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

Marrone G *et al*. BCAAs in cirrhosis

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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

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**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 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).

**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[19]. 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)[21].

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[22]. 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[23].

**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[24], deriving from the Greek words “sarx” (muscle) and “penia” (reduction), to point out thedecline 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[25], affecting about 20%-60% of patients in the latter condition)[26]. 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[27] (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[28]. 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[29]. 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[29-33].

**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[34]. 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[35].

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[36]. 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[37]. The presence of sarcopenia and low plasma levels of total BCAAs have also been associated with a significant reduction of survival in liver cirrhosis[38].

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[39,40]. 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[41]. 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[42]. Zinc is an essential nutrient for human health and its deficiency is often associated with malnutrition and chronic liver disease[43]. 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[44]. 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[45]. 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[46]. 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[47]. 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[48,49].

**β-HYDROXY-β-METHYLBUTYRATE SUPPLEMENTATION**

A different strategy to counteract muscle mass loss, acting on BCAAs metabolism, is ß-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[50].

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[51].

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[52])[53].

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[54].

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[55]. 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[56-59]. 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[60,61]. 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[62]. Zinc deficiency has also been associated with taste alterations in elderly individuals and subjects with chronic diseases, including liver cirrhosis[63,64]. 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[21]. 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[65]. 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[66]. 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[67].

**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.

**REFERENCES**

1 **Bischoff SC**, Bernal W, Dasarathy S, Merli M, Plank LD, Schütz T, Plauth M. ESPEN practical guideline: Clinical nutrition in liver disease. *Clin Nutr* 2020; **39**: 3533-3562 [PMID: 33213977 DOI: 10.1016/j.clnu.2020.09.001]

2 **Dasarathy S**, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. *J Hepatol* 2016; **65**: 1232-1244 [PMID: 27515775 DOI: 10.1016/j.jhep.2016.07.040]

3 **Vilstrup H**, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, Weissenborn K, Wong P. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology* 2014; **60**: 715-735 [PMID: 25042402 DOI: 10.1002/hep.27210]

4 **Amodio P**, Del Piccolo F, Pettenò E, Mapelli D, Angeli P, Iemmolo R, Muraca M, Musto C, Gerunda G, Rizzo C, Merkel C, Gatta A. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. *J Hepatol* 2001; **35**: 37-45 [PMID: 11495040 DOI: 10.1016/S0168-8278(01)00129-5]

5 **Groeneweg M**, Moerland W, Quero JC, Hop WC, Krabbe PF, Schalm SW. Screening of subclinical hepatic encephalopathy. *J Hepatol* 2000; **32**: 748-753 [PMID: 10845661 DOI: 10.1016/S0168-8278(00)80243-3]

6 **Montagnese S**, Bajaj JS. Impact of Hepatic Encephalopathy in Cirrhosis on Quality-of-Life Issues. *Drugs* 2019; **79**: 11-16 [PMID: 30706419 DOI: 10.1007/s40265-018-1019-y]

7 **Bass NM**, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, Sigal S, Sheikh MY, Beavers K, Frederick T, Teperman L, Hillebrand D, Huang S, Merchant K, Shaw A, Bortey E, Forbes WP. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010; **362**: 1071-1081 [PMID: 20335583 DOI: 10.1056/NEJMoa0907893]

8 **Rothenberg ME**, Keeffe EB. Antibiotics in the management of hepatic encephalopathy: an evidence-based review. *Rev Gastroenterol Disord* 2005; **5 Suppl 3**: 26-35 [PMID: 17713457]

9 **Fischer JE**, Baldessarini RJ. False neurotransmitters and hepatic failure. *Lancet* 1971; **2**: 75-80 [PMID: 4103986 DOI: 10.1016/S0140-6736(71)92048-4]

10 **Dam G**, Sørensen M, Buhl M, Sandahl TD, Møller N, Ott P, Vilstrup H. Muscle metabolism and whole blood amino acid profile in patients with liver disease. *Scand J Clin Lab Invest* 2015; **75**: 674-680 [PMID: 26243157]

