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SYSTEMATIC REVIEW

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The impact of branched-chain amino acid supplementation on measures of glucose homeostasis in individuals with hepatic disorders: A systematic review of clinical studies

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Abstract

Background: Branched chain amino acid (BCAA) supplementation may influence glucose metabolism in individuals with an impaired glyceamic profile. This systematic review investigated the effects of isolated BCAA supplementation on measures of glucose homeostasis in individuals with hepatic disorders.

Methods: We searched PubMed, Web of Science, Cochrane Library and Scopus for published clinical trials that investigated the effects of isolated BCAA supplementation on measures of glucose homeostasis, including serum glucose and insulin, glycated haemoglobin (HbA1c) levels and homeostatic model assessment for insulin resistance (HOMA-IR) scores.

Results: Eleven trials met the inclusion criteria. Only one study revealed a decrease in serum glucose from BCAA supplementation compared to three studies that showed increases. Five studies demonstrated no significant changes in serum glucose, and two studies displayed no changes in HbA1c following BCAA supplementation. Serum levels of insulin were decreased in three studies, remained unchanged in one, and increased in the remaining three studies. BCAA supplementation reduced HOMA-IR scores in two studies, increased HOMA-IR scores in another two, or resulted in no changes in two other studies.

Conclusions: BCAA supplementation in isolation had no effect on overall glucose homeostasis in individuals with hepatic disorders, although some improvements on serum insulin levels and HOMA-IR scores were observed. Overall, there is little evidence to support the utilisation of BCAA supplementation as a potential nutritional strategy for improving measures of glucose homeostasis in individuals with hepatic disorders.

KEYWORDS

BCAA, branched chain amino acids, hepatic disorders, liver disease, nutritional supplementation

Key points

- Hepatic disorders such as liver cirrhosis, hepatic encephalopathy and hepatocellular carcinoma are characterised by an impaired circulating branched-chain amino acid (BCAA) profile.

- The aim of this systematic review was to explore the effects of isolated BCAA supplementation on markers of glucose metabolism in adults with hepatic disorders.
- Qualitative analysis revealed limited benefits of isolated BCAA supplementation on overall glucose homeostasis among individuals with hepatic disorders.
- BCAA supplementation as an independent strategy is not an effective tool in improving glucose homeostasis in this population group.

INTRODUCTION

Branched-chain amino acids (BCAAs; leucine, isoleucine, valine) are essential amino acids metabolised primarily in skeletal muscle.[1] Despite their prominent role in skeletal muscle protein metabolism, BCAAs are fractionally catabolised in other organs, including the liver and adipose tissue,[2] contributing to the upregulation of glucose transport and insulin secretion.[3] However, excessive BCAA consumption interferes with lipid oxidation in skeletal muscle,[4] leading to impaired insulin signalling.[3,5–7] Conversely, impaired insulin signalling may cause exacerbated skeletal muscle, adipose tissue and liver proteolysis,[8–10] which could potentially lead to high circulating levels of BCAAs.[11] Epidemiological evidence has proposed that insulin resistance (IR) may drive increased circulating fasting BCAA levels, as opposed to BCAA consumption being the primary driver of IR.[12] Indeed, a recent systematic review of observational studies has reported conflicting results on the association between intake of BCAAs and IR development, with two of the three reported studies suggesting a proportional relationship.[13]

BCAA supplementation has been reported to increase insulin secretion but with minimal influence on glyceamic responses,[14,15] as opposed to protein supplements such as whey protein, which may modulate glucose disposal in an insulin-dependent manner.[14,16–18] Particularly, an improved oral glucose sensitivity index and postprandial insulin secretion have been observed in humans following short (1 week)[19] and longer (4 and 8 weeks)[20,21] dietary BCAA intake restriction; however, longer trials may be warranted to elicit more clinically meaningful findings.

