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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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KeyPoints

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

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- 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.

ABSTRACT

Background

Branched chain amino acid (BCAA) supplementation may influence glucose metabolism in individuals with impaired glycemic 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 hemoglobin (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, whilst 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 utilization of BCAA supplementation as a potential nutritional strategy for improving measures of glucose homeostasis in individuals with hepatic disorders.

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

INTRODUCTION

Branched-chain amino acids (BCAAs: leucine, isoleucine, valine) are essential amino acids metabolized primarily in skeletal muscle (White, 2021). Despite their prominent role in skeletal muscle protein metabolism, BCAAs are fractionally catabolized in other organs, including the liver and adipose tissue (Brosnan and Brosnan, 2006), contributing to the upregulation of glucose transport and insulin secretion (Zhou et al., 2019). However, excessive BCAA consumption interferes with lipid oxidation in skeletal muscle (White et al., 2016), leading to impaired insulin signaling (Crossland et al., 2020, Tremblay et al., 2007, Jang et al., 2016, Zhou et al., 2019). Conversely, impaired insulin signaling may cause exacerbated skeletal muscle, adipose tissue, and liver proteolysis (Lake et al., 2015, Cheng et al., 2015, Lerin et al., 2016), which could potentially lead to high circulating levels of BCAAs (White et al., 2021). 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 (Mahendran et al., 2017). 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 (Vieira et al., 2020).

BCAA supplementation has been reported to increase insulin secretion but with minimal influence on glycemic responses (Smith et al., 2015, Zhang et al., 2011), as opposed to protein supplements such as whey protein which may modulate glucose disposal in an insulin-dependent manner (Pal et al., 2010, Smith et al., 2015, Smith et al., 2020, Stevenson and Allerton, 2018). Particularly, improved oral glucose sensitivity index and postprandial insulin secretion have been observed in humans following short (1 week) (Ramzan et al., 2021) and longer (4 and 8 weeks) (Fontana et al., 2016, Karusheva et al., 2019) 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 characterized by decreased circulating BCAA levels (Tajiri and Shimizu, 2013). Hepatic disorders have long been linked with impaired glucose tolerance and IR, which has more recently been observed to improve upon BCAA supplementation (Sakaida et al., 2004, Kato et al., 1998, Sato et al., 2005, Park et al.,

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2017). Indeed, BCAAs may increase peroxisome proliferator-activated receptor (PPAR)-γ and uncoupling protein 2 (UCP2) in the liver and UCP3 in skeletal muscle, stimulating free fatty acid oxidation and improving insulin sensitivity (Tajiri and Shimizu, 2013). The effects of BCAA consumption on glycemic 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) (Page et al., 2021) 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 embolization” OR “hepatic encephalopathy”. The full search strategy and search terms used are described in 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 authors (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

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authors were resolved by a third and fourth reviewer (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 RCTs: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result (Higgins et al., 2011). 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-randomized (single arm) trials was performed using the Risk Of Bias In Non-Randomized 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.(Sterne et al., 2016) According to ROBINS-I tool, the quality of studies was categorized 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).

Characteristics of the included studies

All relevant information pertained to participant characteristics are summarized in Table 1. Of the 11 studies, seven studies were conducted in Japan (Kitajima et al., 2018, Beppu et al., 2015, Yoshiji et al., 2011, Ichikawa et al., 2010, Kawaguchi et al., 2008, Nakaya et al., 2007, Takeshita et al., 2012), two in Mexico (Ruiz-Margáin et al., 2018, Ocaña-Mondragón et al., 2018), one in Italy (Marchesini et al., 1990), and one in Spain (Hernández-Conde et al., 2021). Two studies were conducted in individuals aged between 50-60 years (Ruiz-Margáin et al., 2018, Takeshita et al., 2012) and nine in individuals ≥ 60 years (Kitajima et al., 2018, Beppu et al., 2015,

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Yoshiji et al., 2011, Ichikawa et al., 2010, Kawaguchi et al., 2008, Nakaya et al., 2007, Ocaña-Mondragón et al., 2018, Marchesini et al., 1990, Hernández-Conde et al., 2021). 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 (Takeshita et al., 2012, Marchesini et al., 1990).