11 **Fischer JE**, Rosen HM, Ebeid AM, James JH, Keane JM, Soeters PB. The effect of normalization of plasma amino acids on hepatic encephalopathy in man. *Surgery* 1976; **80**: 77-91 [PMID: 818729]

12 **James JH**. Branched chain amino acids in heptatic encephalopathy. *Am J Surg* 2002; **183**: 424-429 [PMID: 11975931 DOI: 10.1016/S0002-9610(02)00808-5]

13 **Dam G**, Aamann L, Vistrup H, Gluud LL. The role of Branched Chain Amino Acids in the treatment of hepatic Encephalopathy. *J Clin Exp Hepatol* 2018; **8**: 448-451 [PMID: 30568347 DOI: 10.1016/j.jceh.2018.06.004]

14 **Norenberg MD**, Rama Rao KV, Jayakumar AR. Signaling factors in the mechanism of ammonia neurotoxicity. *Metab Brain Dis* 2009; **24**: 103-117 [PMID: 19104923 DOI: 10.1007/s11011-008-9113-6]

15 **Rossi-Fanelli F**, Freund H, Krause R, Smith AR, James JH, Castorina-Ziparo S, Fischer JE. Induction of coma in normal dogs by the infusion of aromatic amino acids and its prevention by the addition of branched-chain amino acids. *Gastroenterology* 1982; **83**: 664-671 [PMID: 7095369]

16 **Horst D**, Grace ND, Conn HO, Schiff E, Schenker S, Viteri A, Law D, Atterbury CE. Comparison of dietary protein with an oral, branched chain-enriched amino acid supplement in chronic portal-systemic encephalopathy: a randomized controlled trial. *Hepatology* 1984; **4**: 279-287 [PMID: 6706302 DOI: 10.1002/HEP.1840040218]

17 **Muto Y**, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, Kato M, Nakamura T, Higuchi K, Nishiguchi S, Kumada H; Long-Term Survival Study Group. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. *Clin Gastroenterol Hepatol* 2005; **3**: 705-713 [PMID: 16206505 DOI: 10.1016/S1542-3565(05)00017-0]

18 **Les I**, Doval E, García-Martínez R, Planas M, Cárdenas G, Gómez P, Flavià M, Jacas C, Mínguez B, Vergara M, Soriano G, Vila C, Esteban R, Córdoba J. Effects of branched-chain amino acids supplementation in patients with cirrhosis and a previous episode of hepatic encephalopathy: a randomized study. *Am J Gastroenterol* 2011; **106**: 1081-1088 [PMID: 21326220 DOI: 10.1038/ajg.2011.9]

19 **Gluud LL**, Dam G, Les I, Marchesini G, Borre M, Aagaard NK, Vilstrup H. Branched-chain amino acids for people with hepatic encephalopathy. *Cochrane Database Syst Rev* 2017; **5**: CD001939 [PMID: 28518283 DOI: 10.1002/14651858.CD001939.pub4]

20 **Gluud LL**, Dam G, Borre M, Les I, Cordoba J, Marchesini G, Aagaard NK, Risum N, Vilstrup H. Oral branched-chain amino acids have a beneficial effect on manifestations of hepatic encephalopathy in a systematic review with meta-analyses of randomized controlled trials. *J Nutr* 2013; **143**: 1263-1268 [PMID: 23739310 DOI: 10.3945/jn.113.174375]

21 **Park JG**, Tak WY, Park SY, Kweon YO, Jang SY, Lee YR, Bae SH, Jang JY, Kim DY, Lee JS, Suk KT, Kim IH, Lee HJ, Chung WJ, Jang BK, Suh JI, Heo J, Lee WK. Effects of branched-chain amino acids (BCAAs) on the progression of advanced liver disease: A Korean nationwide, multicenter, retrospective, observational, cohort study. *Medicine (Baltimore)* 2017; **96**: e6580 [PMID: 28614215 DOI: 10.1097/MD.0000000000006580]