Hepatic disorders such as liver cirrhosis, hepatic encephalopathy and hepatocellular carcinoma are all characterised by decreased circulating BCAA levels.[22] Hepatic disorders have long been linked with impaired glucose tolerance and IR, which has more recently been observed to improve upon BCAA supplementation.[23–26] Indeed, BCAAs may increase peroxisome proliferator-activated receptor-γ and uncoupling protein (UCP)2 in the liver and UCP3 in skeletal muscle, stimulating free fatty acid oxidation and improving insulin sensitivity.[22] The effects of BCAA consumption on glyceamic profile may depend on dose, duration and individual health status. These observations of improved IR and glucose tolerance with BCAA supplementation contrast considerably with the association of elevated serum BCAAs with IR in some chronic diseases. The aim of this systematic review was to investigate the effects of isolated BCAA supplementation on markers of glucose metabolism in adults with various hepatic disorders.

METHODS

This systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[27] guidelines and the protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (Registration number: CRD42022304636).

Search strategy

Two independent reviewers (KP and RK) searched PubMed, Scopus, Web of Science and Cochrane Library, using the following search terms: "BCAA" OR "branched chain amino acids" OR "leucine" AND "insulin" OR "blood glucose" OR "glycaemic" OR "blood sugar" OR "HbA1c" OR "HOMA-IR" AND "liver disease" OR "hepatic disorder" OR "cirrhosis" OR "hepatitis" OR "hepatocellular carcinoma" OR "portal vein embolisation" OR "hepatic encephalopathy". The full search strategy and search terms used are described in the Supporting information (Table S1). Discrepancies in the literature search process were resolved by a third and fourth investigator (PG and KKT).

Study eligibility

Studies were included based on the following inclusion criteria: (1) human studies in populations with hepatic disorders; (2) clinical trials; (3) BCAAs as an intervention group; and (4) oral route of administration. Studies were excluded based on the following exclusion criteria: (1) non-clinical trials; (2) BCAA co-ingestion with a mixed meal; (3) acute studies lasting < 7 days; and (4) full text not published.

Data extraction and risk of bias

Two reviewers (KP and RPK) extracted data based on name of first author, publication date, country of origin, study design, participant health status, age, sex, sample size, outcome measures, supplemental form, dose and duration. Disagreements between reviewers were resolved by a third and fourth investigator (PG and KSK). The quality of included studies was assessed using the Cochrane Risk-of-Bias 2 (RoB2) for randomised trials tool and evaluated by three independent reviewers (KP, PG and KKT). Appraisal of risk of bias using the RoB2 tool included assessment of the domains of bias in randomised controlled trials (RCTs): (1) randomisation process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome; and (5) selection of the reported result.[28] According to the RoB2 tool scoring system, study quality was defined as low risk of bias, some concerns or high risk of bias. In addition, risk of bias assessment for the non-randomised (single arm) trials was performed using the Risk Of Bias In Non-Randomised Studies—of Interventions (ROBINS-I) tool that classifies studies based on bias due to: (1) confounding factors; (2) selection of participants into the study; (3) the classification of interventions; (4) deviations from intended interventions; (5) missing data; (6) outcome measurements; and (7) selection of the reported result.[29] According to ROBINS-I tool, the quality of studies was categorised as low, moderate or serious risk.

RESULTS

Search results

The literature search yielded 3403 publications. In total, 1318 duplicates were excluded, and 2085 publications were sought for retrieval. Following screening of tittles, abstracts and full texts, 20 studies were retrieved examining the effects of BCAA supplementation on markers of glucose metabolism. Of these, two studies had ineligible interventions, three had incompatible study population and four had missing data. Overall, 11 studies were deemed eligible for inclusion in the review (Figure 1).

