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Branched-chain amino acids and insulin resistance in type 2 diabetes: from metabolic dysregulation to therapeutic targets

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Branched-chain amino acids (BCAAs) are a class of amino acids characterized by a branched aliphatic side chain, and they play critical physiological roles in humans, including protein synthesis, metabolic regulation, and immune system maintenance. Beyond serving as fundamental building blocks for protein biosynthesis, BCAAs and their metabolites also function as signaling molecules that regulate a variety of physiological processes, notably insulin secretion. Accumulating evidence indicates that plasma BCAAs levels are markedly elevated in patients with type 2 diabetes (T2DM), a phenomenon that may result from impaired activity of key enzymes in the BCAAs catabolic pathway, leading to metabolic dysregulation. It is widely recognized that BCAAs can activate the mTOR signaling cascade, thereby affecting insulin receptor sensitivity. In addition, aberrant BCAAs metabolism has been closely linked to alterations in the gut microbiota, which may further aggravate insulin resistance (IR). Taken together, dysregulated BCAAs metabolism may represent a critical mechanism underlying IR in T2DM. Therefore, this review summarizes current knowledge on BCAAs metabolism, explores its potential roles in the pathogenesis of IR in T2DM, and highlights emerging therapeutic strategies to reduce IR by targeting BCAAs metabolism.

KEYWORDS

BCAAs, BCAAs metabolism, insulin resistance, mTOR signaling pathway, T2DM

1 Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by chronic hyperglycemia, primarily caused by insulin resistance (IR) and pancreatic β -cell dysfunction (1). IR is the state in which target cells exhibit reduced sensitivity to insulin, resulting in impaired glucose uptake and subsequent hyperglycemia (2). In parallel with the escalating obesity epidemic, the incidence of T2DM has risen steadily and is now regarded

as one of the most pressing global public health issues. Data from the World Health Organization (WHO) indicate that as of 2022, an estimated 828 million individuals aged 18 years and older were diagnosed with diabetes, with T2DM accounting for the vast majority of cases (3). The prevalence of T2DM has risen most strikingly in developed countries and emerging economies, creating profound impacts on personal health and placing considerable strain on families and healthcare systems.

At present, management of T2DM mainly involves drug therapy, nutritional and physical activity interventions. Drug-based therapies primarily include insulin sensitizers, DPP-4 inhibitors, and SGLT2 inhibitors, all of which improve insulin efficacy and facilitate glycemic control (4–6). Nutritional interventions focus on controlling caloric and carbohydrate intake, aiming to manage body weight and enhance insulin responsiveness (7, 8). Physical activity is strongly advocated because it stimulates fat metabolism and potentiates insulin function (9). Nevertheless, despite these treatment options, a substantial proportion of patients fail to attain adequate blood glucose control, and the risk of diabetes-associated complications continues to increase over time. Consequently, discovering new biomarkers and therapeutic targets, especially those involved in metabolic pathways, has emerged as a major area of contemporary investigation.

Branched-chain amino acids (BCAAs) have recently attracted increasing attention as a class of biologically important amino acids. Comprising leucine, isoleucine, and valine, BCAAs are essential amino acids acquired from the diet, involved in intracellular protein synthesis and energy homeostasis. A growing body of research demonstrates that BCAAs significantly contribute to diabetic metabolism, closely linking them to the development and progression of IR. In individuals with T2DM, circulating BCAAs concentrations are generally higher than in healthy populations, correlating strongly with IR, obesity, and other metabolic abnormalities (10). Experimental data indicate that BCAAs function beyond metabolic intermediates, potentially influencing insulin responsiveness via diverse mechanisms and aggravating IR. The interplay between BCAAs and IR involves intricate regulatory mechanisms. BCAAs engage in cellular growth and metabolic control through mTOR signaling, with hyperactivation of mTOR being strongly associated with IR (11). Moreover, metabolites derived from BCAAs, including α -keto acids and ketone bodies, may compromise β -cell functionality, resulting in diminished insulin output. In recent years, research has increasingly focused on the gut microbiota's involvement in BCAAs metabolism. Evidence suggests that imbalances in gut microbial composition can modulate BCAAs uptake and metabolic processing, indirectly impacting insulin signaling (12).

Although the reasons for elevated BCAAs levels and their association with IR remain unclear, dysfunctional BCAAs catabolism may represent one of the underlying factors. This review aims to provide an in-depth understanding of BCAAs metabolism and its potential role in the pathogenesis of IR in T2DM, as well as to summarize pharmacological and alternative

lifestyle interventions that reduce plasma BCAAs levels and their impact on metabolic health.

2 The relationship between IR and amino acid metabolism

IR was initially characterized in Himsworth's seminal studies (13). Early studies demonstrated that diabetic individuals showed divergent responses to glucose and insulin administration, with some maintaining stable or declining blood glucose and thus categorized as insulin-sensitive; whereas others exhibited marked hyperglycemia, reflecting insulin insensitivity or attenuated insulin responsiveness. This phenomenon typifies IR in metabolic syndrome, characterized by the inability of peripheral tissues to elicit an appropriate glucose-lowering response at normal circulating insulin concentrations, commonly termed reduced insulin sensitivity. Such insulin action encompasses the inhibition of hepatic glucose production, suppression of lipolysis, stimulation of glucose uptake, and augmentation of glycogen synthesis (14–18). IR predominantly impacts skeletal muscle, hepatic tissue, and white adipose depots (19). IR is commonly linked to impairments across multiple insulin signaling cascades, involving ectopic lipid deposition, mitochondrial dysfunction, and enhanced activation of stress-related kinases such as c-Jun N-terminal kinase (JNK) and pro-inflammatory pathways (20).

