

Chapter 18

Branched Chain Amino Acids Supplementation and Glycemic Control

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Key Points

- Currently, BCAAs supplementation is clinically used and covered by insurance only for patients with chronic liver diseases.
- It remains unclear whether BCAAs improve insulin resistance in humans.
- Circulating levels of BCAAs are associated with insulin resistance both in animals and humans.
- BCAAs supplementation therapy, together with their metabolites and their target mTOR-related signaling pathway, may modulate insulin signaling and glucose metabolism depending on their dosage, site of action, duration, and synergies with background lipid profiles.
- BCAAs supplementation may improve energy metabolism and glucose tolerance in liver cirrhosis patients with more skeletal muscle volume.
- BCAAs-enriched supplement may be useful in ameliorating insulin resistance in male patients or in severely insulin-resistant patients with chronic liver disease.
- BCAAs increase muscle mitochondrial function in the young but not in the elderly.
- BCAAs therapy may exert a beneficial effect on HbA1c values in patients with marked insulin resistance in the skeletal muscle.

Keywords BCAA • Chronic liver disease • Glucose tolerance • Insulin resistance • mTOR • Type 2 diabetes

Abbreviations

AUC	Areas under curve
BCAA	Branched chain amino acids
BCATm	Mitochondrial form of BCAA transaminase

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BCKDH	Branched chain ketoacid dehydrogenase complex
BMI	Body mass index
BTR	Branched chain amino acid/tyrosine ratio
CHI	Creatinine height index
FPG	Fasting plasma glucose
HCC	Hepatocellular carcinoma
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HF	High-fat
H-IR	Hepatic insulin resistance index
HOMA-IR	Homeostasis model assessment of insulin resistance
IRI	Immunoreactive insulin
MAPR	Maximal mitochondrial ATP production rate
MCR	Metabolic clearance rate of glucose
mTOR	Mechanistic target of rapamycin
mTORC1	mTOR complex 1
npRQ	Nonprotein respiratory quotient
SC	Standard chow
OGTT	Oral glucose tolerance test

Introduction

Branched chain amino acids (BCAAs) that include valine, leucine, and isoleucine are essential amino acids and are not synthesized *de novo* in organisms. Currently, in Japan, BCAAs supplementation is clinically used and covered by insurance only for patients with chronic liver diseases. BCAA supplementation improves disorders of albumin metabolism, quality of life, subjective symptoms, and prognosis in patients with chronic hepatitis [1]. Insulin resistance increases in chronic liver disease and is a risk factor for the progression of liver pathology, the development of hepatocellular carcinoma (HCC), and a decrease in long-term survival [2, 3]. Therefore, insulin resistance is an important therapeutic target in patients at any stage of chronic liver disease. It remains unclear whether BCAAs improve insulin resistance in humans; both beneficial and deleterious effects of BCAAs are reported based on experimental and clinical observations. In the current review, we focus on the current issues on BCAA and glucose homeostasis from both experimental and clinical points of view.

Circumstantial Evidence of Circulating Levels of BCAAs and Insulin Resistance

It is well known that circulating levels of BCAAs are associated with insulin resistance both in animals and humans. Felig et al. found that plasma levels of valine, leucine, isoleucine, tyrosine, and phenylalanine are increased and correlated with serum insulin in obese subjects compared with age-matched and sex-matched controls [4]. BCAA and related metabolites such as C3 and C5 acylcarnitines are associated with cardiometabolic abnormalities independently of body mass index [5]. In addition, BCAA levels may predict future diabetes. In the Framingham Offspring Study, BCAAs, tyrosine and phenylalanine profiled in baseline specimens predict future diabetes development independently of age, body mass index, and fasting glucose [6]. These observations were confirmed in a comprehensive metabolomics profiling of obese versus lean humans [7]. A principal component analysis revealed that the

component most strongly associated with insulin resistance assessed by HOMA-R was not lipid-related, but rather comprised of the BCAAs and their metabolites C3 and C5 acylcarnitines.