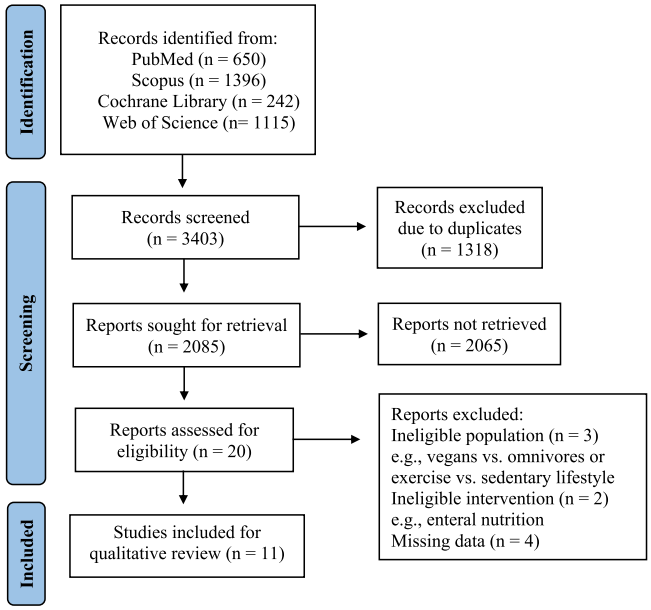

FIGURE 1 Flowchart of the employed literature search

Characteristics of the included studies

All relevant information pertained to participant characteristics are summarised in Table 1. Of the 11 studies, seven studies were conducted in Japan,[30–36] two in Mexico,[38,39] one in Italy[37] and one in Spain.[40] Two studies were conducted in individuals aged between 50 and 60 years[32,39] and nine in individuals ≥ 60 years.[30,31,33–38,40] All studies were cohorts of both males and females. Two studies did not provide relevant information pertained to the total number of males and females.[32,37]

Further, four studies were RCTs,[31,33,34,36] two were double-blinded RCTs,[37,40] one was a crossover, open-label RCT,[32] one was an open label RCT[39] and three were clinical trials.[30,35,38] Moreover, seven used BCAA supplementation alone,[30–34,37,38] three co-supplemented vitamins and minerals[35,36,40] of which one followed a physical activity protocol,[40] and one followed a high-protein/high-fibre diet.[39] BCCA supplementation ranged from 4 weeks to 48 months in terms of duration and from 2.4 to 30 g day^{-1} in terms of dosage.

Amongst the comparator groups, two studies used placebo controls,[37,40] of which one included physical activity,[40] one used an isocaloric control snack,[36] four used a usual diet regime,[31–34] one used a high-protein/high fibre diet[39] and three were single arm trials.[30,35,38]

Six studies included individuals with liver cirrhosis,[30,34,36,37,39,40] of which one experimented with sleep disturbance,[34] one with hepatocellular carcinoma (HCC),[33] two with hepatitis,[32,38] of which one included participants with insulin resistance,[32] one with portal vein embolisation (PVE) and sequential hepatectomy.[31]

Serum insulin

BCAA supplementation led to conflicting results regarding serum insulin levels. Specifically, 8 g day^{-1} of BCAA for 6 months, decreased serum insulin from 13.85 (6.6–18.6) U ml^{-1} to 7.9 (5.0–96.9) U ml^{-1} in patients undergoing PVE; however, similar changes were shown in the control group, which followed their usual diet

TABLE 1 Study and participant characteristics of the included studies

Reference (year)	Country	Study design	Total	BCAA		Comparator		Treatment dose (g day^{-1})	Treatment duration	Health status	Reported outcomes
			n (M/F)	*n* (M/F)	Age (SD)	*n* (M/F)	Age (SD)				
Hernandez-Conde et al.[40]	Spain	Double-blind RCT	32 (28/4)	17 (15/2)	69 (9.7)	15 (13/2)	61 (9.4)	5.2	12 weeks	Cirrhosis	HOMA-IR
Ruiz-Margain et al.[39]	Mexico	Open-label RCT	72 (14/58)	37 (6/31)	54.9 (10.3)	35 (8/27)	47.8 (14.6)	8.6	6 months	Cirrhosis	Glucose
Kitajima et al.[30]	Japan	Clinical Trial	21 (9/12)	21 (9/12)	71.3 (7.9)	–	–	4	48 weeks	Cirrhosis	Insulin Glucose HOMA-IR
Ocana-Mondragon et al.[38]	Mexico	Clinical trial	20 (10/10)	20 (10/10)	53 (45.63)	–	–	30	3 months	Chronic hepatitis C	Insulin Glucose HOMA-IR
Beppu et al.[31]	Japan	RCT	28 (19/9)	13 (9/4)	64 (47–83)	15 (10/5)	72 (56–78)	8	6 months	PVE	Insulin Glucose HbA1c
Takeshita et al.[32]	Japan	Crossover, open label RCT	24	13	58.6 (2.9)	11	64.2 (3.0)	12.5	12 weeks	Hepatitis C IR	Insulin Glucose HOMA-IR HbA1c
Yoshiji et al.[33]	Japan	RCT	42 (26/16)	16 (10/6)	63.7 (10.8)	26 (16/10)	62.5 (11.5)	12	48 months	HCC	Glucose HOMA-IR
Ichikawa et al.[34]	Japan	RCT	21 (10/11)	12 (5/7)	66.2 (8.2)	9 (5/4)	67.4 (9.9)	13.5	8 weeks	Cirrhosis Sleep Disturbance	Glucose
Kawaguchi et al.[35]	Japan	Clinical Trial	12 (5/7)	12 (5/7)	64.3 (2.4)	–	–	6.4	90 days	Chronic liver disease	Insulin Glucose HOMA-IR HbA1c
Nakaya et al.[36]	Japan	RCT	38 (20/18)	19 (13/6)	67 (9)	19 (7/12)	67 (8)	12.3	3 months	Cirrhosis	Insulin Glucose
Marchesini et al.[37]	Italy	Double-blind RCT	61	29	60 (44–70)	32	60 (43–70)	2.4	3 months	Cirrhosis	Insulin Glucose

