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Branched chain amino acids in hepatic encephalopathy and sarcopenia in liver cirrhosis: Evidence and uncertainties

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Abstract

Liver cirrhosis is commonly associated with nutritional alterations, reported in 20% of patients with compensated disease and over 60% of patients with decompensated cirrhosis. Nutritional disturbances are associated with a worse prognosis and increased risk of complication. Serum levels of branched-chain amino acids (BCAAs) are decreased in patients with liver cirrhosis. The imbalance of amino acids levels has been suggested to be associated with the development of complications, such as hepatic encephalopathy and sarcopenia, and to affect the clinical presentation and prognosis of these patients. Several studies investigated the efficacy of BCAAs supplementation as a therapeutic option in liver cirrhosis, but uncertainties remain about the real efficacy, the best route of administration, and dosage.

Key Words: Branched-chain amino acids; Hepatic encephalopathy; Sarcopenia; Liver cirrhosis

Core Tip: Nutritional perturbance is frequent in liver cirrhosis and has been correlated with the development of complications such as hepatic encephalopathy and sarcopenia. Branched-chain amino acids (BCAAs) have been implicated in the pathophysiology of these two complications and supplementation has been proposed as a therapeutic measure. In this review, we will examine the scientific evidence supporting the clinical use of BCAAs in cirrhotic subjects.

INTRODUCTION

Liver cirrhosis is commonly associated with nutritional alterations, being reported in 20% of patients with compensated disease and over 60% of patients with decompensated cirrhosis[1]. In cirrhotic subjects, nutritional disturbances are associated with a worse prognosis and increased risk of complications such as hepatic encephalopathy (HE) and sarcopenia. On the other hand, serum levels of branched-chain amino acids (BCAAs) are decreased in patients with liver cirrhosis, and this has been associated with the development of complications[2]. Several studies investigated the efficacy of BCAAs supplementation in liver cirrhosis for the treatment and prevention of both HE and sarcopenia. The aim of this review is to analyze scientific evidence supporting the administration of BCAAs in patients with liver cirrhosis affected by HE and sarcopenia (Table 1).

HE

HE is one of the main complications of advanced cirrhosis. It consists of a wide spectrum of non-specific neurological or psychiatric abnormalities, ranging from subclinical alterations to coma, caused by liver failure and/or porto-systemic shunting. According to the West Haven classification HE is classified, as covert HE (CHE), including minimal HE (MHE) and grade 1 HE, and overt HE (OHE), including grade 2, grade 3, and grade 4 HE of the West Haven classification[3]. The prevalence of OHE in liver cirrhosis is 30%-40% at any time during the clinical course of the disease[4] while MHE or CHE occurs in 20%-80% of patients with cirrhosis[5]. HE is associated with a poor prognosis, and high socioeconomic costs and also carries a psychological burden on patients and families[6]. According to the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines, episodes of OHE should be actively treated[3]. The therapeutic approach encompasses the active treatment of precipitant factors (*e.g.*, infections, variceal bleeding), administration of non-absorbable disaccharides, such as lactulose, and non-absorbable antibiotics, such as rifaximin[7]. Secondary prophylaxis with oral rifaximin is recommended after an episode of OHE. In case of recurrent and intractable OHE associated with advanced liver disease, the patients should be evaluated for liver transplantation[3]. Other treatments such as metronidazole, neomycin, or intravenous administration of L-ornithine L-aspartate, have been proposed for the treatment of HE, but the evidence supporting their use is still limited or under debate[8]. According to EASL guidelines, despite their limited efficacy, the use of these medications is advocated as an additional treatment for patients -non-responsive to conventional therapies[3].