Decreased catabolism of BCAA mediated by the mitochondrial form of BCAA transaminase (BCATm) and the branched chain ketoacid dehydrogenase complex (BCKDH) in the adipose tissue [8, 9], rather than increased consumption of BCAA [6], may contribute to increases in BCAA levels in insulin-resistant states. Indeed, adipose tissue expression of the genes involved in BCAA catabolism such as BCATm and BCKDH was positively associated with increase in insulin sensitivity after 3-month treatment with thiazolidinediones in humans [9]. In addition, plasma levels of BCAAs are reduced by surgical weight loss intervention by Roux-en-Y gastric bypass in human subjects with increased expression of genes for BCATm and BCKDH in the adipose tissue [8].

BCAA-Induced Insulin Resistance and Its Possible Underlying Mechanisms

Previous experimental studies have reported conflicting effects of BCAAs on glucose metabolism *in vivo*. BCAAs promote glucose uptake in skeletal muscle in a rat model of liver cirrhosis [10] and in sucrose-lipid-fed rats [11]. In adipocytes from diabetic db/db mice, leucine permits insulin to stimulate Akt when PI 3-kinase is inhibited [12]. Leucine reduces hepatic glucose production and insulinemia in insulin-resistant obese Zucker fa/fa rats [11]. In skeletal muscle isolated from nondiabetic rats [13], leucine promotes glucose uptake under insulin-free conditions by enhancing translocation of GLUT4 to the plasma membrane via PI3K and protein kinase C pathways independently of mechanistic target of rapamycin (mTOR), a serine/threonine protein kinase that senses and integrates a variety of environmental cues to regulate organismal growth and homeostasis [14]. However, in general, BCAAs/amino acids activate mTOR and thereby induce phosphorylation of 4E-BP1, stimulate the enzymatic activity of p70 S6K, and reverse hypoalbuminemia in the cirrhotic liver [15]. The mTOR signaling is also activated in obese/over-nutrient state and plays crucial roles in regulating metabolism in various organs responsible for energy homeostasis [14]. mTOR complex 1 (mTORC1) activation promotes adipogenesis by activating PPAR- γ in adipose tissue, enhances protein synthesis, mitochondrial biogenesis, and oxidative metabolism in muscles, promotes hepatic insulin resistance, gluconeogenesis, and lipogenesis by activating SREBP1, and promotes β cell growth and proliferation [14]. Paradoxically to the effect of mTORC1 in maintaining muscle mass, mTORC1 negatively regulates insulin-mediated PI3K activity by degrading insulin receptor substrates in skeletal muscle cells during long-term insulin treatment [16]. Because chronic activation of mTORC1 in the tissues of obese mice and humans appears to play a role in the development of insulin resistance and type 2 diabetes, the potential of mTOR inhibition with rapamycin to improve metabolic parameters has been tested in a variety of animal models. Unexpectedly, treatment of rodents with rapamycin leads to a deterioration of the metabolic profile. Rapamycin reduces adipose tissue size and β -cell mass and function, promotes hepatic gluconeogenesis, and thereby causes insulin resistance, hyperlipidemia, and glucose intolerance [14]. mTOR signal crosstalks with ERRalpha that is involved in the TCA cycle and lipid biosynthesis. Rapamycin treatment exacerbates hepatic lipid accumulation via inhibition of ERRalpha [17]. Indeed, we have experienced a case of type 2 diabetes whose glycemic control and fatty liver were exacerbated after administration of an anticancer drug everolimus that works as an inhibitor of mTOR (manuscript in preparation). On the other hand, rapamycin extends lifespan in mice despite metabolic impairment. Fang et al. recently found that detrimental metabolic effects of rapamycin treatment are only observed during the early stages of treatment and are reversed or diminished in mice treated for longer period (20 weeks), with better metabolic profiles, increased oxygen consumption and ketogenesis, and markedly enhanced insulin sensitivity [18]. These findings suggest that rapamycin treatment may exert both deleterious and beneficial metabolic effects depending on the treatment period. Therefore, the relation between mTORC1 activity and insulin sensitivity and

metabolic profile is suggested to follow a U-shaped curve, where too little or too much mTORC1 activity has a negative impact on systemic metabolism [14].

