76] reported that leucine stimulates protein synthesis. Leucine, isoleucine, and valine may directly or indirectly affect metabolism (Fig. 3).

Clinical Perspectives on Therapeutic Potential

When managing a patient with cancer cachexia, potential treatment approaches may include implementing a diet low in protein to deprive the tumor of nutrients or a diet high in protein to alleviate the severe wasting associated with cachexia [77]. Several research studies have reported the effectiveness of targeted BCAA supplementation in preventing protein breakdown, promoting protein synthesis, and perhaps aiding in muscle repair, specifically for skeletal muscle [78]. Supplementing with BCAAs may enhance the body's protein synthesis needs while limiting the availability of amino acids for tumor growth. It is essential to assess the influence of BCAA supplementation on the progression

of insulin resistance during the formulation of treatment strategies. The insulin resistance was only detected within the framework of a high-fat diet. It indicates that the total nutritional condition of a person has a significant impact on the possibility of BCAA supplementation to cause diabetes. Branched-chain amino acid supplementation has been extensively studied for its therapeutic potential in treating advanced liver illnesses, namely hepatocellular carcinoma (HCC). Abe et al. [79] performed longitudinal research that focused on monitoring the progression of HCC in individuals with cirrhosis resulting from hepatitis C over several years. This study included a control cohort that received standard nutritional supplements and another administered with a BCAA supplement. The researchers noted a decrease in the incidence of HCC in the group that received BCAA. The Long Term Survival experiment (LOTUS) performed in Japan examined the impact of BCAA supplementation on the development of sequelae, including death, liver failure, and HCC, among those diagnosed with cirrhosis, as shown by a study involving 70 cases. The group that was administered BCAA saw a lower occurrence of problems when compared to the control diet. The hazard ratio was 0.67, with a 95% confidence range spanning from 0.49 to 0.93. By categorizing the participants based on their susceptibility to hepatocellular carcinoma (HCC), namely those with a body mass index over 25 kg/m2, it was shown that the inclusion of BCAA impeded the progression of HCC. Tsuchiya discovered that providing patients who had radical therapy for HCC with long-term BCAA supplementation led to a reduction in recurrence rates and an enhancement in the overall survival rate [80].

A recent study has shown that supplementing with BCAA in persons with liver cirrhosis significantly improved their insulin sensitivity and lowered hyperinsulinemia, hence decreasing the likelihood of developing HCC. BCAA supplementation is believed to decrease insulin resistance by improving the uptake of glucose by skeletal muscle independently of insulin and boosting the body's glucose tolerance [81]. A comparative study investigating the impacts of enteral feeding and BCAA supplementation in liver failure showed that BCAA supplementation enhanced the preservation of blood albumin levels, which act as a marker for protein synthesis [82]. A significant discovery in this research revealed that the group receiving enteral nourishment saw an elevation in glycated hemoglobin and other indicators that suggest a decrease in glucose tolerance. In contrast, no such changes were seen in the BCAA group. Thus, the elevated dietary intake of BCAAs does not have the same impact on glucose regulation as sustained increases. Recent *in-vitro* research has elucidated the specific mechanisms by which branched-chain amino acids affect liver metabolism and cancer.

Research investigating hepatic stellate cells discovered that the presence of leucine resulted in the increased release of hepatocyte growth factor (HGF) [83]. HGF is regarded as a pleiotropic factor synthesized by cells in several organs and affects cell growth, function, and motility [84]. HGF, triggered by leucine, can enhance the process of liver regeneration in cases of liver diseases such as HCC. Recent research on HepG2 cells showed that VEGF mRNA degradation occurred in the presence of all three branched-chain amino acids [85]. Administering BCAAs to persons with cirrhosis may decrease the occurrence of HCC by inhibiting the synthesis of vascular endothelial growth factor (VEGF). A recent study on H4IIE hepatic cancer cell lines demonstrated that BCAAs impeded the growth of cells stimulated by insulin [86]. The observed outcome was ascribed to an augmentation in apoptosis rather than a decrease in cellular proliferation.