22 **Wang T**, Suzuki K, Kakisaka K, Onodera M, Sawara K, Takikawa Y. L-carnitine prevents ammonia-induced cytotoxicity and disturbances in intracellular amino acid levels in human astrocytes. *J Gastroenterol Hepatol* 2019; **34**: 1249-1255 [PMID: 30278111 DOI: 10.1111/jgh.14497]

23 **Tajiri K**, Futsukaichi Y, Kobayashi S, Yasumura S, Takahara T, Minemura M, Sugiyama T. L-Carnitine for the Treatment of Overt Hepatic Encephalopathy in Patients with Advanced Liver Cirrhosis. *J Nutr Sci Vitaminol (Tokyo)* 2018; **64**: 321-328 [PMID: 30381621 DOI: 10.3177/jnsv.64.321]

24 **Rosenberg IH**. Summary comments. *Am J Clin Nutr* 1989; **50**: 1231-1233 [DOI: 10.1093/ajcn/50.5.1231]

25 **Cruz-Jentoft AJ**, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; **48**: 16-31 [PMID: 30312372 DOI: 10.1093/ageing/afy169]

26 **Meza-Junco J**, Montano-Loza AJ, Baracos VE, Prado CM, Bain VG, Beaumont C, Esfandiari N, Lieffers JR, Sawyer MB. Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. *J Clin Gastroenterol* 2013; **47**: 861-870 [PMID: 23751844 DOI: 10.1097/MCG.0b013e318293a825]

27 **Kumar A**, Davuluri G, Silva RNE, Engelen MPKJ, Ten Have GAM, Prayson R, Deutz NEP, Dasarathy S. Ammonia lowering reverses sarcopenia of cirrhosis by restoring skeletal muscle proteostasis. *Hepatology* 2017; **65**: 2045-2058 [PMID: 28195332 DOI: 10.1002/hep.29107]

28 **Kamimura H**, Sato T, Natsui K, Kobayashi T, Yoshida T, Kamimura K, Tsuchiya A, Murayama T, Yokoyama J, Kawai H, Takamura M, Terai S. Molecular Mechanisms and Treatment of Sarcopenia in Liver Disease: A Review of Current Knowledge. *Int J Mol Sci* 2021; **22** [PMID: 33572604 DOI: 10.3390/ijms22031425]

29 **Ponziani FR**, Picca A, Marzetti E, Calvani R, Conta G, Del Chierico F, Capuani G, Faccia M, Fianchi F, Funaro B, Josè Coelho-Junior H, Petito V, Rinninella E, Paroni Sterbini F, Reddel S, Vernocchi P, Cristina Mele M, Miccheli A, Putignani L, Sanguinetti M, Pompili M, Gasbarrini A; GuLiver study group. Characterization of the gut-liver-muscle axis in cirrhotic patients with sarcopenia. *Liver Int* 2021; **41**: 1320-1334 [PMID: 33713524 DOI: 10.1111/liv.14876]

30 **Patel VC**, Lee S, McPhail MJW, Da Silva K, Guilly S, Zamalloa A, Witherden E, Støy S, Manakkat Vijay GK, Pons N, Galleron N, Huang X, Gencer S, Coen M, Tranah TH, Wendon JA, Bruce KD, Le Chatelier E, Ehrlich SD, Edwards LA, Shoaie S, Shawcross DL. Rifaximin-α reduces gut-derived inflammation and mucin degradation in cirrhosis and encephalopathy: RIFSYS randomised controlled trial. *J Hepatol* 2022; **76**: 332-342 [PMID: 34571050 DOI: 10.1016/j.jhep.2021.09.010]

31 **Ponziani FR**, Bhoori S, Castelli C, Putignani L, Rivoltini L, Del Chierico F, Sanguinetti M, Morelli D, Paroni Sterbini F, Petito V, Reddel S, Calvani R, Camisaschi C, Picca A, Tuccitto A, Gasbarrini A, Pompili M, Mazzaferro V. Hepatocellular Carcinoma Is Associated With Gut Microbiota Profile and Inflammation in Nonalcoholic Fatty Liver Disease. *Hepatology* 2019; **69**: 107-120 [PMID: 29665135 DOI: 10.1002/hep.30036]