Given BCAAs as mTOR activators, BCAAs may also play a dual role in systemic glucose metabolism depending on their dosage, site of action, and duration. Indeed, interventions that alter circulating levels of BCAAs have exhibited quite paradoxical phenotypes in mice. Mice deleted with *BCATm* gene, which encodes the enzyme catalyzing the first step in peripheral BCAA catabolism, exhibited elevated plasma BCAAs and decreased adiposity and body weight, despite eating more food. *BCATm*^{-/-} mice also exhibited increased energy expenditure, improvements in glucose and insulin tolerance, and protection from diet-induced obesity. These observations suggest that elevated BCAAs and/or loss of BCAA catabolism in peripheral tissues play an important role in regulating insulin sensitivity and energy expenditure. In this regard, elevation in circulating levels of BCAAs in insulin resistant animals and humans may be a compensation to keep energy homeostasis.

On the other hand, Newgard et al. fed Wistar rats on high-fat (HF), HF with supplemented BCAA (HF/BCAA), or standard chow (SC) diets [7]. Rats fed the HF/BCAA diet consumed less food than the HF group. Despite having reduced food intake and a low rate of weight gain equivalent to the SC group, HF/BCAA rats revealed impaired insulin signaling in liver and muscle equally as HF rats. Insulin resistance induced by HF/BCAA feeding was accompanied by chronic phosphorylation of mTOR, JNK, and Ser307 of IRS1 and by accumulation of multiple acylcarnitines in muscle, which were reversed by the mTOR inhibitor, rapamycin [7]. These findings suggest an interaction between excess fat and BCAA in development of insulin resistance that can occur independently of body weight. Pair-feeding of HF diet to match the HF/BCAA animals or BCAA addition to SC diet did not cause insulin resistance [7], suggesting that in the context of a dietary pattern such as high-fat diet, BCAA contributes to development of obesity-associated insulin resistance.

Clinical Interventions of BCAAs Supplementation

BCAA supplementation is clinically used for patients with chronic liver diseases. In a single-arm short period administration study [19] (Fig. 18.1), energy metabolism and glucose tolerance were evaluated using an indirect calorimeter and 75 g oral glucose tolerance test (75 g OGTT) before and after 1 week of oral supplementation with a BCAA nutrient (Livact® 4.15 g/pack, Ajinomoto Pharma, Tokyo, Japan) three times a day (after breakfast, dinner, and before sleep) in patients with liver cirrhosis (hepatitis B virus (HBV) in 2 cases, hepatitis C virus (HCV) in 26 cases, alcohol in 1 case and unknown cause in 1 case, complicated with HCC in 19 cases). Nonprotein respiratory quotient (npRQ) as well as branched chain amino acid/tyrosine ratio (BTR) showed significant improvement, especially in patients with a marker for skeletal muscle volume, creatinine height index (CHI, calculated as 24-h urine creatinine multiplied by 100 over the expected 24-h urine creatinine for height) greater than 80. npRQ after 1 week of BCAA supplementation significantly correlated with the CHI (Fig. 18.1a). The patients with CHI greater than 80 and those with borderline pattern assessed by 75 g OGTT showed significant improvement in impaired glucose tolerance [19] (Fig. 18.1b). Authors concluded that liver cirrhosis patients with CHI greater than 80 suggestive of more skeletal muscle volume are the first candidates for BCAA supplementation; these patients show improvement in energy metabolism, BTR, and glucose tolerance [19].

In another single-arm small scale study [20], 12 patients with chronic viral liver disease were given a BCAA-enriched supplement after breakfast and at bedtime for 90 days (Fig. 18.2). BCAA-enriched supplement significantly decreased an insulin resistance index HOMA-IR only in the male group (left panel), in which baseline HOMA-IR levels were significantly elevated compared with the female group (right panel) [20] (Fig. 18.2b). This suggests that BCAA-enriched supplement may be useful in ameliorating insulin resistance in male patients or in severely insulin resistant patients with chronic liver disease.