In recent years, dysregulation of BCAAs metabolism has received increasing attention in obesity-related disorders, including IR, T2D and cardiovascular diseases. A plasma metabolomic analysis comparing obese and lean individuals revealed significant differences in BCAAs-related metabolites, suggesting that enhanced BCAAs catabolism is associated with IR. This finding has been further validated in mouse plasma metabolomic studies (21–23). Moreover, in a prospective cohort study, targeted metabolomic analysis demonstrated that elevated levels of several amino acids, including BCAAs, were significantly associated with an increased risk of developing T2D (24). These findings indicate that BCAAs may serve as both biomarkers and key mediators in obesity and related metabolic disorders. In addition, a strong correlation has been observed between circulating BCAA levels and IR (25, 26). Furthermore, high BCAAs concentrations have been shown to impair insulin sensitivity and induce IR. In animal studies, acute elevation of circulating BCAAs led to increased blood glucose and insulin levels and significantly reduced whole-body insulin sensitivity during hyperinsulinemic-euglycemic clamp experiments, whereas lowering BCAAs levels improved glucose tolerance in obese mice (27). A randomized, double-blind study investigated the effect of modulating BCAAs metabolism on insulin sensitivity in 16 patients with mild to moderate T2D using sodium phenylbutyrate (NaPB), a drug that promotes BCAAs catabolism. The results showed that NaPB treatment significantly reduced plasma BCAAs levels and improved peripheral insulin sensitivity by approximately 27%, accompanied by enhanced skeletal muscle mitochondrial

oxidative capacity, increased glucose oxidation, and decreased blood glucose levels (28).

The two major mechanisms by which plasma BCAAs are related to IR are as follows: First, impaired mitochondrial BCAAs metabolism plays a critical role (29). Patients with T2DM exhibit higher plasma BCAAs levels compared to healthy individuals, while their mitochondrial oxidative capacity is markedly reduced (30). Elevated plasma BCAAs may result from diminished mitochondrial oxidative capacity, suggesting a close link between mitochondrial function and IR (31). When BCAAs metabolism is impaired, large amounts of BCAAs-derived metabolites (such as 3-hydroxyisobutyrate, 3-HIB) accumulate in plasma, which may exert toxic effects on cells and ultimately lead to IR (32). Reportedly, a community-based observational study including 15 patients with T2DM, 13 first-degree relatives (FDR), and 17 controls (CON, all overweight or obese) assessed muscle mitochondrial oxidative capacity using high-resolution respirometry, and in some participants combined hyperinsulinemic-euglycemic clamp with ^{13}C -leucine tracer to measure *in vivo* BCAAs oxidation. Results showed that plasma BCAAs levels in T2DM patients were higher than in controls and were significantly negatively correlated with muscle mitochondrial oxidative capacity ($r = -0.44$, $P < 0.001$). Furthermore, their whole-body leucine oxidation rate was significantly reduced under basal conditions (0.202 vs. $0.275 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $P < 0.05$), and also showed a downward trend under hyperinsulinemic conditions (30).

The second mechanism involves activation of the mTOR signaling pathway by BCAAs metabolism, thereby disrupting insulin signaling (33). In addition to their role in protein synthesis, BCAAs act as signaling molecules regulating multiple physiological activities (34). Studies have shown that plasma leucine can influence glucose metabolism by activating the mTOR signaling pathway in skeletal muscle. Linn et al. reported that during hyperinsulinemic-euglycemic clamp experiments, ingestion of whey protein or an equivalent amount of leucine led to a significant $\sim 30\%$ increase in muscle p-mTOR (Ser2448) levels (35). Conversely, studies with the mTOR inhibitor rapamycin provide supporting evidence from the opposite perspective: in patients with type 1 diabetes, short-term rapamycin pretreatment prior to islet transplantation significantly reduced daily insulin requirements (-8 ± 6 U/day, $p < 0.001$) and led to sustained improvement in hepatic insulin sensitivity one year post-transplant, as indicated by a significant decrease in hepatic glucose production (-1.1 ± 1.1 mg/kg/min, $p = 0.04$) (36). In addition, insulin can activate mTOR through the PI3K-Akt signaling pathway (37). When BCAAs continuously activate mTOR, the downstream effector S6 kinase (p70S6K) phosphorylates insulin receptor substrate 1 (IRS-1) on serine residues, thereby further inhibiting Akt signaling, reducing glucose transport, and promoting the development of IR (38, 39).

Therefore, BCAAs are not only metabolic biomarkers of IR but may also serve as one of the key drivers in the development of IR.