32 **Schneider KM**, Mohs A, Gui W, Galvez EJC, Candels LS, Hoenicke L, Muthukumarasamy U, Holland CH, Elfers C, Kilic K, Schneider CV, Schierwagen R, Strnad P, Wirtz TH, Marschall HU, Latz E, Lelouvier B, Saez-Rodriguez J, de Vos W, Strowig T, Trebicka J, Trautwein C. Imbalanced gut microbiota fuels hepatocellular carcinoma development by shaping the hepatic inflammatory microenvironment. *Nat Commun* 2022; **13**: 3964 [PMID: 35803930 DOI: 10.1038/s41467-022-31312-5]

33 **Gómez-Hurtado I**, Santacruz A, Peiró G, Zapater P, Gutiérrez A, Pérez-Mateo M, Sanz Y, Francés R. Gut microbiota dysbiosis is associated with inflammation and bacterial translocation in mice with CCl4-induced fibrosis. *PLoS One* 2011; **6**: e23037 [PMID: 21829583 DOI: 10.1371/journal.pone.0023037]

34 **European Association for the Study of the Liver**. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. *J Hepatol* 2022; **77**: 807-824 [PMID: 35724930 DOI: 10.1016/j.jhep.2022.06.001]

35 **Hey P**, Gow P, Testro AG, Apostolov R, Chapman B, Sinclair M. Nutraceuticals for the treatment of sarcopenia in chronic liver disease. *Clin Nutr ESPEN* 2021; **41**: 13-22 [PMID: 33487256 DOI: 10.1016/j.clnesp.2020.11.015]

36 **Holeček M**, Vodeničarovová M. Muscle wasting and branched-chain amino acid, alpha-ketoglutarate, and ATP depletion in a rat model of liver cirrhosis. *Int J Exp Pathol* 2018; **99**: 274-281 [PMID: 30637824 DOI: 10.1111/iep.12299]

37 **Saeki C**, Kanai T, Nakano M, Oikawa T, Torisu Y, Saruta M, Tsubota A. Low Serum Branched-Chain Amino Acid and Insulin-Like Growth Factor-1 Levels Are Associated with Sarcopenia and Slow Gait Speed in Patients with Liver Cirrhosis. *J Clin Med* 2020; **9** [PMID: 33050430 DOI: 10.3390/jcm9103239]

38 **Sano A**, Tsuge S, Kakazu E, Iwata T, Ninomiya M, Tsuruoka M, Inoue J, Masamune A. Plasma free amino acids are associated with sarcopenia in the course of hepatocellular carcinoma recurrence. *Nutrition* 2021; **84**: 111007 [PMID: 33745507 DOI: 10.1016/j.nut.2020.111007]

39 **Nishitani S**, Takehana K, Fujitani S, Sonaka I. Branched-chain amino acids improve glucose metabolism in rats with liver cirrhosis. *Am J Physiol Gastrointest Liver Physiol* 2005; **288**: G1292-G1300 [PMID: 15591158 DOI: 10.1152/AJPGI.00510.2003]

40 **Tsien C**, Davuluri G, Singh D, Allawy A, Ten Have GA, Thapaliya S, Schulze JM, Barnes D, McCullough AJ, Engelen MP, Deutz NE, Dasarathy S. Metabolic and molecular responses to leucine-enriched branched chain amino acid supplementation in the skeletal muscle of alcoholic cirrhosis. *Hepatology* 2015; **61**: 2018-2029 [PMID: 25613922 DOI: 10.1002/hep.27717]

41 **Uojima H**, Sakurai S, Hidaka H, Kinbara T, Sung JH, Ichita C, Tokoro S, Masuda S, Sasaki A, Koizumi K, Egashira H, Kako M, Kobayashi S. Effect of branched-chain amino acid supplements on muscle strength and muscle mass in patients with liver cirrhosis. *Eur J Gastroenterol Hepatol* 2017; **29**: 1402-1407 [PMID: 28984678 DOI: 10.1097/MEG.0000000000000968]