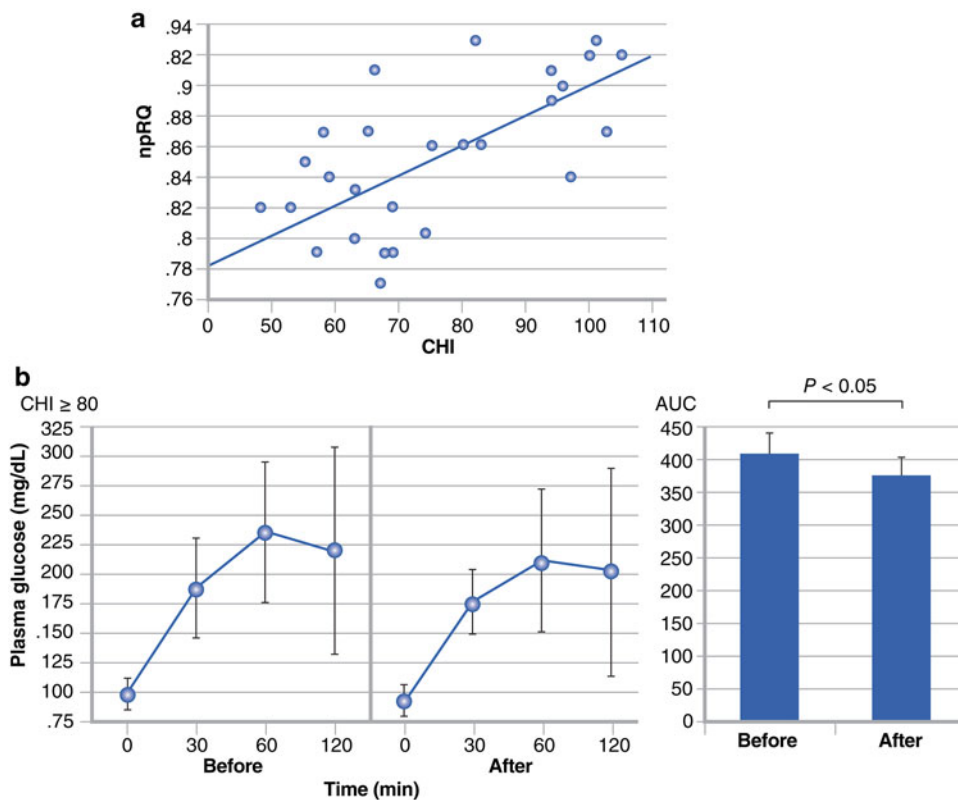


Fig. 18.1 The effect of 1-week supplementation with BCAAs in patients with liver cirrhosis (modified from [19]). (a) Significant correlation between the creatinine height index (CHI) and nonprotein respiratory quotient (npRQ) value after 1-week supplementation with BCAAs in liver cirrhosis patients. $n=30$, $r=0.644$, $P<0.01$. (b) Change of blood glucose level in 75 g OGTT after 1-week supplementation with BCAAs in liver cirrhosis patients with a CHI ≥ 80 . AUC, area under the curve made at four points by 75 g OGTT

In a crossover human study [21] (Fig. 18.3), it was examined whether an 8-h infusion of BCAAs or saline enhances maximal mitochondrial ATP production rate (MAPR) in skeletal muscle biopsy samples of 12 healthy young (23.0 ± 0.8 years) and 12 healthy elderly (70.7 ± 1.1 years) participants matched for sex and body mass index. In young participants, MAPR with the substrates glutamate plus malate (GM, supplying electrons to complex I) (Fig. 18.3a) and succinate plus rotenone (SR, complex II) (Fig. 18.3b) increased in response to BCAAs infusion, relative to a decline in MAPR in response to the saline infusion. In contrast, MAPR was unaffected by BCAAs infusion in the elderly participants [21] (Fig. 18.3). These findings suggest that BCAAs increase muscle mitochondrial function in the young but not in the elderly.