3 BCAAs metabolism and regulation

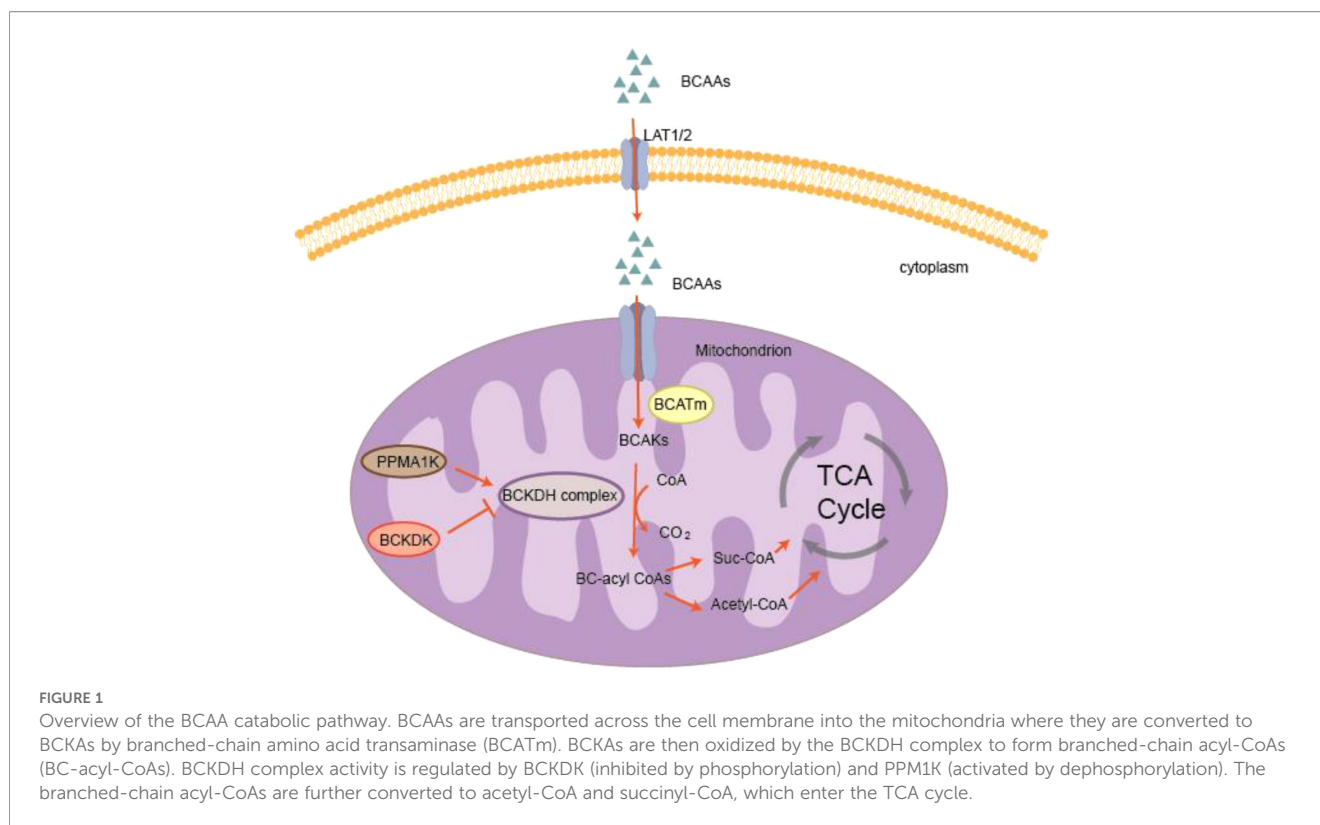
3.1 BCAAs metabolic pathways

Plasma BCAAs mainly originate from three sources: dietary intake, tissue proteolysis, and gut microbial synthesis (40), among which dietary intake is the primary source. After ingestion, BCAAs are primarily absorbed in the intestine via peptide transporters (41), and subsequently transported into cells through multiple amino acid transporters, such as LAT1 (encoded by SLC7A5) and LAT2 (encoded by SLC7A8) (42) (see Figure 1). The first two steps of BCAAs metabolism are catalyzed by branched-chain aminotransferase (BCAT) and branched-chain α -keto acid dehydrogenase (BCKDH), respectively. BCAT consists of two isoenzymes, BCAT1 and BCAT2 (43). BCAT1 is a cytosolic enzyme distributed in tissues such as embryos, ovaries, and the brain, whereas the mitochondrial enzyme BCAT2 is expressed in most tissues, particularly in skeletal muscle and adipose tissue. The first step of BCAAs metabolism is a reversible transamination reaction catalyzed by BCAT, producing branched-chain α -keto acids (BCKAs). Specifically, leucine, isoleucine, and valine are converted to α -ketoisocaproate, α -keto- β -methylvalerate, and α -ketoisovalerate, respectively (44). The second step is an irreversible oxidative decarboxylation catalyzed by BCKDH complex (45), which converts BCKAs into various branched-chain acyl-CoA derivatives. The BCKDH complex is composed of three catalytic subunits: α -keto acid dehydrogenase (E1 component), dihydrolipoyl transacylase (E2 component), and dihydrolipoyl dehydrogenase (E3 component). Its activity is tightly regulated by phosphorylation and dephosphorylation (46). Under the action of BCKDH complex, the CoA derivatives generated from BCKAs are further metabolized into acetyl-CoA and succinyl-CoA, which subsequently enter the tricarboxylic acid (TCA) cycle (47).

3.2 Factors affecting BCAAs metabolism

3.2.1 Dietary intake

Diet is the primary determinant of plasma BCAAs levels. High-protein diets, particularly those rich in animal protein, can acutely elevate circulating BCAAs. A randomized double-blind crossover study involving 27 healthy adults demonstrated that postprandial BCAAs metabolism is significantly influenced by dietary protein content. After consuming isocaloric high-protein (HP) and low-protein (LP) meals, plasma BCAAs and their catabolic products were monitored over 5 hours. Results showed that BCAAs, related keto acids, and acylcarnitines were significantly higher in the HP group than in the LP group, with the exception of the branched-chain α -keto acid α -ketoisovalerate, which exhibited higher postprandial concentrations following LP intake; however, when BCAAs levels exceeded a certain threshold, their catabolic products decreased (48). On the other hand, the effects of long-term diet may



differ. A one-month intervention study involving 102 healthy adults found that, although dairy protein intake differed significantly between groups, fasting BCAAs levels and insulin sensitivity did not change significantly (49).

Notably, dietary composition influences not only the absolute levels of BCAAs but also their distribution within metabolic networks. For instance, the combined effect of high-fat diets and elevated BCAAs intake has been found to exacerbate obesity and IR. Moreover, certain micronutrients, such as thiamine (vitamin B1), may indirectly modulate BCAAs catabolism by regulating BCKDC activity (50).

3.2.2 Gut microbiota

The gut microbiota is a critical regulator of host metabolism, playing central roles in immunity, metabolism, structural integrity, and neuroregulation (51–53). BCAAs, as essential amino acids and key components of proteins, are abundant in animal-based diets. Through their involvement in intestinal physiological processes, the gut microbiota influences host metabolism and overall health. In recent years, dysbiosis has been implicated in obesity and other metabolic disorders (54). Notably, patients with diabetes often exhibit an imbalance in the gut microbiota, characterized by an enrichment of BCAAs -producing bacteria (e.g., *Staphylococcus aureus*, *Prevotella copri*) (55, 56) and a depletion of BCAAs -degrading beneficial bacteria (e.g., *Faecalibacterium prausnitzii*) (57). This imbalance promotes the accumulation of circulating BCAAs, thereby aggravating IR. Studies have shown that interventions such as mulberry leaf extract and pyridostigmine can remodel the gut microbial composition, reduce BCAAs

biosynthesis, and enhance BCAAs catabolism, ultimately improving insulin sensitivity (58, 59).

3.2.3 Enzymatic molecules and regulation

As with many metabolic pathways, the regulation of BCAAs catabolism primarily occurs at its rate-limiting steps. In the first transamination reaction, BCAT2 (also known as mitochondrial branched-chain aminotransferase, BCATm) serves as the key enzyme, playing a critical role in the initial phase of BCAAs metabolism. Its deficiency leads to the accumulation of BCAAs and BCKAs (60). In a study of cardiac-specific BCATm knockout mice, researchers observed reduced cardiac BCAAs oxidation, elevated BCAAs levels, and decreased BCKA levels. Interestingly, insulin-stimulated glucose oxidation in the heart was enhanced, accompanied by increased Phosphorylated Akt (p-AKT), indicating improved insulin sensitivity. Further experiments demonstrated that high levels of BCKA infusion markedly suppressed insulin-stimulated glucose oxidation, reduced p-AKT, and inactivated pyruvate dehydrogenase (61). In the second oxidative decarboxylation step, the BCKDH complex acts as the rate-limiting enzyme. Defects in the BCKDH complex result in the accumulation of metabolic intermediates and mitochondrial dysfunction. Moreover, impaired BCKDH complex activity can disrupt BCKA metabolism, leading to their accumulation and perturbation of normal BCAAs catabolic pathways. For example, in patients with maple syrup urine disease, BCKDH complex activity is markedly reduced (62), and fibroblasts derived from these patients exhibit elevated levels of reactive oxygen species (ROS) (63). Such defects not only impair BCKA metabolism but

may also interfere with insulin signaling and disrupt lipid metabolism, thereby contributing to the development of IR.