BCAAS AND HE

In recent years, growing interest in the role of BCAAs in liver cirrhosis has been observed in the scientific literature. A common feature in patients with liver cirrhosis is decreased BCAA plasmatic levels associated with the increase of aromatic amino acids (AAA), namely tyrosine and phenylalanine, thus leading to a low BCAA/AAA ratio, the so-called "Fisher ratio"[9]. This ratio is negatively correlated with the Child-Turcotte-Pugh score (CTP) and the severity of liver disease[10]. A low Fisher ratio is also associated with the development of HE and an excellent correlation has been found between this ratio and the grade of HE[11]. The role of BCAAs in the development of HE was first advocated in the "false neurotransmitters" hypothesis in the 80s[12]. Both AAA and BCAAs compete for the same transporter across blood-brain barrier. According to this hypothesis, the increased concentration of AAA in liver cirrhosis leads to an increased availability of aromatic neurotransmitters precursors, which cause a "false" dopaminergic transmission and inhibition of dopamine synthesis, resulting in neuro-depression[13]. Other studies focused on the key role of increased ammonia levels in the development of HE, underling its neurotoxic role[14]. Despite this evidence, mechanisms involved in the pathogenesis of HE remain poorly understood.

The increase in blood ammonia is a consequence of impaired liver function and portosystemic shunts. Skeletal muscle is a key site of extrahepatic ammonia detoxification by the absorption of plasma ammonia and the conversion of α-ketoglutarate to glutamate, and then of glutamate to glutamine through glutamate dehydrogenase and glutamine synthetase enzymes, which remove two moles of

Table 1 Selected published studies on beneficial effects of branched chain amino acids in liver cirrhosis

Ref.	Study design	Participants	Intervention	Route	Treatment duration	Associated treatments	Outcomes	Results
Horst *et al* [16], 1984	Multicentric RCT	37 cirrhotic patients with OHE	BCAAs (20 g/d increased to 80 g/d) *vs* isonitrogenous diet (placebo)	Oral	4 wk	No	Mortality and hepatic encephalopathy assessed after 4 wk	HE recurrence (decreased). No differences in nitrogen balance
Muto *et al* [17], 2005	Multicentric RCT	646 patients with decompensated cirrhosis	BCAAs (12 g/d) *vs* standard diet (1.0-1.4 protein kg/d)	Oral	2 yr	No	Mortality, development of liver cancer, rupture of esophageal varices, or progress of hepatic failure (event-free survival)	EFS (increased), health-related quality of life, mortality (decreased). No differences in improvement of HE
Les *et al*[18], 2011	Double-blind multicentric RCT	40 cirrhotic patients with previous episodes of minimal hepatic encephalopathy	BCAAs (30 g/d) *vs* isocaloric placebo (maltodextrin)	Oral	56 wk	No	Mortality and hepatic encephalopathy assessed after 56 wk	Improvement in MHE symptoms and muscle mass. No reduction of HE recurrence
Gluud *et al* [19], 2017	Meta-analysis of RCT	11 RCT; 14 RCT	BCAAs *vs* diets, antibiotics (neomycin) and non-absorbable disaccharides	Oral and IV	Variable	No	Effect on HE manifestations and prevention of HE episodes	Oral BCAAs improve HE manifestations and prevention of HE episodes. No effects for IV BCAA
Gluud *et al* [20], 2013	Systematic review with meta-analysis	8 RCT: 382 cirrhotic patients with recurrent MHE or OHE	BCAAs (0.25 g/kg body weight/day) *vs* no intervention/placebo/control supplements	Oral	Variable	No	Effect on HE manifestations, mortality, nutritionalstatus, and adverse events in patients with recurrent HE	Improvement in the recurrent HE manifestation (more evident in OHE than MHE). No differences in survival
Gluud *et al* [19], 2017	Cochrane systematic review	16 RCT: 827 cirrhotic patients with OHE or MHE	BCAAs *vs* placebo/no intervention/other (diet, lactulose, neomycicn)	Oral and IV	Variable	No	Beneficial or harmful effects of BCAA versus any control intervention in HE	Oral BCAAs improve HE manifestation (no effect *vs* lactulose or neomycicn). No effect on mortality
Park *et al* [21], 2017	Multicentric retrospective cohort study	307 cirrhotic patients with CTP 8-10	BCAAs (4.15 g/d or 8.3 g/d or 12.45 g/d) *vs* normal diet	Oral	24 wk	No	Changes in MELD score, CP score, incidence of cirrhosis-related complications and event-free survival over 2 yr	Improvement in MELD score, serum bilirubin and CTP score in 12.45/d BCAAs. No differences in HE manifestation
Tajiri *et al* [23], 2018	Retrospective observational study	53 cirrhotic patients with OHE	IV BCAAs and conventional therapies *vs* IV BCAAs and conventional therapies + IV L-carnitine	IV	Median 5 d (range 2-20 d)	L-carnitine conventional therapies (non-absorbable disaccharides and non-absorbable antibiotics)	Effect on HE manifestation, recurrence-free-survival and overall-survival	L-carnitine + BCAAS improve HE manifestation and reduce HE recurrence