Further, four studies were RCTs (Beppu et al., 2015, Yoshiji et al., 2011, Ichikawa et al., 2010, Nakaya et al., 2007), two were double-blinded RCTs (Hernández-Conde et al., 2021, Marchesini et al., 1990), one was a crossover, open-label RCT (Takeshita et al., 2012), one was an open label RCT (Ruiz-Margáin et al., 2018), and three were clinical trials (Kitajima et al., 2018, Ocaña-Mondragón et al., 2018, Kawaguchi et al., 2008). Moreover, seven used BCAA supplementation alone (Kitajima et al., 2018, Ocaña-Mondragón et al., 2018, Beppu et al., 2015, Yoshiji et al., 2011, Takeshita et al., 2012, Ichikawa et al., 2010, Marchesini et al., 1990), three co-supplemented vitamins and minerals (Hernández-Conde et al., 2021, Kawaguchi et al., 2008, Nakaya et al., 2007) of which one followed a physical activity protocol (Hernández-Conde et al., 2021), and one followed a high-protein/high-fiber diet (Ruiz-Margáin et al., 2018). BCCA supplementation ranged from 4 weeks to 48 months in terms of duration and from 2.4 to 30 g/day in terms of dosage.

Amongst the comparator groups, two studies used placebo controls (Marchesini et al., 1990, Hernández-Conde et al., 2021), of which one included physical activity (Hernández-Conde et al., 2021), one used an isocaloric control snack (Nakaya et al., 2007), four used a usual diet regime (Beppu et al., 2015, Yoshiji et al., 2011, Takeshita et al., 2012, Ichikawa et al., 2010), one used a high-protein/high fiber diet (Ruiz-Margáin et al., 2018), while three were single arm trials (Kitajima et al., 2018, Ocaña-Mondragón et al., 2018, Kawaguchi et al., 2008).

Six studies included individuals with liver cirrhosis (Hernández-Conde et al., 2021, Ruiz-Margáin et al., 2018, Kitajima et al., 2018, Ichikawa et al., 2010, Nakaya et al., 2007, Marchesini et al., 1990), of which one experimented with sleep disturbance (Ichikawa et al., 2010), one with hepatocellular carcinoma (HCC) (Yoshiji et al., 2011), two with hepatitis (Ocaña-Mondragón et al., 2018, Takeshita et al., 2012), of which one included participants with insulin resistance (Takeshita et al., 2012), one with portal vein embolization (PVE) and sequential hepatectomy (Beppu et al., 2015).

Serum insulin

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BCAA supplementation led to conflicting results regarding serum insulin levels. Specifically, 8 g/d of BCAA for 6 months, decreased serum insulin from 13.85 (6.6 – 18.6) U/mL to 7.9 (5.0 – 96.9) U/mL in patients undergoing PVE, however, similar changes were shown in the control group, which followed their usual diet (13.50 (4.4 – 18.8) U/mL to 9.2 (2.7 – 38.8) U/mL) (Beppu et al., 2015). Furthermore, another study in patients with liver cirrhosis showed that 3 months of 2.4 g/d BCAA slightly improved serum insulin (25 ± 17 μU/L to 23 ± 17 μU/l) compared to placebo (casein) group (19 ± 10 μU/l to 22 ± 17 μU/l), although no significant changes were observed (Marchesini et al., 1990). On the contrary, in patients with hepatitis C and insulin resistance, BCAA supplementation (12.5 g/d) increased serum insulin levels after 12 weeks (13.8 ± 1.6 μU/l to 17.8 ± 3.6 μU/l) as opposed to participants following their usual dietary patterns (23.3 ± 8.0 μU/l to 21.2 ± 4.6 μU/l) (Takeshita et al., 2012). Furthermore, another study showed a substantial increase of serum insulin (16.2 ± 6.8 μU/mL to 32.9 ± 34.5 μU/mL) compared to an isocaloric control snack (21.3 ± 19.5 μU/mL to 20.9 ± 14.4 μU/mL) in patients with liver cirrhosis (Nakaya et al., 2007). 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/d) was slightly effective in reducing serum insulin levels (16 (11 – 31) μU/l to 14 (9 – 22) μU/l) in patients with chronic hepatitis C when administered for 30 months (Ocaña-Mondragón et al., 2018), while another study displayed a significant decrease of serum insulin (22.8 ± 9.7 μU/mL to 13.3 ± 1.9 μU/mL) after BCAA supplementation (6.4 g/d) with vitamins and minerals after 90 days in patients with chronic liver disease (Kawaguchi et al., 2008). Finally, one study demonstrated a small increase in serum insulin (14.2 ± 11.8 μU/mL to 15.7 ± 16.5 μU/mL) following a low BCAA dose (4 g/d) in patients with liver cirrhosis for 48 weeks (Kitajima et al., 2018).