In addition, there are two key enzymes that play important roles in regulating the activity of the BCKDH complex. One of them is branched-chain α -keto acid dehydrogenase kinase (BCKDK, also known as BCKDK), whose phosphorylation inactivates the BCKDH complex, leading to BCAAs accumulation (64). Studies have shown that inhibition of BCKDK can promote metabolic benefits. For example, thiazole-based BCKDK inhibitors can improve heart failure and metabolic function in mice (65), while the small-molecule allosteric BCKDK inhibitor BT2 can effectively alleviate non-alcoholic fatty liver disease and multifactorial metabolic disorders in mice (66). The other enzyme that regulates the BCKDH complex is protein phosphatase mitochondrial 1K (PPM1K), which activates the complex through dephosphorylation (67). Research has found that female mice with PPM1K deficiency exhibit elevated BCAAs levels and associated metabolic disturbances (68); in humans, PPM1K deficiency can lead to BCKDH complex deficiency, resulting in mild maple syrup urine disease (69).

3.2.4 Tissues, organs, and functions

BCAAs are not only essential substrates for protein synthesis but also play pivotal roles in energy metabolism and signal transduction. Their systemic levels are jointly determined by dietary intake, metabolic utilization, and regulation by multiple organs and tissues. Distinct organs exhibit tissue-specific functions in BCAAs metabolism and clearance, thereby profoundly influencing circulating BCAAs concentrations and metabolic health.

Skeletal muscle serves as the primary site for BCAAs catabolism, with the highest activities of branched-chain aminotransferase (BCAT) and BCKDH complex, followed by adipose tissue and the brain (47). Unlike most amino acids, which are primarily catabolized in the liver, BCAAs undergo limited initial metabolism in this organ. Instead, they are preferentially taken up by skeletal muscle, where they are transaminated by mitochondrial BCAT (BCATm) to generate BCKAs, which subsequently enter mitochondrial oxidative metabolism. Beyond serving as energy substrates, BCAAs in skeletal muscle also regulate insulin signaling and the mTOR pathway, making muscle mass and metabolic state critical determinants of BCAAs clearance efficiency (70). In obesity or IR, impaired muscle utilization of BCAAs leads to elevated circulating levels (71).

Adipose tissue also plays an important role in the regulation of BCAAs metabolism. Mammalian adipose tissue includes white and brown adipose tissues (WAT and BAT, respectively) (72). WAT is a robust energy-storage and endocrine organ and is essential for maintaining metabolic health during aging (73). In multiple obesity models (fa/fa rats, db/db mice, and diet-induced obese mice), the protein level of the branched-chain α -ketoacid dehydrogenase (BCKD) complex (E1 α subunit) is significantly reduced in WAT. When insulin action is impaired and/or metabolic signaling is disrupted in WAT, BCAAs utilization by WAT may be compromised (74). BAT is not only a thermogenic organ but also

an important “metabolic filter” that regulates BCAAs metabolism and maintains systemic metabolic health. It has been reported that under cold stimulation, BAT transports BCAAs into mitochondria via SLC25A44 for oxidation, thereby supporting thermogenesis and promoting whole-body BCAAs clearance. Impaired BCAAs metabolism in BAT leads to reduced BCAAs clearance and limited thermogenic capacity, which in turn promotes high-fat diet-induced obesity and glucose intolerance. In addition, studies have shown that differentiating adipocytes increase BCAAs utilization and release metabolic intermediates such as 3-hydroxyisobutyrate (3-HIB), which enhances fatty acid uptake and storage, thereby exacerbating obesity and IR (75). To some extent, WAT and BAT can interconvert. Acetyl-CoA derived from branched-chain keto acids (BCKAs) can acetylate PR domain-containing protein 16 (PRDM16) at lysine 915 (K915), thereby suppressing WAT browning. In contrast, depletion of acetyl-CoA markedly promotes WAT browning and enhances energy expenditure (76).

The brain critically depends on BCAAs homeostasis for normal function. The blood–brain barrier transporter SLC7A5 plays a central role in mediating BCAAs entry into the brain, and its dysfunction leads to altered brain amino acid composition, impaired protein synthesis, severe neurological abnormalities, and has been linked to autism spectrum disorders (77). Furthermore, BCAAs and aromatic amino acids (ArAAs) compete for transport into the brain. Elevated plasma BCAAs levels increase brain uptake of BCAAs while reducing ArAA availability, thereby suppressing the synthesis of neurotransmitters such as serotonin and catecholamines, ultimately affecting mood regulation, hormonal balance, and blood pressure control (78). Importantly, BCAAs serve as major nitrogen donors for glutamate synthesis in the brain, with approximately one-third of glutamate nitrogen derived from BCAAs, particularly leucine. Through the astrocyte–neuron “leucine–glutamate cycle,” nitrogen transfer and recycling are maintained, supporting neurotransmitter synthesis and buffering excessive glutamate to prevent excitotoxicity (79).

4 Effects of BCAAs on IR

BCAAs are not only important biomarkers of IR but may also directly contribute to its development. In an acute supplementation experiment, intravenous BCAAs infusion transiently reduced blood glucose in mice, likely through stimulation of insulin secretion. However, beginning 10 minutes post-infusion, plasma insulin and glucose levels both rose and remained elevated until the end of the experiment. Hyperinsulinemic–euglycemic clamp studies further demonstrated reduced systemic insulin sensitivity, accompanied by hyperactivation of hypothalamic AgRP neurons and increased food intake. These effects were reversed when BCAAs levels were reduced (27). Thus, BCAAs can acutely impair glucose metabolism and insulin sensitivity, while dietary restriction of BCAAs has shown beneficial effects in experimental models. In a protein diet study, reducing all three BCAAs by 67% in the control amino acid (Ctrl AA) diet (Low BCAAs) exerted distinct effects on

obese mice. Specifically, isoleucine restriction reprogrammed hepatic and adipose metabolism, enhanced hepatic insulin sensitivity and ketogenesis, increased energy expenditure, and activated the FGF21–UCP1 axis. Valine restriction induced similar but milder metabolic benefits, whereas leucine restriction had no significant effect (80, 81).