BCAAs: Branched chain amino acids; RCT: Randomized control trial; OHE: Overt hepatic encephalopathy; HE: Hepatic encephalopathy; EFS: Early feeding skill; MELD: Model for end stage liver disease; CP: Child-pugh score; CTP: Child-Turcotte-Pugh score.

ammonia for each α-ketoglutarate molecule. Muscle uptake of plasma BCAAs increases with ammonia concentration in patients with liver cirrhosis, suggesting that BCAAs play an important role in ammonia detoxification in muscle and can contribute to preventing HE[13] (Figure 1).
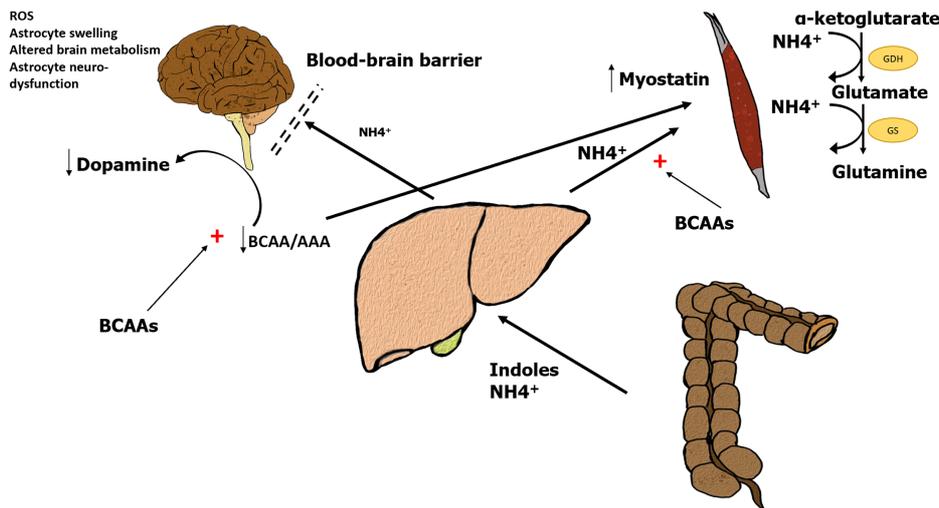
Figure 1 Gut derived ammonia and other aromatic compounds pass into the systemic circulation due to reduced liver function and the presence of porto-systemic shunts. A low plasma branched chain amino acids (BCAA)/aromatic amino acids (AAA) ratio has been observed in liver cirrhosis. BCAA and AAA compete for the same transporter at blood-brain barrier. The increased availability of AAA causes an increase in aromatic neurotransmitter precursors resulting in a false dopaminergic transmission and a reduction in dopamine synthesis. At brain level, ammonia causes astrocyte metabolism changes including reactive oxygen species increase, altered glucose and protein metabolism and astrocyte swelling, resulting in altered neurotransmission. Muscle is a key site of ammonia detoxification by means of the sequential action of glutamate dehydrogenase and glutamine synthetase. Ammonia increases myostatin expression, thus resulting in reduced protein synthesis and inhibition of myogenesis. The administration of BCAAs can increase muscle ammonia uptake from blood and can interfere with amino acids pass throughout the blood brain barrier with beneficial effects on both hepatic encephalopathy and sarcopenia. BCAAs: Branched chain amino acids; AAA: Aromatic amino acids; NH4+: Ammonia; ROS: Reactive oxygen species; GDH: Glutamate dehydrogenase; GS: Glutamine synthetase.