Mechanisms Connecting BCAAs to Insulin Resistance

The precise processes by which BCAAs contribute to insulin resistance are complex and are currently being investigated. The buildup of harmful metabolites, such as BCKAs, produced during the breakdown of BCAAs may disrupt insulin signaling pathways by blocking crucial enzymes such as pyruvate dehydrogenase (PDH) and insulin receptor substrate (IRS) [87]. The interference mentioned may disturb the movement of glucose transporters to the cell's outer layer, decreasing glucose absorption and adding to high blood sugar levels. BCKAs can stimulate stress-related enzymes, such as the c-Jun N-terminal kinase (JNK) and mTOR, which might affect ins could. Another method is modifying the gut microbiota. BCAAs may affect the makeup and operation of gut bacteria, resulting in alterations in the production of microbial substances such as lipopolysaccharides (LPS) and short-chain fatty acids (SCFAs). High levels of LPS may trigger an inflammatory reaction by activating toll-like receptors (TLRs), which affects insulin resistance [88]. Conversely, any deviation in the synthesis of SCFAs could interfere with the secretion of hormones such as GLP-1 and PYY. These hormones are crucial for regulating insulin secretion and appetite [89]. Moreover, BCAAs are linked to increased adiposity and visceral fat buildup, both risk factors for insulin resistance. BCAAs stimulate lipogenesis and hinder fatty acid oxidation via stimulating the mTOR pathway and inhibiting AMP-activated protein kinase (AMPK). This simultaneous process might result in fat buildup and a decrease in the breakdown of fatty acids, which can contribute to metabolic disruptions. Comprehending these intricate connections is essential for creating specific therapies to alleviate the negative consequences of increased BCAAs in metabolic diseases.

Mitochondrial Dysfunction in Obesity: The Role of BCAAs

Metabolic illnesses, such as obesity and diabetes, are distinguished by the existence of mitochondrial dysfunction. Mitochondria are vital in generating energy, and their operation is critical for maintaining metabolic balance. BCAAs, which consist of leucine, isoleucine, and valine, have a cru-

cial impact on the generation and operation of mitochondria by acting as key substances for the TCA cycle. This process is crucial in cellular respiration since it generates the high-energy molecules ATP, NADH, and FADH2, vital for several biological functions. BCAAs have a role in the TCA cycle, which helps produce ATP, an essential molecule for energy-intensive actions, especially in muscle cells [90]. An abundance of BCAAs might result in mitochondrial overload, in which the mitochondria become overburdened by the excessive intake of metabolic substrates [91]. This excessive burden may lead to increased reactive oxygen species (ROS) produced due to cellular metabolism and have harmful effects. An overabundance of ROS may result in oxidative stress, which occurs when the body's antioxidant defense systems cannot counteract the formation of unstable molecules. Oxidative stress can damage mitochondrial DNA, proteins, and lipids, compromising mitochondrial function. Cell death may occur due to the dysfunction of mitochondria's energy synthesis and the initiation of apoptotic pathways. The accumulation of ROS and subsequent damage to the mitochondria may exacerbate metabolic inefficiency, contributing to insulin resistance development [92]. Insulin resistance refers to a condition in which cells have diminished responsiveness to insulin, hindering glucose absorption and causing an increase in blood glucose levels. Hence, it is crucial to appreciate the impact of BCAAs on mitochondrial health to understand their dual function in enhancing energy generation and possibly inducing metabolic damage. Acquiring this information might advance targeted dietary and pharmacological strategies to mitigate the adverse effects of BCAAs in metabolic diseases.

Conclusion

BCAAs, particularly leucine, isoleucine, and valine, are vital components of human metabolism, playing critical roles in muscle protein synthesis, energy production, and glucose metabolism. While their essentiality in maintaining muscle health and regulating metabolic processes is well-established, recent research highlights the complex and dual nature of BCAAs in health and disease. Elevated levels of BCAAs have been linked to the development of insulin resistance, obesity, and type 2 diabetes (T2D), suggesting that an imbalance in BCAA metabolism could contribute to metabolic disorders. The mechanistic insights reveal that BCAAs influence the mTOR signaling pathway, lipid metabolism, and insulin sensitivity, with potential implications for therapeutic strategies. However, the paradoxical relationship between BCAA supplementation determines the need for further investigation. Understanding the nuanced effects of BCAAs in different physiological contexts is crucial for developing targeted dietary and pharmacological interventions to optimize metabolic health. As research continues to unravel the intricacies of BCAA metabolism, it becomes evident that both their benefits and risks must be carefully considered, especially in the context of metabolic diseases such as T2D and obesity.

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