Mechanistically, BCAAs contribute to IR through several pathways. First, excessive BCAAs and their metabolites (e.g., BCKAs and corresponding acylcarnitines) accumulate in skeletal muscle and liver, impairing mitochondrial energy metabolism and inhibiting fatty acid oxidation, leading to by-product accumulation and further disruption of insulin signaling. Second, BCAAs activate the mTORC1 pathway, inducing serine phosphorylation of IRS-1 and weakening downstream insulin receptor signaling, thereby reducing cellular insulin sensitivity. Third, elevated BCAAs levels promote M1 polarization of adipose tissue macrophages, increasing proinflammatory cytokines such as interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and monocyte chemoattractant protein-1 (MCP-1), which further exacerbate IR (82).

5 BCAAs and mTOR signaling pathway activation

Mammalian target of rapamycin (mTOR) is an evolutionarily conserved serine/threonine protein kinase and a key member of the phosphatidylinositol 3-kinase-related kinase (PIKK) family (83). mTOR regulates core processes of cell proliferation and growth in response to signals such as insulin, amino acids, energy status, and oxygen (84). It coordinates upstream signals with downstream effectors, including transcriptional and translational mechanisms, to modulate fundamental cellular activities such as energy utilization, protein synthesis, autophagy, cell growth, and

proliferation (85). As a catalytic subunit, mTOR exists in two distinct multiprotein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), which phosphorylate different substrates and exhibit diverse physiological functions (86).

Patients with obesity and insulin-resistant T2DM exhibit significantly elevated serum BCAAs levels (87, 88). Clinical studies show that elevated BCAAs levels are positively correlated with the degree of IR (89). BCAAs, including leucine, isoleucine, and valine, are essential amino acids and potent activators of mTORC1 (90). Leucine can synergize with insulin to activate mTORC1. Persistent mTORC1 activation leads to phosphorylation of S6K1, which subsequently phosphorylates serine residues on insulin receptor substrates IRS-1 and IRS-2 impairing downstream insulin signaling and potentially targeting IRS-1 for proteasomal degradation (38, 39) (see Figure 2). For example, a study found that when rat extensor muscles were cultured with varying concentrations of leucine, AMP-activated protein kinase (AMPK) activity was suppressed, while the mTORC1/p70S6K1 signaling pathway was activated, resulting in IR (91).

Grb10 is an intracellular adaptor protein that can directly bind to multiple growth factor receptors, including the insulin receptor and the insulin-like growth factor-1 (IGF-1) receptor, and negatively regulate their actions (92). mTORC1 can stabilize Grb10 by phosphorylating its tyrosine residues, preventing its degradation and thereby continuously inhibiting the interaction between IRS and the insulin receptor. This leads to increased IR and places an additional burden on pancreatic glucose handling. Consequently, BCAAs may contribute to pancreatic dysfunction or the development of T2DM through sustained activation of mTORC1.

BCAAs, particularly leucine, directly act on downstream targets S6K1 and Grb10 via mTORC1 signaling. Activation of S6K1

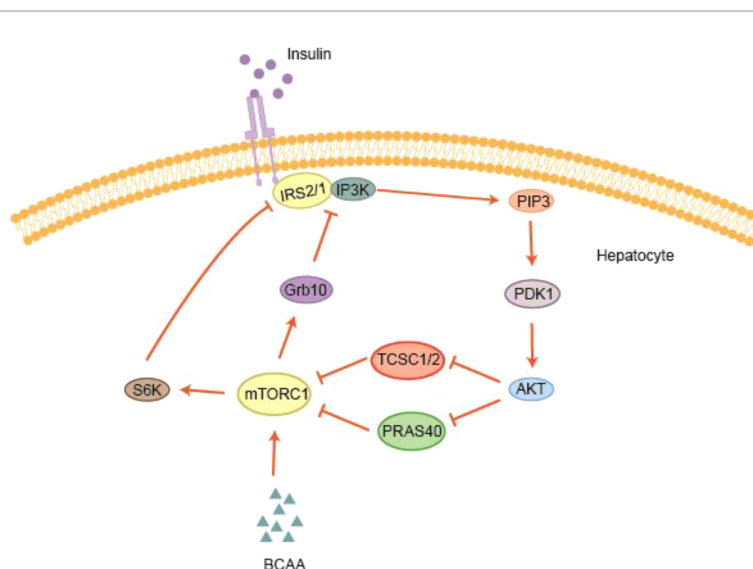


FIGURE 2

BCAA activation of the mTOR signaling pathway. BCAAs can stimulate mTORC1 in the PI3K/AKT signaling pathway, which activates downstream molecules such as S6K1 and Grb10. S6K1 and Grb10 mediate the degradation of IRS, thereby disrupting insulin signaling.

promotes protein synthesis and cell growth, while Grb10 mediates negative feedback to suppress insulin signaling, helping maintain metabolic homeostasis. A deeper understanding of the roles of S6K1 and Grb10 in the mTORC1 pathway is critical for elucidating the contribution of BCAAs to T2DM-associated IR and provides potential targets for therapeutic strategies based on mTOR signaling.

6 Effects of increased BCAAs on insulin signaling disruption

Insulin promotes the translocation of GLUT4 in adipocytes through activation of the PI3K/AKT signaling pathway (see Figure 3), facilitating glucose uptake into fat cells. Intracellular glucose is metabolized via glycolysis to pyruvate, which participates in triacylglycerol (TAG) synthesis and *de novo* lipogenesis (93). Adipocyte IR is an early hallmark of obesity and T2DM. BCAAs can impair insulin action through sustained activation of mTORC1, with leucine being a key activator. mTORC1 is involved in multiple physiological processes, including cell growth, metabolism, and glucose homeostasis (94). Studies have shown that in rats fed a high-fat (HF) diet supplemented with BCAAs, IR can be reversed by the mTORC1 inhibitor rapamycin (22). Additionally, the

microbiota-dependent tryptophan metabolite 5-hydroxyindole-3-acetic acid (5-HIAA) can enhance hepatic insulin signaling by directly activating the aryl hydrocarbon receptor (AhR), stimulating TSC2 transcription, and suppressing mTORC1 signaling, thereby alleviating HF diet-induced IR (95).