Based on the experimental findings discussed above, we hypothesized that BCAAs play a dual role in glucose metabolism in skeletal muscle, enhancing glucose uptake under normoinsulinemic conditions while causing insulin resistance under hyperinsulinemic conditions. In this regard, the effects of BCAA administration on glucose metabolism depend on the balance between insulin-dependent and insulin-independent BCAA signaling pathways [10]. We tested this hypothesis in our open-label, randomized, controlled crossover intervention trial [22] that addressed the effects of BCAAs on glucose tolerance and insulin sensitivity in patients with chronic hepatitis C and insulin resistance. Eligible participants were randomly assigned to the BCAAs group or a control group, and were then

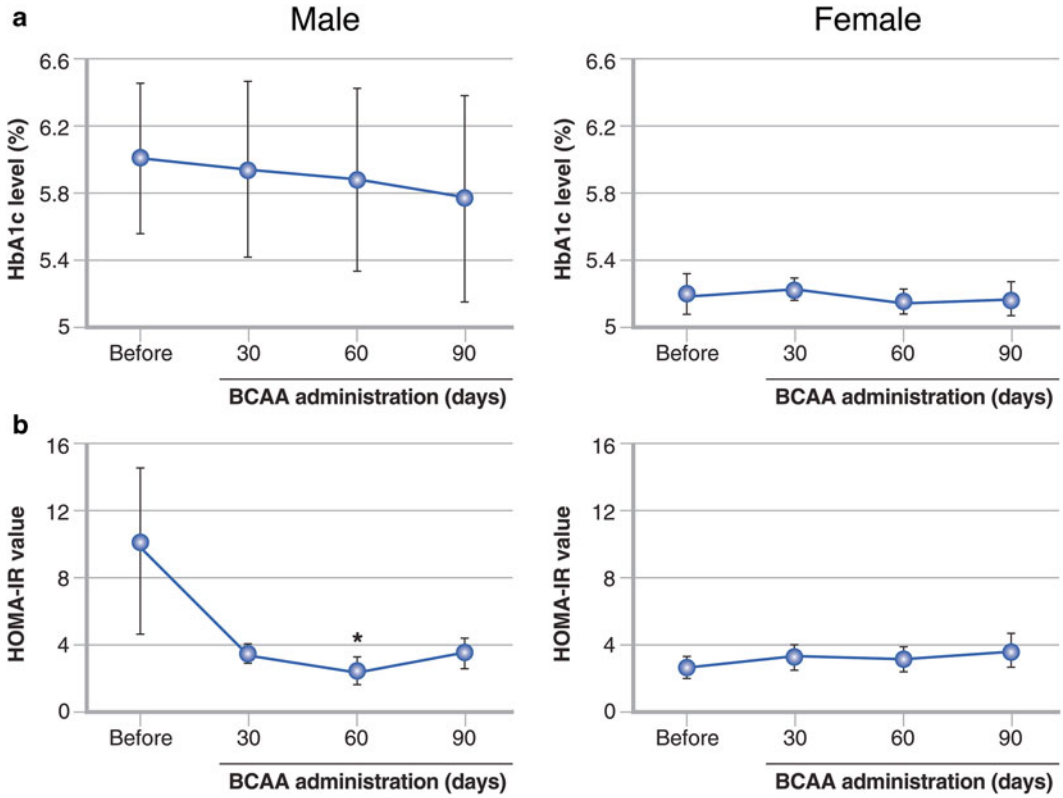


Fig. 18.2 The effects of BCAAs-enriched supplementation on HbA1c levels (a) and HOMA-IR values (b) in the male (left panel, n=5) and female (right panel, n=7) patients with chronic liver disease. Statistical comparisons between before and after 30, 60, or 90 days of the administration was performed by Wilcoxon’s test. *P<0.05. Modified from [20]