EVIDENCE SUPPORTING THE THERAPEUTIC USE OF BCAAS IN HEPATIC ENCEPHALOPATHY

A possible therapeutic role of BCAAs supplementation in HE was first evaluated in animal models. In dogs with portocaval shunt, which developed HE, neurological manifestations induced by the simultaneous infusion of 1% tryptophan and 1% phenylalanine were prevented by the concomitant infusion of BCAAs (0.63% leucine + 0.4% isoleucine + 0.46% valine)[15]. Subsequently, several clinical studies evaluated the role of BCAAs in the treatment and prevention of HE in cirrhotic subjects. In the early 80s, a randomized study evaluated the effect of BCAAs in protein-intolerant cirrhotic. Enrolled subjects were fed with increasing amounts of either dietary protein or a BCAAs solution until they attained an intake of 80 g protein per day or until they developed stage 2 encephalopathy. Oral BCAAs supplements induced a positive nitrogen balance as an equivalent amount of dietary protein but decreased the risk of HE recurrence[16]. In 2005, a multicenter randomized controlled trial evaluated oral BCAAs (12 g/d for 2 years) compared with diet therapy with defined daily food intake (1.0-1.4 g protein kg/day) in patients with decompensated cirrhosis. The group who received BCCA showed an improvement in event-free survival and consequently, a reduction in mortality, but no statistically significant differences were found in HE[17]. Another randomized, double-blind, multicenter study evaluated subjects with cirrhosis with a previous episode of HE. The two groups of patients received a standard diet and a supplement of 30 g of BCAAs or maltodextrin over 56 wk. BCAAs supplementation was not associated with a reduction in HE recurrence but an improvement in MHE and muscle mass recovery were found in the BCAA-treated group[18]. A meta-analysis of randomized trials, performed by Gluud *et al*[19], confirmed that oral BCAAs administration has a beneficial effect on the clinical manifestation of HE, but no similar results were found for intravenous administration. Based on this evidence, the authors suggested using nonabsorbable disaccharides as the first-line treatment for HE, with a more beneficial effect through the addition of nonabsorbable antibiotics, while oral BCAAs may be considered as a second-line treatment. Another systematic review with meta-analysis evaluated the effects of oral BCAAs compared with placebo or control supplements in patients with HE. The administration of oral BCAAs was found to be associated with an improvement in HE recurrence {87 of 172 patients in the BCAAs group *vs* 56 of 210 in controls, risk ratio (RR) = 1.71 [95% confidence interval (CI): 1.17-2.51]}. The effect of oral BCAAs was higher in patients with OHE rather than in patients with MHE, but no difference in survival was found. These results strengthen the recommendation of oral BCAAs in patients who developed HE during enteral nutrition and in the case of recurrent HE. Most of the analyzed studies used the same dose of oral BCAAs (0.25 g/kg body weight/die) and no adverse events (including nausea and diarrhea) were reported[20]. A Cochrane systematic review, updated in 2017, evaluated the beneficial and harmful effects of BCAAs *vs* any control intervention for people with HE.