In obese and diabetic rodents and humans, the downstream molecule of mTORC1, ribosomal S6K1, is activated (96). S6K1 is regarded as a negative regulator of IRS signaling (38, 39) (96–98). Experimental evidence indicates that high concentrations of BCAAs stimulate mTOR, subsequently inducing IR through serine phosphorylation of IRS-1 (99). In addition, dysregulated BCAA metabolism can cause BCAAs accumulation in the aorta, leading to mitochondrial reactive oxygen species (ROS) damage and inflammatory responses via excessive mTOR activation (100). Recent studies have further demonstrated that BCAAs metabolic defects may result in local leucine accumulation, which promotes α -cell proliferation through the mTOR pathway (101). Activation of the BCAAs/mTORC1 axis is also associated with insulin sensitivity (11, 102, 103). Mitochondrial BCAAs aminotransferase (BCATm) markedly elevates plasma BCAAs levels, but is not affected by high-fat diet-induced obesity and IR (104, 105), suggesting that BCAA-mediated effects such as mTOR activation alone are insufficient to induce IR.

Furthermore, activation of mTORC1 stabilizes Grb10, reducing its degradation. Grb10 inhibits the interaction between insulin

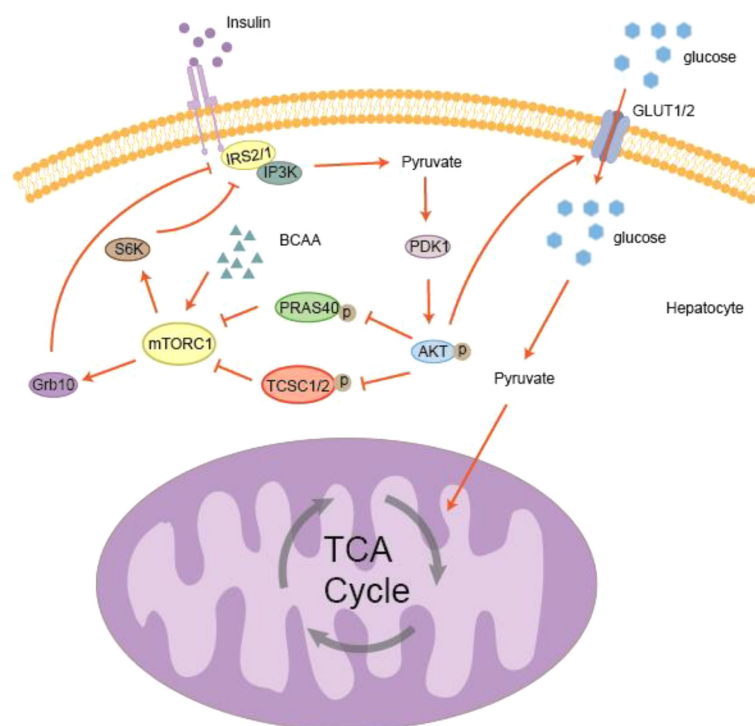


FIGURE 3

BCAA metabolism and insulin resistance. Elevated BCAA levels promote mTORC1 activation, which negatively regulates insulin signaling through phosphorylation of the downstream targets S6K and Grb10. First, PI3K activates AKT upon activation of the insulin receptor substrate (IRS). Activated AKT phosphorylates and inhibits TSC2, while phosphorylation of PRAS40 further enhances mTORC1 activity. Subsequently, mTORC1 activates S6K and Grb10. Increased S6K activity results in negative feedback phosphorylation of IRS, leading to IRS degradation and inhibition of insulin signaling. At the same time, Grb10 activation also suppresses IRS function. These mechanisms ultimately disrupt GLUT1/4 translocation, reducing glucose uptake and utilization, leading to insulin resistance.

receptor substrates (IRS) and the insulin receptor via tyrosine phosphorylation, thereby impairing insulin signaling. Studies have shown that eight weeks of treadmill training in T2DM rats effectively reduced elevated Grb10 levels in the hippocampus, restored the mTOR/AMPK signaling pathway, alleviated spatial learning and memory deficits, and enhanced GLUT4 translocation, ultimately improving diabetes-associated cognitive impairment (106). Moreover, evidence shows that β -cell mass and function are increased in diabetic mice with β -cell-specific Grb10 knockout (107), and transcriptome analysis of diabetic mouse liver revealed significant downregulation of Grb10 expression (108). It has also been reported that the food additive carrageenan can impair insulin signaling through two mechanisms: on the one hand, inducing inflammation that elevates Ser(P)307-IRS1 and suppresses insulin signaling; on the other hand, enhancing the GRB10 promoter, whereby GRB10 inhibits Tyr(P)-IRS1, further reducing Ser(P)473-AKT activation. Together, these changes alter IRS1 phosphorylation status and insulin sensitivity (109). Therefore, BCAAs may activate mTORC1 by increasing Grb10 expression, disrupt insulin signaling pathways, and ultimately lead to IR.

Overactivation of the mTORC1 signaling pathway is considered a key mechanism in this process. mTORC1 plays a central role in regulating cell growth and metabolism, while simultaneously inhibiting insulin signaling, thereby affecting glucose uptake and utilization. This inhibitory effect reduces cellular insulin responsiveness and promotes the development of IR. Consequently, modulation of mTORC1 activity may provide a potential therapeutic strategy for diabetes.

7 Strategies for reducing IR in T2DM by modulating BCAAs metabolism

BCAAs are closely associated with T2DM and IR, making them a promising therapeutic target for alleviating these conditions. In the field of BCAAs-targeted drug development, several potential candidates have attracted research attention. One class of drugs comprises BCAAs synthesis inhibitors, such as BT2 (3,6-dichloro-2-carboxybenzo[b]thiophene) (110), which block endogenous BCAAs synthesis, thereby reducing circulating levels. Another class of drugs aims to lower BCAAs levels by promoting their oxidation and clearance, including NaPB (28) and fibrate compounds (111), which reduce plasma BCAAs concentrations by enhancing their metabolism and excretion.