Serum glucose

Conflicting results were also observed on serum glucose after BCAA supplementation. In one study using 8.6 g/d BCAA (Ruiz-Margáin et al., 2018), a small increase in serum glucose levels in the intervention (110.8 ± 52.9 mg/dl to 112 ± 52 mg/dl) group was observed as opposed to the control group (104.3 ± 45.4 mg/dl to 94.1 ± 17.4 mg/dl) in patients with liver cirrhosis when administered 6 months. Likewise, another study displayed a similar trend following 12.3 g/d BCAA co-supplemented vitamins and minerals (107 ± 23 mg/dl to 118 ± 39 mg/dl) compared to

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an isocaloric snack group (99 ± 26 mg/dl to 95 ± 10 mg/dl) (Nakaya et al., 2007). Furthermore, another study also showed a small increase in the intervention (92.1 ± 2.1 mg/dl to 96.6 ± 2.1 mg/dl) compared to the usual diet group (100.6 ± 2.9 mg/dl to 96.2 ± 2.0 mg/dl) (Takeshita et al., 2012). On the other hand, a significant decrease in serum glucose levels (126.0 (75 – 184) mg/dl to 98.0 (84 – 242) mg/dl) was reported after 6 months with 8 g/d BCAA supplementation compared to usual diet (101.0 (87 – 123 mg/dl to 104.0 (90- 125) mg/dl) in patients with PVE (Beppu et al., 2015). No changes were seen in serum glucose levels of patients with HCC between the intervention (102.7 ± 30.6 mg/dl to 95.4 ± 31.1 mg/dl) and the control group (113.4 ± 28.8 mg/dl to 107.8 ± 31.2 mg/dl) following 12 g/d for 48 months (Yoshiji et al., 2011). In addition, an identical trend was depicted in patients with liver cirrhosis and sleep disturbance after 13.5 g/d BCAA for 8 weeks (107.5 ± 27.2 mg/dl to 105.7 ± 73.2 mg/dl) against usual diet (115.4 ± 27.2 mg/dl to 111.6 ± 24.2 mg/dl) (Ichikawa et al., 2010). In the single arm studies, serum glucose was reduced in each trial, however, no significant decrease was displayed (113.6 ± 31.7 mg/dl to 108.5 ± 27.7) (Kitajima et al., 2018); (124.2 ± 9 mg/dl to 120.6 (109.9 – 133.3) mg/dl) (Ocaña-Mondragón et al., 2018); (104.5 ± 6.4 mg/dl to 102.8 ± 5.4 mg/dl) (Kawaguchi et al., 2008).

Glycated haemoglobin

No changes in HbA1c were observed following 12.45 g/d 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%) (Takeshita et al., 2012). Additionally, no changes on HbA1c were revealed after consumption of 6.4 g/d BCAA for 90 days (5.5 ± 0.2% to 5.4 ± 0.3%) (Kawaguchi et al., 2008).

Homeostatic Model Assessment for Insulin Resistance

The overall score of HOMA-IR was reduced following 5.2 g/d 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) (Hernández-Conde et al., 2021). Similarly, identical findings were identified following 12 g/d 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) (Yoshiji et al., 2011). Interestingly, an increase in HOMA-IR score was demonstrated after 12.45 g/d 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) (Takeshita et

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al., 2012). 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) (Kawaguchi et al., 2008) and (3.5 (2.6 – 7.9) to 3.2 (1.9 – 5.0) (Ocaña-Mondragón et al., 2018). Finally, a study revealed higher HOMA-IR scores following a 4 g/d BCAA dose for 48 weeks (3.9 ± 3.0 to 4.5 ± 5.4) (Kitajima et al., 2018).

Risk of bias

According to RoB2, risk of bias was high in one study (Beppu et al., 2015) due to 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 due to participants possibly knowing about the type of intervention (Takeshita et al., 2012, Ichikawa et al., 2010, Nakaya et al., 2007). A detailed traffic light plot is presented in Figure 2.

According to ROBINS-I, moderate risk of bias was displayed in one study due to insufficient control for confounders (i.e., physical activity) (Kitajima et al., 2018). Serious risk of bias was observed in two studies due to no control for major confounding factors (i.e., diet and physical activity) (Ocaña-Mondragón et al., 2018). 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 T2D and cardiovascular disease (Skyler et al., 2009, Nichols et al., 2013). A contributing factor to poor glycemic control is IR. Epidemiological data has shown that IR and clinical diagnoses of T2D and pre-diabetes are associated with elevated serum BCAAs (Long et al., 2020). In 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 (Yoshizawa, 2012). 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) (Mahendran et al., 2017).

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Animal models have revealed that a mechanism for the potentially beneficial effects of BCAA supplementation on glycemic 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 (Zhu et al., 2021). 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 (Nishitani et al., 2005). 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 (Nishitani et al., 2005). Such increased synthesis of glycogen by taking excess serum glucose out of circulation and storing it in skeletal muscle, could assist with overall glycemic regulation.