The study analyzed 16 randomized clinical trials, including 827 patients with OHE (12 trials) or MHE (4 trials). Control groups received placebo/no intervention in 2 trials, diets in 10 trials, lactulose in 2 trials, or neomycin in 2 trials. BCAAs were administrated orally in 8 trials and intravenous in 7 trials. No differences in mortality were found between BCAAs groups and control groups (RR = 0.88, 95%CI: 0.69-1.11). Reduced mortality was noted only when excluding trials in which control groups were treated with lactulose or neomycin (RR = 0.76, 95%CI: 0.63-0.92). The analysis also showed that BCAAs supplementation was associated with a beneficial effect on HE compared with controls (RR = 0.73, 95%CI: 0.61-0.88). Subgroup analyses showed that oral BCAAs but not intravenous BCAAs had a beneficial effect on overt encephalopathy. These differences were not found for MHE[21]. This systematic review supported the use of oral BCAAs in clinical practice but did not provide enough evidence to evaluate the benefit of BCAAs compared with other interventions. The most adequate dosage and duration of BCAAs supplementation is also a debated issue, since homeostasis of BCAAs in the body is extremely rapid, and circulating values quickly return to baseline after administration. A multicenter retrospective cohort study evaluated the effects of long-term BCAAs supplementation (at least 6 mo) compared with diet in patients with advanced liver disease (CTP 8-10) compared with no BCAAs enriched diet. Patients in the BCAAs group were divided into 3 subgroups according to the dose administrated: 4.15 g, 8.3 g, or 12.45 g/d. Statistical analysis revealed differences in the model for end-stage liver disease (MELD) score, serum albumin levels, and CTP score between the BCAAs group and control group at the baseline. Patients enrolled in the BCAAs group showed lower albumin levels and higher CTP scores, MELD scores, and HE grades (mostly grades 1-2). This was probably related to the propensity of physicians to prescribe BCAAs to patients with a worsened deterioration of hepatic function. Sub-group analysis showed a significant improvement in MELD score, serum bilirubin levels, and CTP score in patients who received the highest dose of BCAAs (12.45 g daily), whereas no significant differences were found in albumin levels. Conversely, only improvement in the serum bilirubin levels was observed in patients who received the lowest dose of BCAAs (4.15 g). This evidence provides a relationship between BCAAs dosage and its beneficial effect on prognostic scores in liver cirrhosis, suggesting high-dose BCAAs supplementation to achieve benefits. The study did not find significant differences in HE manifestations between the two groups. This was probably related to the shorter duration of BCAAs supplementation than in previous studies (about 30% of patients discontinued BCAAs within one year)[22].

A possible synergic role of L-carnitine and BCAAs on HE has been postulated. L-carnitine is a vitamin-like bio-factor that has been shown to induce ureagenesis, and improve energy metabolism leading to a reduction in blood and ammonia levels, thus protecting human astrocytes from ammonia-induced acute cytotoxicity[23]. A study on cirrhotic patients affected by OHE treated with intravenous BCAAs supplementation and conventional therapy (lactulose and non-absorbable antibiotics, showed that the addition of L-carnitine provided an improvement in blood ammonia concentration and Glasgow Coma Scale) with an improvement in HE recurrence. Despite the preliminary nature of the study, these results suggest a possible synergic role between L-carnitine and BCAAs in HE treatment[24].

SARCOPENIA IN LIVER CIRRHOSIS

Patients with chronic liver disease are at risk of malnutrition and sarcopenia[2]. The first definition of sarcopenia was proposed by Rosenberg[25], deriving from the Greek words "sarx" (muscle) and "penia" (reduction), to point out the decline in muscle mass and strength that occurs with healthy aging. The European Working Group on Sarcopenia in Older People in 2019 defined sarcopenia as a progressive and generalized skeletal muscle disorder that consists of decreased muscle quality or quantity and decreased physical function or muscle strength. Sarcopenia is distinguished as primary, or age-related in the absence of other evident specific cause, and secondary when the causal factor is a systemic, neoplastic, or inflammatory disease (*e.g.,* malignancy, inflammatory disease, or organ failure such as liver cirrhosis[26], affecting about 20%-60% of patients in the latter condition)[27]. In cirrhotic patients, the pathogenetic cascade is multifactorial: Since muscle mass is the result of protein anabolism and catabolism balance, reduced liver function, together with portosystemic shunts, causes decreased protein synthesis and ammonia detoxification, thus promoting sarcopenia and hyperammonemia. Hyperammonemia leads to increased muscle expression of the cytokine myostatin, a negative regulator of muscle growth by inhibition of myogenesis[28] (Figure 1). Other involved factors are BCAAs deficiency, which plays a key role in maintaining muscle mass and strength, and perturbation of sex hormone levels, with reduction of testosterone and concomitant increase in estrogen-to-androgen ratio. Hormonal changes suppress myoblast differentiation in skeletal muscle thus promoting sarcopenia[29]. Recently, changes in the intestinal microbiome (reduction of Methanobrevibacter, Prevotella e Akkermansia) and in the intestine-liver-muscle axis with increased bowel inflammation and bacterial translocation have been described in sarcopenic cirrhotic[30]. The role of gut microbiota is crucial for energy extraction from nutrients, in controlling low-grade systemic inflammation and bacterial infections, and has been involved in the genesis of HE, sarcopenia, and hepatocellular carcinoma (HCC) in liver cirrhosis[30-34].