7.1 BT2

BT2 is a commonly used preclinical inhibitor of BCKDK. BCKDK is a key negative regulator of the BCKDH complex, as it phosphorylates the E1 α subunit of BCKDH, leading to enzymatic inactivation and suppression of BCAA oxidation. BT2 promotes BCAA oxidation by inhibiting BCKDK activity, thereby preventing BCKDH phosphorylation and maintaining the complex in an active, dephosphorylated state, which helps restore the

homeostasis of BCAAs and BCKAs (112–114). Studies have shown that BT2 inhibits BCKDK, leading to dephosphorylation of the E1 α subunit of BCKD complex, reactivating BCAAs catabolism (100) and improving IR (115). Additionally, research indicates that BT2 can significantly enhance BCAAs catabolism in the colonic tissue of ulcerative colitis (UC) mice by suppressing mTORC1 activation and cyclooxygenase-2 (COX-2) expression (116–118). These findings suggest that dysfunction of BCAAs catabolism plays a key role in the progression of metabolic diseases.

Metformin is a first-line therapeutic agent for patients with T2DM (119). Studies have shown that during the treatment of obese mice, metformin inhibits BCAAs catabolism, leading to elevated circulating BCAAs levels and thereby, to some extent, limiting its own therapeutic efficacy in the treatment of T2DM. In contrast, BT2 enhances BCAAs catabolism, significantly potentiates the glucose-lowering effect of metformin, and reduces circulating BCAAs levels in ob/ob mice and diet-induced obese (DIO) mice (120). Similarly, dietary restriction of BCAAs intake produced comparable effects. In summary, BT2 is a pharmacological agent capable of directly modulating BCAAs catabolism via activation of BCKD complex. It effectively restores BCAAs catabolism across multiple tissues, alleviates defects in BCAAs catabolic pathways, improves insulin sensitivity, and can synergize with other drugs to enhance glucose-lowering efficacy.

However, recent studies have revealed that, in addition to inhibiting BCKDK and promoting BCAAs oxidation, BT2 also exhibits significant off-target effects: it strongly binds to plasma albumin, displacing albumin-bound tryptophan, thereby markedly reducing plasma tryptophan levels and promoting its degradation into kynurenine, a process independent of classical tryptophan-metabolizing enzymes (121). This finding suggests that while BT2 regulates BCAAs metabolism, it may simultaneously interfere with the tryptophan–kynurenine pathway, raising potential safety concerns. Therefore, although BT2 has demonstrated beneficial effects in multiple animal models, including the improvement of IR, recovery from heart failure, and anti-tumor activities, its potential adverse effects have prevented it from entering clinical application to date (121).

7.2 NaPB

NaPB has attracted widespread attention in the biomedical field due to its potential role in BCAAs regulation. Its unique property lies in its ability to lower systemic BCAAs levels, alleviate endoplasmic reticulum (ER) stress, and improve BCAAs-mediated IR (122, 123). Studies have demonstrated that NaPB effectively reduces BCAAs levels (124), and lowering BCAAs concentrations has significant potential to enhance insulin sensitivity and mitigate IR, which is particularly relevant in the treatment of T2DM. In a randomized controlled trial involving T2DM patients, fasting blood samples were collected after oral administration of NaPB or placebo to measure BCAAs, their metabolic intermediates, insulin, triglycerides, free fatty acids (FFA), and glucose levels. Compared to placebo, NaPB increased

peripheral insulin sensitivity by 27%, improved mitochondrial oxidation capacity driven by pyruvate in skeletal muscle, enhanced whole-body carbohydrate oxidation under insulin stimulation, and reduced plasma BCAAs and glucose levels, and no adverse events were reported (28).

The mechanism by which NaPB lowers BCAAs levels is attributed to its ability to enhance BCAAs catabolism, thereby accelerating BCAAs degradation and reducing circulating concentrations. NaPB inhibits kinase activity by binding to the specific allosteric pocket of BCKDK, leading to reduced BCAAs levels (114). Abnormally elevated BCAAs levels are closely associated with IR and multiple metabolic disorders, highlighting the significance of NaPB in BCAAs regulation.

In a study involving overweight or obese men, although circulating plasma BCAAs levels were not measured, the results suggested that NaPB may partially ameliorate lipid-induced IR (125). To better understand the regulatory effects of NaPB on human BCAAs catabolism and its metabolic consequences, it is crucial to investigate its impact on insulin signaling and glucose uptake in primary human skeletal muscle cells. Therefore, elucidating the precise molecular mechanisms by which NaPB lowers BCAAs levels, and determining optimal dosing and treatment duration, are of significant importance for future therapeutic applications. In the context of T2DM research, exploring the potential of NaPB holds substantial value.

7.3 Targeting the gut microbiota

In recent years, targeting the gut microbiota to regulate metabolic diseases has become a research hotspot. Increasing evidence indicates that the gut microbiota not only participates in host energy metabolism and inflammation regulation but is also closely associated with BCAAs levels. Abnormal BCAAs levels, in turn, are closely linked to IR and T2DM as well as other metabolic disorders. In addition, clinical studies have also suggested that holistic gut microbiota interventions can improve IR. For example, a recent study found that FMT (fecal microbiota transplantation), whether used alone or in combination with metformin, significantly improved HOMA-IR and body mass index in patients with T2DM. Moreover, by promoting donor microbiota engraftment, FMT reshaped the recipients' gut microbial diversity, thereby facilitating metabolic improvement (126).

In both mouse and human studies, multiple bacterial genera and their related interventions have been shown to regulate BCAAs levels. Notably, in different disease models, the gut microbiota plays a key role in modulating BCAAs metabolism. *Parabacteroides merdae* can promote BCAAs catabolism via its *porA* gene, thereby alleviating atherosclerosis (127). *Clostridium butyricum* (C.B), as a typical short-chain fatty acid (SCFA)-producing bacterium, can not only lower plasma BCAAs levels in high-fat diet-fed mice by suppressing intestinal BCAAs-producing microbiota, but also ameliorate obesity-related metabolic abnormalities induced thereby, including impaired glucose tolerance, dyslipidemia, and systemic inflammation. Thus, it plays an important role in restoring BCAAs catabolism and alleviating IR

(128). *Faecalibacterium prausnitzii* is capable of absorbing and consuming serum BCAAs (57). *Bacteroides ovatus*, under the influence of polymethoxylated flavone-enriched extracts (PMFE), can lower BCAAs levels and improve metabolic syndrome (129). Conversely, certain bacterial genera or environmental factors may elevate BCAAs levels. *Staphylococcus aureus* increases BCAAs via acetolactate synthase (ALS), promoting T2DM development (55); *Bacteroides vulgatus*, regulated by berberine, increases BCAAs accumulation and exacerbates ulcerative colitis (130); triclosan (TCS) raises plasma BCAAs levels by increasing the *Firmicutes/Bacteroidetes* ratio, thereby impairing glucose tolerance (99). In addition, *Prevotella copri* has BCAAs metabolic capabilities and may contribute to BCAAs levels by producing them in the gut or promoting their absorption (56).