Insulin sensitivity may be further affected by increased utilization of glucose as fuel through glycolysis, via upregulation of GLUT2 and glucokinase in the liver, leading to improved bioactivity of the glucose-sensing apparatus (Higuchi et al., 2011). Specifically, glucokinase is involved in the regulation of hepatic glycolysis and glucose oxidation, glycogen synthase, glycogenolysis and gluconeogenesis amongst others (Matschinsky, 2009). 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 (Schwenk and Haymond, 1987). Nevertheless, the aforementioned study involved venous infusion and not dietary supplementation of BCAAs, indicating that elevated serum levels of BCAAs may interfere with glycemic 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 (Shulman, 2000). In mouse models, supplementation with the BCAA isoleucine has been reported to reduce accumulation of TG in both skeletal muscle and liver tissue (Nishimura et al., 2010, Arakawa et al., 2011). This is speculated to occur via upregulation of peroxisome proliferator-activated receptor (PPAR)-α and uncoupling protein (UCP) 2 in liver tissue and UCP3 in the skeletal muscle tissue.

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Thus, leading to increased free fatty acid oxidation, which results in improvements of insulin sensitivity induced by lipotoxicity (Arakawa et al., 2011, Guerre-Millo et al., 2000).

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 due to 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), 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 generalizability 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.

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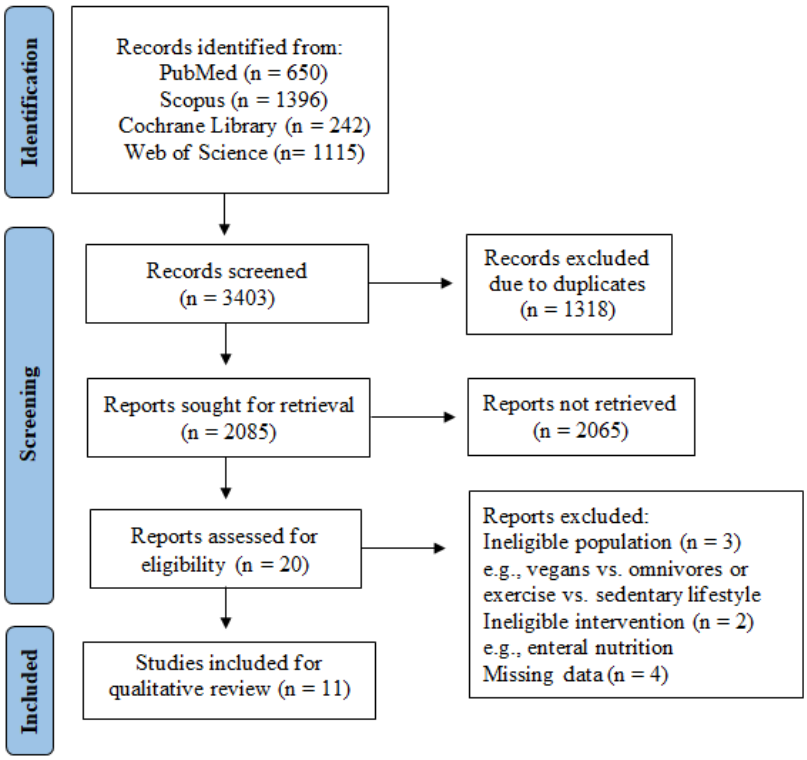