BCAA IN THE TREATMENT OF SARCOPENIA

Despite growing interest in the clinical role of sarcopenia, few evidence-based therapeutic interventions are available to revert this condition in the context of liver cirrhosis. Current literature changed the old concept of protein restriction in patients with liver cirrhosis and daily recommended protein intake has been changed accordingly[35]. According to the European Society for Clinical Nutrition and Metabolism, high protein intake, variable from 1.2 g/kg/d protein in patients with compensated liver cirrhosis to 1.5 g/kg/d protein in patients with malnutrition and/or sarcopenia, is considered safe, well-tolerated, and recommended in liver cirrhosis. Another suggested dietary intervention is to shorten fasting periods by consuming three to five meals per day and taking a late evening snack. The aim of these suggestions is to reduce protein catabolism during overnight fasting and to reverse anabolic resistance and sarcopenia[1].

A nutritional interventional strategy aimed at increasing protein synthesis and preventing sarcopenia is BCAAs exogenous supplementation. BCAAs play a key role in protein synthesis and glucose metabolism. Leucine is involved in the activation of the intracellular mammalian target of rapamycin (mTOR) complex 1 pathway and inhibition of ubiquitin-proteasome signaling, thus resulting in increased protein synthesis, skeletal muscle hypertrophy, and reduced muscle turnover[36].

In experimental animal models of carbon tetrachloride-induced liver cirrhosis, muscle mass loss was described in association with decreased BCAAs and increased AAA plasma levels, while decreased α-ketoglutarate and ATP concentration in muscles was found[37]. A Japanese study evaluating cirrhotic subjects demonstrated a high prevalence of sarcopenia, low serum levels of BCAAs, and insulin-like growth factor 1. Patients with lower baseline levels of BCAAs had also a higher prevalence of CTP class B and C, lower albumin and zinc blood concentration, and lower body mass index (BMI), associated with risk of malnutrition, disease complication, and poor prognosis[38]. The presence of sarcopenia and low plasma levels of total BCAAs have also been associated with a significant reduction of survival in liver cirrhosis[39].

Several studies were performed to evaluate the effect of BCAAs administration to prevent sarcopenia and its complication in cirrhotic patients. In animal models, the administration of BCAAs reversed the metabolic alterations in skeletal muscles, promoting glucose uptake, which improves ATP production and muscle function[40,41]. In patients affected by alcoholic cirrhosis, skeletal muscle biopsy showed increased myostatin expression, dysfunctional mTOR pathway, and increased autophagic proteolysis when compared to well-matched healthy controls. These pathologic alterations were reversed after the administration of a single oral BCAAs mixture enriched with leucine. A monocentric prospective study on adult cirrhotics showed that oral BCAAs powder administration (13.5 g twice a day) for 24-wk was able to improve muscle strength with limited increase in muscle mass. It suggests that BCAAs supplementation alone could not be enough to achieve effective improvement of sarcopenia in cirrhotic patients and that aerobic and resistance exercise could also be necessary to induce protein synthesis response[42]. A prospective, randomized double-blind clinical trial in patients with liver cirrhosis and sarcopenia assessed by computed tomography (CT) scan, showed that BCAAs supplementation, in addition to a nutritional intervention and physical activity, could improve albumin levels and muscle mass. Administration of BCAAs also increased zinc levels after 12 wk of intervention[43]. Zinc is an essential nutrient for human health and its deficiency is often associated with malnutrition and chronic liver disease[44]. Improvement of hypoalbuminemia after BCAAs supplementation is correlated with improved glucose metabolism and a decrease in skeletal muscle fat infiltration, miming exercise training. In these patients, an improvement in liver-related event-free survival (including refractory pleural effusion, ascites, or both, varices rupture or treatment, and hepatocarcinogenesis) was observed and it might contribute to a better prognosis[45]. Today, in liver cirrhosis, an intervention program including physical exercise is considered useful to decelerate sarcopenia progression, but it can't completely prevent skeletal muscle atrophy[46]. The combination of BCAAs supplementation and walking exercise was found to be more effective than exercise alone in improving muscle mass and function and it should be considered a good therapeutic strategy in patients with overt sarcopenia and a prevention strategy in patients at risk of sarcopenia[47]. In a retrospective cohort study, patients with liver cirrhosis were classified into low, intermediate, and high-risk according to the presence of hypoalbuminemia and/or sarcopenia. The high-risk group, including patients with both sarcopenia ad hypoalbuminemia, had significantly lower overall survival than the low-risk group, including patients without both hypoalbuminemia and sarcopenia, regardless of HCC occurrence. The administration of BCAAs improved overall survival and prognosis in treated patients. The survival benefit of BCAAs supplementation was pronounced in the high and intermediate-risk groups[48]. Lastly, in cirrhotic patients, sarcopenia contributes to hyperammonemia due to the reduced capacity of sarcopenic muscle to detoxify circulating ammonia which increases the risk of HE. On the other hand, hyperammonemia through myostatin upregulation, mitochondrial dysfunction, and cellular stress response, induces further muscle depletion, generating a vicious circle. On these bases, nutritional interventions against sarcopenia, including BCAA supplementation, may have a beneficial effect also on HE[49,50].