Some natural extracts and pharmacological agents have also been shown experimentally to target gut microbiota abundance, reducing BCAAs levels and improving metabolic outcomes. For example, mulberry leaf aqueous extracts and pibobendan can modulate gut microbial composition to lower BCAAs levels, serving as interventions for T2DM and diabetic cardiomyopathy (58) (Table 1).

8 Effects of restricting dietary BCAAs intake

studies have shown that dietary restriction of BCAAs can enhance insulin sensitivity through multiple mechanisms and may play a role in diabetes management (131). In an obese mouse model, dietary BCAAs restriction without altering total protein or energy intake resulted in reduced body weight and improved insulin sensitivity and glucose tolerance (132). Another study found that feeding obese mice a diet selectively low in BCAAs improved metabolic health, enhanced glucose tolerance, and reduced fat accumulation (80). These findings indicate that BCAAs restriction can improve insulin sensitivity through multiple mechanisms, thereby alleviating IR (133).

In a 4-week isocaloric intervention with protein intake fixed at 1 g/kg body weight, 12 patients with T2DM consumed diets in which approximately 60% of the protein was provided as an amino acid mixture during weeks 2 and 4. The intervention group received a BCAAs-depleted formula, whereas the control group received a complete amino acid formula. BCAAs restriction reduced fasting, clamp, and postprandial BCAAs levels by 17%, 13%, and 62%, respectively, and was associated with a 24% increase in the oral glucose sensitivity index, a 28% reduction in postprandial insulin secretion, and a 21% increase in circulating Fibroblast Growth Factor 21 (FGF21) levels. In addition, BCAAs restriction was accompanied by downregulation of mTOR signaling in white adipose tissue, an increased mitochondrial respiratory control ratio, and alterations in gut microbiota composition, characterized by an increase in Bacteroidetes and a decrease in Firmicutes. However, under hyperinsulinemic–euglycemic clamp conditions, no significant changes in whole-body or hepatic insulin sensitivity were observed (134).

TABLE 1 Mechanisms by which different gut microbiota target BCAAs.

Microbiome composition	Targeted microbiota drug	Mechanism	Model	Organism	Reference
<i>Gut Parabacteroides merdae</i>	\	BCAAs catabolism mediated by the <i>porA</i> gene in <i>P. merdae</i>	Atherosclerosis	Mouse	(127)
<i>Staphylococcus aureus</i>	\	Acetolactate synthase (ALS) leads to elevated BCAAs levels	T2DM	Human, Mouse	(55)
<i>Prevotella copri</i>	\	Positively correlated with BCAAs metabolism	Sarcopenia	Human, Mouse	(56)
<i>Clostridium butyricum</i> (C.B)	\	Suppression of BCAAs-producing bacterial populations	High-fat diet-induced obesity	Mouse	(128)
<i>Bacteroides vulgatus</i>	Bergenin	Promotes BCAAs production/accumulation	Ulcerative colitis	Mouse	(130)
<i>Firmicutes/Bacteroidetes ratio</i>	Triclosan (TCS)	TCS increases <i>Firmicutes/Bacteroidetes</i> ratio, leading to elevated BCAAs levels	Impaired glucose tolerance	Rat	(99)
<i>Faecalibacterium prausnitzii</i>	\	Absorbs/consumes serum BCAAs	\	Human	(57)
<i>Bacteroides ovatus</i>	Polymethoxylated flavone-enriched extracts (PMFE)	Reduces BCAAs levels	Metabolic syndrome (MetS)	Mouse	(129)
\	Mulberry leaf water extract	Alters gut microbiota, reduces BCAAs	T2DM	Mouse	(58)
\	Pyridostigmine	Alters gut microbiota, reduces BCAAs	Diabetic cardiomyopathy	Mouse	(59)

This table summarizes the major gut microbial genera reported in current studies that target BCAAs metabolism, along with their mechanisms of action.

It is important to note that numerous studies have revealed a close association between elevated BCAAs levels and IR, providing mechanistic support for the theory that “lowering BCAAs levels may improve metabolic disorders.” Nevertheless, at the intervention level, there is currently a lack of direct evidence demonstrating that simply reducing dietary BCAAs intake can reverse IR. Since BCAAs are essential amino acids, excessive restriction may lead to nutritional imbalance, making it a pressing challenge to “meet physiological needs while avoiding excessive accumulation.” Therefore, future research should explore alternative strategies, such as modulating the gut microbiota or developing small-molecule drugs that selectively inhibit BCAAs synthesis or metabolism, to achieve more precise regulation of BCAAs levels.

9 Conclusion

IR is one of the central features of T2DM and is closely associated with BCAAs metabolic dysregulation. Increasing evidence indicates that impaired BCAAs metabolism is tightly linked to the metabolic abnormalities and IR observed in T2DM. As essential amino acids, BCAAs play critical roles in protein synthesis and energy metabolism. Multiple studies consistently demonstrate that elevated circulating BCAAs levels are closely associated with the development and progression of IR in T2DM (135–137) supporting the involvement of BCAAs metabolic dysregulation in T2DM pathogenesis.

Moreover, a brief review of BCAAs metabolic pathways reveals that BCAAs catabolism is mediated by multiple enzymes and transporters, generating various intermediates. These intermediates have been shown

to regulate key pathways related to glucose and lipid homeostasis as well as insulin sensitivity. Notably, BCAAs not only play a pivotal role in the pathogenesis of T2DM but also represent potential therapeutic targets. Modulating BCAAs metabolism and its associated pathways may improve IR and glycemic control in T2DM patients. Furthermore, elucidating the precise molecular mechanisms by which BCAAs influence IR could facilitate the development of novel interventions and personalized therapeutic strategies, enhancing T2DM management.

In summary, BCAAs metabolic dysregulation is closely associated with metabolic dysfunction and IR in T2DM. A deeper understanding of the complex relationship between BCAAs and IR will provide valuable insights into T2DM pathophysiology and may open new avenues for the treatment of this prevalent metabolic disorder.

Author contributions

JM: Writing – review & editing, Writing – original draft. FY: Writing – review & editing, Funding acquisition, Supervision. QG: Writing – review & editing, Funding acquisition.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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