Abbreviations: BCAA, branched chain amino acid; F, female; HbA1c, glycated haemoglobin; HCC, hepatocellular carcinoma; HOMA-IR, homeostatic model assessment for insulin resistance; IR, insulin resistance; M, male; PVE, portal vein embolisation; RCT, randomised controlled trial.

(13.50 (4.4–18.8)–9.2 (2.7–38.8) U ml^{-1}).[31] Furthermore, another study in patients with liver cirrhosis showed that 3 months of 2.4 g day^{-1} BCAA slightly improved serum insulin (25 ± 17 to 23 ± 17 μU L^{-1}) compared to placebo (casein) group (19 ± 10 to 22 ± 17 μU L^{-1}), although no significant changes were observed.[37] By contrast, in patients with hepatitis C and insulin resistance, BCAA supplementation (12.5 g day^{-1}) increased serum insulin levels after 12 weeks (13.8 ± 1.6 to 17.8 ± 3.6 μU L^{-1}) as opposed to participants following their usual dietary patterns (23.3 ± 8.0 to 21.2 ± 4.6 μU L^{-1}).[32] Furthermore, another study showed a substantial increase of serum insulin (16.2 ± 6.8 to 32.9 ± 34.5 μU ml^{-1}) compared to an isocaloric control snack (21.3 ± 19.5 to 20.9 ± 14.4 μU ml^{-1}) in patients with liver cirrhosis.[36] However, in this case the supplementary product consisted of BCAAs alongside vitamins and minerals. In the single arm studies, a high BCAA dose (30 g day^{-1}) was slightly effective in reducing serum insulin levels (16 [11–31] to 14 [9–22] μU L^{-1}) in patients with chronic hepatitis C when administered for 30 months,[38] whereas another study displayed a significant decrease of serum insulin (22.8 ± 9.7 to 13.3 ± 1.9 μU ml^{-1}) after BCAA supplementation (6.4 g day^{-1}) with vitamins and minerals after 90 days in patients with chronic liver disease.[35] Finally, one study demonstrated a small increase in serum insulin (14.2 ± 11.8 to 15.7 ± 16.5 μU ml^{-1}) following a low BCAA dose (4 g day^{-1}) in patients with liver cirrhosis for 48 weeks.[30]