β-HYDROXY-β-METHYLBUTYRATE SUPPLEMENTATION

A different strategy to counteract muscle mass loss, acting on BCAAs metabolism, is β-Hydroxy-β-methylbutyrate (HMB) supplementation. HMB is a natural derivative of the BCAA leucine, which has shown a positive effect on muscle mass and strength in malnourished subjects. Recently, the randomized, placebo-controlled, double-blind, parallel design strengthening health in the elderly through nutrition trial showed a significant improvement in weight, BMI, mid-arm circumference, and leg strength in elderly subjects receiving an HMB containing oral nutritional supplement along with dietary counseling over six months. Female treated subjects also showed a significant increase in handgrip strength and the whole population showed an improvement in nutritional parameters (including vitamin D levels, fat, protein, and carbohydrate intakes), but no significant difference was found in overall survival and hospital (re)admission rate[51].

A prospective non-randomized interventional cohort study evaluating the effectiveness of HMB supplements in the prehabilitation program of sarcopenic patients undergoing gastrointestinal surgery (HEROS trial, NCT05344313) is ongoing. The effect of HMB supplementation on muscle health and nutritional status has also been evaluated in liver cirrhosis. HMB supplementation in cirrhotic rats was able to increase plasma levels of BCAAs but showed detrimental effects on muscle and liver protein content and was associated with higher mortality and lower weight gain[52].

Despite some conflicting data in the experimental animal, recently, a small pilot randomized controlled clinical trial conducted in Italy demonstrated a significant improvement in muscle mass and performance in cirrhotic subjects receiving HMB supplements as well as dietary and lifestyle counseling. In the HMB-treated group a statistically significant improvement was found in muscle performance assessed through a six-minute walking test and chair stand test. HMB supplementation was also associated with a significant increase in muscle mass at the quadriceps level and with improvement in frailty (evaluated using liver frailty index[53])[54].

In a similar prospective randomized trial, HMB supplementation was evaluated in addition to standard BCAAs supplementation in two matched groups. Both HMB + BCAAs and BCAAs alone treatment have been associated with a significant longitudinal decrease in MELD score, an increase in BMI and fat mass but without significant changes in fat-free mass and handgrip strength. No significant differences were found between the two treated groups[55].

In both studies in cirrhotic subjects HMB supplements were well tolerated and no significant adverse events were reported. HMB supplementation represents an interesting therapeutic approach in the treatment of cirrhotic subjects with sarcopenia, but it is unclear whether it has additional positive effects compared to BCAAs supplementation. Adequately powered prospective studies are needed to assess efficacy, duration, and dose requirements.