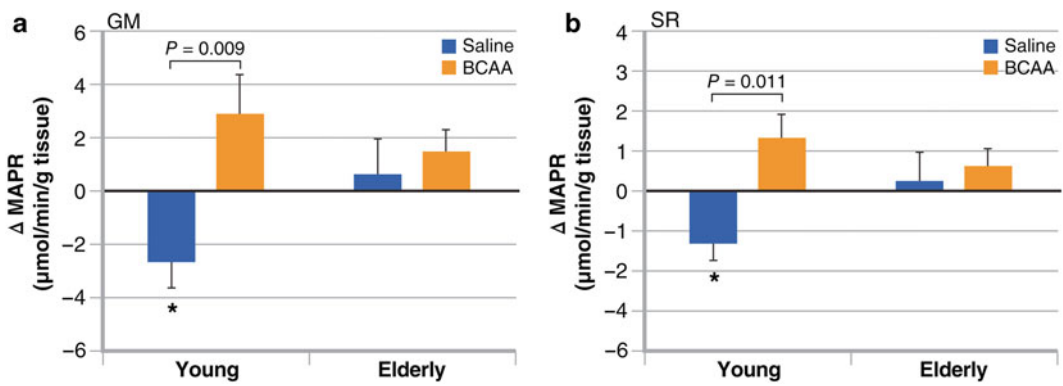


Fig. 18.3 The effect of BCAAs on skeletal muscle mitochondrial function in young and elderly adults (reprinted from [21]). (a and b) Change in maximal mitochondrial ATP production rate (MAPR) in response to saline (open bars) or BCAA (filled bars) normalized to tissue weight. MAPR was significantly lower in the elderly participants than the young when GM (complex I) was used (a) and a trend when SR (complex II) was used (b). Data presented as mean ± SEM. Mixed-effects ANOVA was used to test the main effects of age and treatment and their interaction

Table 18.1 Effects of BCAAs on body composition, protein, lipid and glucose metabolism in chronic hepatitis C patients with insulin resistance

	BCAA group	Control group	P value
Body weight (kg)	61.1±1.9	60.5±1.9	N.S
Waist circumference (cm)	87.8±1.7	88.9±1.7	N.S
BMI (kg/m ²)	24.9±0.5	24.7±0.4	N.S
FPG (mg/dL)	96.6±2.1	96.2±2.0	N.S
HbA1c (%)	4.9±0.1	5.0±0.1	N.S
IRI (IU/L)	17.8±3.6	21.2±4.6	N.S
HOMA-IR	4.5±1.1	5.3±1.3	N.S
TC (mg/dL)	157.6±7.2	164.9±7.3	N.S
TG (mg/dL)	78.3±6.3	80.9±5.3	N.S
HDL-C (mg/dL)	49.4±2.9	50.0±2.7	N.S
AST (IU/L)	61.2±6.9	46.0±3.0	P=0.047*
ALT (IU/L)	68.3±11.0	44.2±4.8	P=0.049*
BUN (mg/dL)	14.6±1.0	12.9±0.7	N.S
HpT (%)	86.8±4.2	91.4±5.7	N.S
Total protein (g/dL)	7.5±0.1	7.6±0.1	N.S
Albumin (g/dL)	4.0±0.1	4.0±0.1	N.S
BCAA (μmol/L)	472.6±27.0	403.5±21.0	P=0.050*
Matsuda index	2.9±0.3	2.5±0.2	N.S
H-IR×10 ⁶	6.6±0.1	6.2±0.6	N.S
MCR (mg/kg/min)	9.8±0.8	10.3±1.0	N.S

Modified from [22]

All data are expressed as the mean and standard error. Statistical comparisons between data from before administration of the BCAAs and data obtained after 12 and 24 weeks were performed using a Wilcoxon matched-pairs signed rank test. *BMI* body mass index, *FPG* fasting plasma glucose, *IRI* immunoreactive insulin, *HOMA-IR* homeostasis model assessment of insulin resistance, *H-IR* hepatic insulin resistance index, *MCR* glucose metabolic clearance rate

*Difference between the BCAA group and control group. *P* values of <0.05 were considered significant