Serum glucose

Conflicting results were also observed on serum glucose after BCAA supplementation. In one study using 8.6 g day^{-1} BCAA,[39] a small increase in serum glucose levels in the intervention (110.8 ± 52.9 to 112 ± 52 mg dl^{-1}) group was observed as opposed to the control group (104.3 ± 45.4 to 94.1 ± 17.4 mg dl^{-1}) in patients with liver cirrhosis when administered 6 months. Likewise, another study displayed a similar trend following 12.3 g day^{-1} BCAA co-supplemented vitamins and minerals (107 ± 23 to 118 ± 39 mg dl^{-1}) compared to an isocaloric snack group (99 ± 26 to 95 ± 10 mg dl^{-1}).[36] Furthermore, another study also showed a small increase in the intervention (92.1 ± 2.1 to 96.6 ± 2.1 mg dl^{-1}) compared to the usual diet group (100.6 ± 2.9 to 96.2 ± 2.0 mg dl^{-1}).[32] On the other hand, a significant decrease in serum glucose levels (126.0 [75–184] to 98.0 (84–242) mg dl^{-1}) was reported after 6 months with 8 g day^{-1} BCAA supplementation compared to usual diet (101.0 [87–123 to 104.0 (90–125) mg dl^{-1}) in patients with PVE.[31] No changes were seen in serum glucose levels of patients with HCC between the intervention (102.7 ± 30.6 to 95.4 ± 31.1 mg dl^{-1}) and the control group (113.4 ± 28.8 to 107.8 ± 31.2 mg dl^{-1}) following 12 g day^{-1} for 48 months.[33] In addition, an identical trend was depicted in patients with liver cirrhosis and sleep disturbance after 13.5 g day^{-1} BCAA for 8 weeks (107.5 ± 27.2 to 105.7 ± 73.2 mg dl^{-1}) against usual diet (115.4 ± 27.2 to 111.6 ± 24.2 mg dl^{-1}).[34] In the single arm studies, serum glucose was reduced in each trial, however, no significant decrease was displayed (113.6 ± 31.7 to 108.5 ± 27.7 mg dl^{-1})[30]; (124.2 ± 9 to 120.6 [109.9–133.3] mg dl^{-1})[38]; (104.5 ± 6.4 to 102.8 ± 5.4 mg dl^{-1}).[35]

Glycated haemoglobin

No changes in HbA1c were observed following 12.45 g day^{-1} BCAA supplementation for 12 weeks compared to usual diet in IR patients with hepatitis C (5.0% ± 0.1% to 4.9% ± 0.1% vs. 4.9% ± 0.1% to 5.0% ± 0.1%).[32] Additionally, no changes on HbA1c were revealed after consumption of 6.4 g/day BCAA for 90 days (5.5% ± 0.2% to 5.4% ± 0.3%).[35]

Homeostatic model assessment for insulin resistance

The overall score of HOMA-IR was reduced following 5.2 g day^{-1} BCAA co-supplemented with vitamins, minerals and physical activity after 12 weeks (4.9 ± 6.7 to 3.2 ± 1.8); however, no differences were observed compared to the physical activity and placebo group (6.3 ± 8.6 to 4.7 ± 3.2).[40] Similarly, identical findings were identified following 12 g day^{-1} of BCAA supplementation for 12 weeks (3.55 ± 3.01 to 2.75 ± 2.08) against placebo (3.79 ± 2.92 to 3.61 ± 2.88).[33] Interestingly, an increase in HOMA-IR score was demonstrated after 12.45 g day^{-1} for 12 weeks of BCAA (3.2 ± 0.4 to 4.5 ± 1.1) compared to usual diet that reduced HOMA-IR (6.1 ± 2.2 to 5.3 ± 1.3).[32] In the single arm studies, BCAA supplementation led to a decrease in HOMA-IR after 90 days as observed in (5.5 ± 2.1 to 3.5 ± 0.6)[35] and (3.5 (2.6–7.9) to 3.2 (1.9–5.0).[38] Finally, a study revealed higher HOMA-IR scores following a 4 g day^{-1} BCAA dose for 48 weeks (3.9 ± 3.0 to 4.5 ± 5.4).[30]

Risk of bias

According to RoB2, risk of bias was high in one study[31] as a result of lack of information relevant to treatment allocation concealment and participants and trial personnel knowing about the type of intervention. Finally, some concerns were raised in three studies as a result of participants possibly knowing about the type of intervention.[32,34,36] A detailed traffic light plot is presented in Figure 2.