THE ROLE OF ZINC IN HEPATIC ENCEPHALOPATHY AND SARCOPENIA

Another condition that can influence protein metabolism and nutritional status in cirrhosis, acting as a bridge between HE and sarcopenia, is zinc deficiency. Zinc is a trace element that is essential for the structure and function of various human proteins and enzymes[56]. Zinc deficiency has been described in cirrhotic subjects, resulting from multiple mechanisms including, among others, reduced dietary intake, reduced intestinal absorption, increased urinary excretion, reduced hepatic extraction, and hypoalbuminemia[57-60]. Ammonia metabolism in the liver requires urea cycle activity, which key enzyme, ornithine transcarbamylase, is a zinc enzyme. It has been reported that zinc supplementation in cirrhotic subjects results in an increase in urea cycle activity with an improvement, though not normalization, of the capacity for ammonia detoxification in the liver[61,62]. The reduction of ammonia detoxification in the liver, at least in part due to zinc deficiency, is associated with increased ammonia uptake in the muscle. In skeletal muscles, BCAAs serve as a glutamate source for glutamine-synthetase reaction to detoxify ammonia. It is therefore possible to link zinc deficiency with reduced plasma BCAAs levels in liver cirrhosis and with the above-described consequences of such condition on HE and sarcopenia[63]. Zinc deficiency has also been associated with taste alterations in elderly individuals and subjects with chronic diseases, including liver cirrhosis[64,65]. Taste alterations in cirrhosis go together with the reduction of appetite caused by abdominal distension due to ascites or osmotic laxatives and with reduced nutrient absorption due to portal hypertensive enteropathy and intestinal dysbiosis. All the described alterations contribute to the worsening of the nutritional status of patients with liver cirrhosis.

BCAAS AND LIVER FUNCTION

As reported above, some evidence exists regarding the effect of BCAA supplementation on overall liver function. Long-term BCAAs supplementation has been associated with improvement in MELD, CPT score, and bilirubin reduction in a retrospective Korean study, but no clear difference was reported in event-free survival[22]. A recent prospective study from the same research group confirmed the

improvement in prognostic scores in subjects receiving long-term BCAAs supplementation, but no differences in albumin and bilirubin levels were found. Interestingly, a significant increase in event-free survival, mainly regarding ascites and HE, was observed in the BCAAs-treated group, but no difference was noted regarding survival[66]. BCAAs supplementation has been investigated also in subjects undergoing treatment for HCC, showing some improvement in liver function after locoregional treatments. Three months of supplementation with a late evening snack enriched with a BCAAs mixture was associated with a rapid improvement in albumin and bilirubin levels and CPT score after radiofrequency ablation[67]. In subjects undergoing trans-arterial chemo-treatment for HCC, BCAAs supplementation was associated with an improvement in albumin but not in bilirubin values. Improved CPT score and survival were also observed in the BCAAs treated group but only in CPT class B patients[68].

CONCLUSION

Today it is widely accepted that low plasma levels of BCAAs levels play a key role in the development of cirrhosis complications such as sarcopenia and HE. The restoration of normal amino acid levels with BCAAs supplementation may improve the clinical course of HE and sarcopenia with few side effects. For these reasons, BCAAs administration should be considered in adult patients with advanced liver disease. BCAAs administration alone improves HE manifestation and reduces HE recurrence but has no significant improvement in mortality. Conversely, the use of BCAAs in addition to conventional therapies, such as non-absorbable disaccharides and non-absorbable antibiotics, shows benefits also in survival. In patients with sarcopenia, the administration of BCAAs improves muscle mass, muscle strength, and albumin levels with a consequent improvement in survival. All these beneficial effects are amplified when BCAAs are used in combination with physical exercise and nutritional intervention. These evidences supports the use of BCAAs supplements in clinical practice, especially in patients affected by concomitant HE and sarcopenia. BCAAs supplements should be used in combination with standard treatments. There is a need to identify patients at high risk of malnutrition and sarcopenia who could have an increased benefit from early nutritional intervention and BCAAs supplementation. According to the scientific literature, oral administration is more effective than intravenous administration and should be preferred. Early discontinuation of BCAAs administration is associated with reduced benefit so a long-term supplementation should be preferred. A minimum dose of 12 g/d of oral BCAAs is more effective than lower doses but further studies are needed to evaluate the most adequate dose and duration of BCAAs treatment.

FOOTNOTES

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