crossed over to the other treatment for a further 12 weeks. Those in the BCAAs group were prescribed oral supplementation with three packs of a BCAAs nutrient (Livact® 4.15 g/pack), taken three times a day: after breakfast, after dinner, and before sleep for 12 weeks. Clinical features, laboratory markers, fatty acid levels, and insulin sensitivity, assessed with 75 g OGTT and a hyperinsulinemic euglycemic clamp (metabolic clearance rate, MCR), were examined before and 12 and 24 weeks after the beginning of the study (Table 18.1). Of the 27 patients who completed the study (ages 61.3±2.1 years, 8 men and 19 women, BMI 24.6±2.0 kg/m², mean±standard error), the plasma amino acid component that showed the strongest difference between the BCAAs and control groups was the combination of leucine, valine, phenylalanine, threonine, and proline (*P*<0.05) (Table 18.2). BCAA therapy did not have significant adverse or beneficial effects on glucose tolerance, insulin sensitivity, or lipid profiles in patients with chronic hepatitis C and insulin resistance (Table 18.1). These trends were similar in subgroups stratified by glucose tolerance (as diabetes, borderline glucose intolerance, and normal glucose tolerance). Additionally, unlike previous reports that suggested that BCAA-mediated improvements in insulin resistance are only observed in male patients [20], there were no significant sex differences in the effects of BCAA. HbA1c values were improved in 10 patients (37.0 %) and worsened or remained unchanged in 17 patients (63.0 %). As shown in Table 18.3, the only predictive variable for change in HbA1c was the baseline Matsuda index (1.8±0.2 in the HbA1c improved group, 2.9±0.3 in the HbA1c non-improved group, *P*=0.014) calculated from 75 g OGTT. Furthermore, the percentage change in HbA1c tended to be correlated with the percentage change in the Matsuda index (*r*=−0.405, *P*=0.069): the lower the index, the greater the improvement in HbA1c values [22].

Table 18.2 Effects of BCAAs on amino acids levels in chronic hepatitis C patients with insulin resistance

	Baseline	BCAA	Control	<i>P</i> value*
BCAA ($\mu\text{mol/L}$)	465.3 \pm 99.4	461.4 \pm 120.2	418.6 \pm 99.6	N.S.
Phenylalanine	103.7 \pm 10.9	112.8 \pm 23.9	105.5 \pm 14.7	<i>P</i> =0.014
Threonine	139.7 \pm 26.1	121.3 \pm 31.6	132.3 \pm 28.4	<i>P</i> =0.016
Proline	193.5 \pm 59.7	172.8 \pm 49.1	200.7 \pm 86.0	<i>P</i> =0.024
Leucine	140.3 \pm 28.6	144.2 \pm 40.8	129.5 \pm 31.4	<i>P</i> =0.025
Valinip	753.9 \pm 56.0	747.5 \pm 61.8	719.7 \pm 48.6	<i>P</i> =0.040
Glycine	334.5 \pm 46.2	306.6 \pm 49.7	376.6 \pm 272.5	N.S.
Tryptophan	64.9 \pm 11.9	64.9 \pm 13.9	62.2 \pm 12.9	N.S.
Arginine	135.5 \pm 31.9	125.9 \pm 36.5	136.6 \pm 37.5	N.S.
Ornithine	124.8 \pm 27.2	114.0 \pm 28.9	122.6 \pm 37.1	N.S.
Isoleucine	71.2 \pm 17.4	69.7 \pm 21.4	69.3 \pm 23.8	N.S.
Methionine	32.1 \pm 11.5	35.5 \pm 9.7	34.6 \pm 7.5	N.S.
Glutamine	277.2 \pm 169.5	365.2 \pm 191.2	406.5 \pm 157.4	N.S.
Lysine	20.8.7 \pm 37.7	194.9 \pm 41.2	193.3 \pm 44.9	N.S.
Histidine	96.3 \pm 10.7	92.7 \pm 13.4	90.8 \pm 12.3	N.S.
Citrulline	41.3 \pm 11.9	40.9 \pm 11.6	40.5 \pm 11.1	N.S.
Asparagine	37.5 \pm 10.4	43.2 \pm 11.2	44.1 \pm 7.4	N.S.
Alanine	485.5 \pm 84.9	441.7 \pm 78.5	463.4 \pm 152.1	N.S.
Threonine	139.7 \pm 26.1	121.3 \pm 31.6	132.3 \pm 28.4	N.S.
Tyrosine	131.5 \pm 27.0	129.6 \pm 24.9	130.3 \pm 22.3	N.S.