According to ROBINS-I, moderate risk of bias was displayed in one study as a result of insufficient control for confounders (i.e., physical activity).[30] Serious risk of

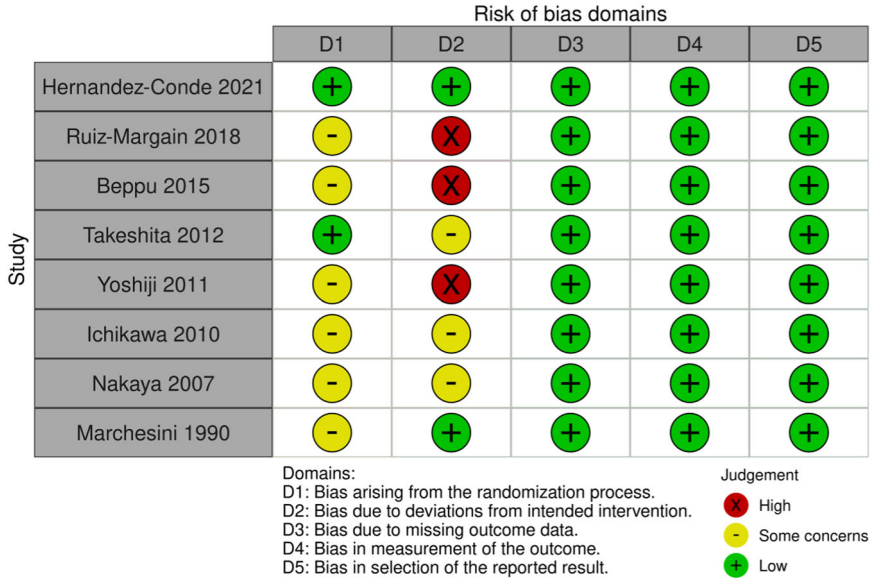

FIGURE 2 Quality assessment of the included studies according to the Cochrane Risk-of-Bias 2 (RoB2) tool for randomised trials

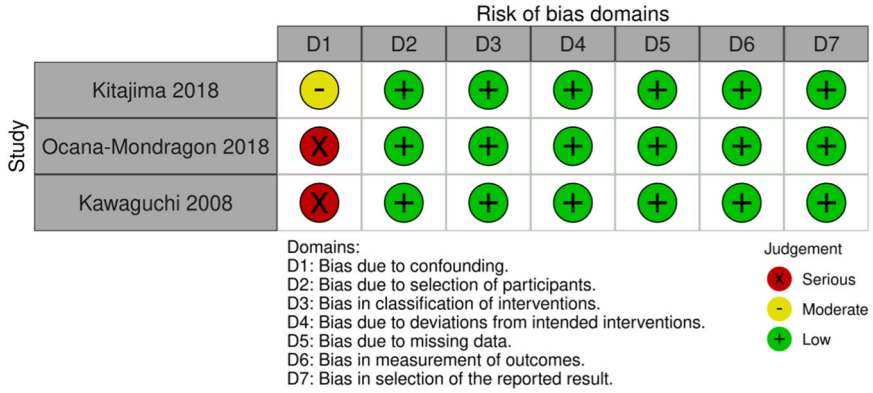

FIGURE 3 Quality assessment of the included non-randomised (single arm) studies according to the Risk Of Bias In Non-randomised Studies-of Interventions tool (ROBINS-I)

bias was observed in two studies as a result of no control for major confounding factors (i.e., diet and physical activity).[38] A detailed traffic light plot is presented in Figure 3.

DISCUSSION

In this systematic review, we identified 11 studies examining the effects of BCAA supplementation on markers of glucose metabolism in participants with hepatic disorders. Overall, BCAA supplementation resulted in small decreases in serum insulin and HOMA-IR scores with no effect on serum glucose levels or changes in HbA1c.

The maintenance of physiological serum glucose is an essential component of glucose homeostasis, with impaired glycaemic control linked to a greater risk of chronic diseases such as type 2 diabetes (T2D) and cardiovascular disease.[41,42] A contributing factor to poor glyceamic control is IR. Epidemiological data has shown that IR and clinical diagnoses of T2D and prediabetes are associated with elevated serum BCAAs.[43] By contrast to the observation of higher serum BCAA levels in those with IR or T2D, BCAA supplementation has been reported in some cases to improve measures of glucose homeostasis.[44] Recent research using Mendelian randomisation analysis has further clarified that elevated serum BCAAs are likely driven by the presence of IR and not the other way around (i.e., elevated serum BCAA do not drive IR).[12]

Animal models have revealed that a mechanism for the potentially beneficial effects of BCAA supplementation on glyceamic control is the activation of phosphoinositide-3 kinase (PI3K). This increase in insulin sensitivity and upregulation of glucose transporter protein 4 (GLUT4) may facilitate non-insulin mediated entry of glucose into cells.[45] Additional research in rat models has duplicated the observation of increased GLUT4 translocation to the skeletal muscle cell membrane as well as increased translocation of the GLUT1 glucose transporter protein.[46] The same research group observed an upregulation of glycogen synthase activity in leucine treated rats, which resulted in increased glycogen

content in soleus muscle compared to controls.[46] Such increased synthesis of glycogen by taking excess serum glucose out of circulation and storing it in skeletal muscle, could assist with overall glyceamic regulation.