Figure 1. Flowchart of the employed literature search

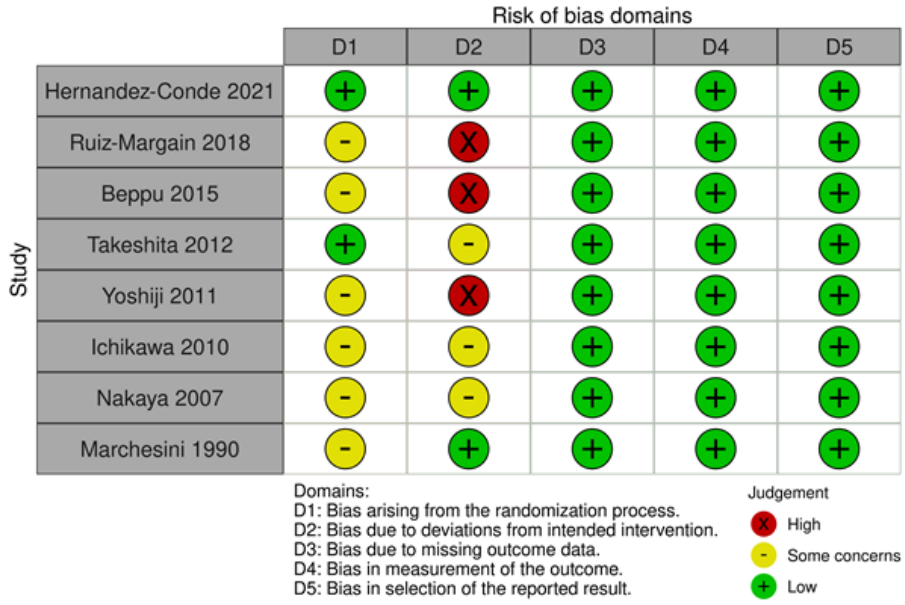

Figure 2. Quality assessment of the included studies according to the Cochrane risk-of-bias tool for randomised trials (RoB2).

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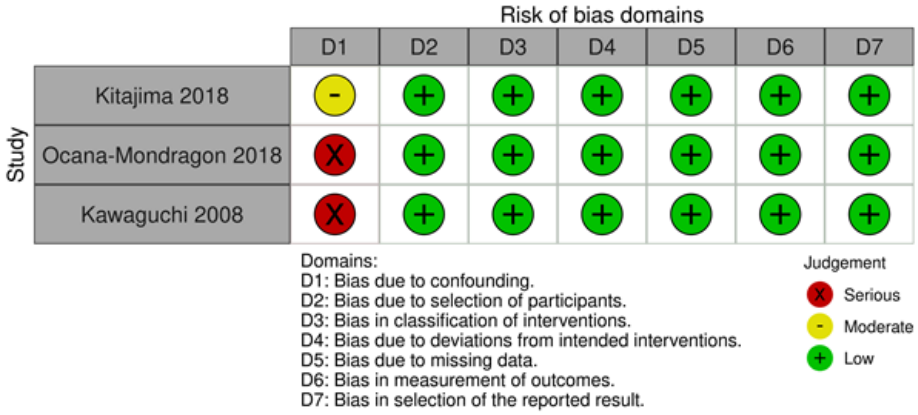

Figure 3. Quality assessment of the included non-randomized (single arm) studies according to the Risk Of Bias In Non-randomised Studies-of Interventions tool (ROBINS-I).

Table 1. Study and participant characteristics of the included studies.

Study year	Country	Study design	Total	BCAA		Comparator		Treatment dose (g/d)	Treatment duration	Health status	Reported outcomes
			n (M/F)	*n* (M/F)	Age (SD)	*n* (M/F)	Age (SD)				
Hernandez-Conde 2021	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 2018	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	Japan	Clinical	21 (9/	21 (9/	71.3	-	-	4	48 week	Cirrhosis	Insulin

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2018*		Trial	12)	12)	(7.9)			s		Glucose HOMA-IR Insulin Glucose HOMA-IR Insulin Glucose HbA1c Insulin Glucose HOMA-IR HbA1c Glucose HOMA-IR Gluc
Ocana-Mondragon 2018*	Mexico	Clinical Trial	20 (10/10)	20 (10/10)	53 (45.63)	-	-	30	3 months	Chronic Hepatitis C
Beppu 2015	Japan	RCT	28 (19/9)	13 (9/4)	64 (47-83)	15 (10/5)	72 (56-78)	8	6 months	PVE
Takeshita 2012	Japan	Crossover, open label RCT	24	13	58.6 (2.9)	11	64.2 (3.0)	12.5	12 weeks	Hepatitis C IR
Yoshiji 2011	Japan	RCT	42 (26/16)	16 (10/6)	63.7 (10.8)	26 (16/10)	62.5 (11.5)	12	48 months	HCC
Ichik	Japa	RCT	21	12	66.	9	67.	13.5	8	Cirrh Gluc

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awa 2010	n		(10/11)	(5/7)	2 (8.2)	(5/4)	4 (9.9)		weeks	osis Sleep Disturbance	ose
Kawaguchi 2008*	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 2007	Japan	RCT	38 (20/18)	19 (13/6)	67 (9)	19 (7/12)	67 (8)	12.3	3 months	Cirrhosis	Insulin Glucose
Marchesini 1990	Italy	Double-blind RCT	61	29	60 (44-70)	32	60 (43-70)	2.4	3 months	Cirrhosis	Insulin Glucose

Abbreviations: HbA1c, glycated haemoglobin; HCC, hepatocellular carcinoma; HOMA-IR, homeostatic model assessment for insulin resistance; IR, insulin resistance; PVE, portal vein embolization; RCT, randomized controlled trial.

*Studies with single-arm clinical trial design.

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