Modified from [22]

All data are expressed as the mean and standard error. Statistical comparisons between data from before administration of the BCAAs and data obtained after 12 and 24 weeks were performed using a Wilcoxon matched-pairs signed rank test

*Difference between the BCAA group and control group. *P* values of <0.05 were considered significant

Table 18.3 Baseline clinical features and laboratory markers associated with changes in HbA1c after 12 weeks of administration of BCAAs in chronic hepatitis C patients with insulin resistance

	HbA1c non-improved (<i>N</i> = μ 17)	HbA1c improved (<i>N</i> =10)	<i>P</i> value*
Body weight (kg)	61.6 \pm 2.4	57.6 \pm 2.2	N.S.
Waist circumference (cm)	87.7 \pm 1.8	87.6 \pm 1.5	N.S.
BMI (kg/m ²)	24.7 \pm 0.6	24.4 \pm 0.3	N.S.
FPG (mg/dL)	97.6 \pm 2.7	97.9 \pm 3.1	N.S.
HbA1c (%)	4.9 \pm 0.1	5.0 \pm 0.1	N.S.
IRI (IU/L)	14.0 \pm 1.6	29.0 \pm 11.1	N.S.
HOMA-IR	3.5 \pm 0.4	7.4 \pm 3.1	N.S.
TC (mg/dL)	160.7 \pm 11.4	146.8 \pm 7.7	N.S.
TG (mg/dL)	91.6 \pm 9.0	70.3 \pm 7.2	N.S.
HDL-C (mg/dL)	48.8 \pm 4.1	45.1 \pm 4.0	N.S.
AST (IU/L)	49.1 \pm 3.9	60.3 \pm 8.7	N.S.
ALT (IU/L)	43.9 \pm 5.1	60.2 \pm 17.1	N.S.
BUN (mg/dL)	13.9 \pm 1.1	13.1 \pm 1.4	N.S.
HpT (%)	89.5 \pm 6.5	84.1 \pm 3.8	N.S.
Total protein (g/dL)	7.6 \pm 0.2	7.4 \pm 0.2	N.S.
Albumin (g/dL)	4.1 \pm 0.1	3.9 \pm 0.1	N.S.
BCAA ($\mu\text{mol/L}$)	412.3 \pm 21.4	412.8 \pm 40.0	N.S.
Matsuda index	2.9 \pm 0.3	1.8 \pm 0.2	<i>P</i> =0.014*
H-IR \times 10 ⁶	5.5 \pm 0.6	6.7 \pm 1.0	N.S.
MCR (mg/kg/min)	10.1 \pm 1.0	8.6 \pm 1.3	N.S.

Modified from [22]

All data are expressed as the mean and standard error. Differences between the two groups were analyzed by a Mann-Whitney *U* test. *BMI* body mass index, *FPG* fasting plasma glucose, *IRI* immunoreactive insulin, *HOMA-IR* homeostasis model assessment of insulin resistance, *H-IR* hepatic insulin resistance index, *MCR* glucose metabolic clearance rate

*Difference between the HbA1c-non-improved group and the HbA1c-improved group. *P* values of <0.05 were considered significant

On the other hand, serum immunoreactive insulin (IRI), hepatic insulin resistance index (H-IR), and HOMA-IR, which are thought to be hepatic insulin resistance indices, did not significantly predict changes in HbA1c values (Table 18.3.). Therefore, BCAA supplementation therapy did not have adverse effects on glucose tolerance or insulin sensitivity in patients with chronic hepatitis C or insulin resistance. BCAAs did not significantly improve overall glycemic control in the present study. However, contrary to our initial hypothesis, BCAA therapy may exert a beneficial effect on HbA1c values in patients with marked insulin resistance in the skeletal muscle.

Conclusions

BCAAs supplementation therapy, together with their metabolites and their target mTOR-related signaling pathway, may modulate insulin signaling and glucose metabolism depending on their dosage, site of action, duration, and synergies with background lipid profiles, which follow a U-shaped curve, where too little or too much has a negative impact on systemic metabolism.

Toward comprehensive understanding of clinical BCAAs supplementation therapy on glucose metabolism, future clinical trials should also evaluate the effect of BCAAs in patients with type 2 diabetes.

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