Insulin sensitivity may be further affected by increased utilisation of glucose as fuel through glycolysis, via upregulation of GLUT2 and glucokinase in the liver, leading to improved bioactivity of the glucose-sensing apparatus.[47] Specifically, glucokinase is involved in the regulation of hepatic glycolysis and glucose oxidation, glycogen synthase, glycogenolysis and gluconeogenesis amongst others.[48] Therefore, BCAA supplementation may act as a partial substitute for insulin in glucose transport regulation by increasing glycogen synthesis in both skeletal muscle and liver. However, it should be noted that some research has reported conflicting results. Specifically, infusion of amino acids including leucine and isoleucine in human subjects has been reported to compete with glucose as an oxidative fuel, reducing glucose uptake.[49] Nevertheless, the aforementioned study involved venous infusion and not dietary supplementation of BCAAs, indicating that elevated serum levels of BCAAs may interfere with glyceamic control and not necessarily dietary intake.

Moreover, increased adiposity and in particular, skeletal muscle and liver tissue triglyceride (TG) accumulation are known to interfere with GLUT4 translocation and glucose uptake, mediated via the activation of insulin-stimulated PI3K, which may lead to IR.[50] In mouse models, supplementation with the BCAA isoleucine has been reported to reduce accumulation of TG in both skeletal muscle and liver tissue.[51,52] This is speculated to occur via upregulation of peroxisome proliferator-activated receptor-α and UCP2 in liver tissue and UCP3 in the skeletal muscle tissue. Thus, leading to increased free fatty acid oxidation, which results in improvements of insulin sensitivity induced by lipotoxicity.[51,53]

Limitations

This systematic review is the first to examine the effects of isolated BCAA supplementation on markers of glucose metabolism in patients with hepatic disorders. The prevailing limitation of this review was the inability to produce a meta-analysis as a result of the heterogeneity in study designs. The large heterogeneity in protocols that can be observed in the populations included, the varied dosage of BCAA supplementation (2.4–30 g day^{-1}), and study duration (4 weeks to 48 months). Furthermore, of the 11 studies included, seven involved Japanese populations, with the remaining four studies from the USA, Spain, Mexico and Italy, which may raise concerns regarding the generalisability of the results to other geographical regions or ethnicities. Finally, inconsistencies among dietary intakes among studies, in which there was no control is a critical confounding factor in extrapolating more accurate conclusions regarding the effects of BCAA supplements in isolation.

CONCLUSIONS

This systematic review revealed limited effects of isolated BCAA supplementation on overall glucose homeostasis among individuals with hepatic disorders, however, some improvements on serum insulin and HOMA-IR scores were observed. Studies should be aware of controlling strictly for dietary intake to omit the potential impact of other nutrients on glucose homeostasis and incorporate a placebo group as a comparator that would reduce bias risk. BCAA supplementation as an independent strategy appears to may not be an effective tool in improving glucose homeostasis in patients with hepatic disorders.

AUTHOR CONTRIBUTIONS

Study concept and design: Konstantinos Prokopidis and Panagiotis Giannos. *Acquisition of data*: Konstantinos Prokopidis, Richard P. Kirwan and Konstantinos K. Triantafyllidis. *Analysis and interpretation of data*: Konstantinos Prokopidis, Richard P. Kirwan and Konstantinos S. Kechagias. *Drafting of the manuscript*: Konstantinos Prokopidis, Richard P. Kirwan and Panagiotis Giannos. *Critical revision of the manuscript for important intellectual content*: Konstantinos Prokopidis, Richard P. Kirwan, Panagiotis Giannos, Scott C. Forbes and Darren G. Candow.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

TRANSPARENCY DECLARATION

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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