42 **Hernández-Conde M**, Llop E, Gómez-Pimpollo L, Fernández Carrillo C, Rodríguez L, Van Den Brule E, Perelló C, López-Gómez M, Abad J, Martínez-Porras JL, Fernández-Puga N, Ferre C, Trapero M, Fraga E, Calleja JL. Adding Branched-Chain Amino Acids to an Enhanced Standard-of-Care Treatment Improves Muscle Mass of Cirrhotic Patients With Sarcopenia: A Placebo-Controlled Trial. *Am J Gastroenterol* 2021; **116**: 2241-2249 [PMID: 34074812 DOI: 10.14309/ajg.0000000000001301]

43 **Barbara M**, Mindikoglu AL. The role of zinc in the prevention and treatment of nonalcoholic fatty liver disease. *Metabol Open* 2021; **11**: 100105 [PMID: 34337376 DOI: 10.1016/j.metop.2021.100105]

44 **Kitajima Y**, Takahashi H, Akiyama T, Murayama K, Iwane S, Kuwashiro T, Tanaka K, Kawazoe S, Ono N, Eguchi T, Anzai K, Eguchi Y. Supplementation with branched-chain amino acids ameliorates hypoalbuminemia, prevents sarcopenia, and reduces fat accumulation in the skeletal muscles of patients with liver cirrhosis. *J Gastroenterol* 2018; **53**: 427-437 [PMID: 28741271 DOI: 10.1007/s00535-017-1370-x]

45 **Koya S**, Kawaguchi T, Hashida R, Goto E, Matsuse H, Saito H, Hirota K, Taira R, Matsushita Y, Imanaga M, Nagamatsu A, Shirono T, Shimose S, Iwamoto H, Niizeki T, Kuromatsu R, Miura H, Shiba N, Torimura T. Effects of in-hospital exercise on liver function, physical ability, and muscle mass during treatment of hepatoma in patients with chronic liver disease. *Hepatol Res* 2017; **47**: E22-E34 [PMID: 27062043 DOI: 10.1111/hepr.12718]

46 **Hiraoka A**, Michitaka K, Kiguchi D, Izumoto H, Ueki H, Kaneto M, Kitahata S, Aibiki T, Okudaira T, Tomida H, Miyamoto Y, Yamago H, Suga Y, Iwasaki R, Mori K, Miyata H, Tsubouchi E, Kishida M, Ninomiya T, Kohgami S, Hirooka M, Tokumoto Y, Abe M, Matsuura B, Hiasa Y. Efficacy of branched-chain amino acid supplementation and walking exercise for preventing sarcopenia in patients with liver cirrhosis. *Eur J Gastroenterol Hepatol* 2017; **29**: 1416-1423 [PMID: 29016470 DOI: 10.1097/MEG.0000000000000986]

47 **Hanai T**, Nishimura K, Miwa T, Maeda T, Ogiso Y, Imai K, Suetsugu A, Takai K, Shimizu M. Usefulness of nutritional therapy recommended in the Japanese Society of Gastroenterology/Japan Society of Hepatology evidence-based clinical practice guidelines for liver cirrhosis 2020. *J Gastroenterol* 2021; **56**: 928-937 [PMID: 34533633 DOI: 10.1007/s00535-021-01821-z]

48 **Iqbal U**, Jadeja RN, Khara HS, Khurana S. A Comprehensive Review Evaluating the Impact of Protein Source (Vegetarian vs. Meat Based) in Hepatic Encephalopathy. *Nutrients* 2021; **13** [PMID: 33530344 DOI: 10.3390/nu13020370]

49 **Lattanzi B**, D'Ambrosio D, Merli M. Hepatic Encephalopathy and Sarcopenia: Two Faces of the Same Metabolic Alteration. *J Clin Exp Hepatol* 2019; **9**: 125-130 [PMID: 30765945 DOI: 10.1016/j.jceh.2018.04.007]

50 **Chew STH**, Tan NC, Cheong M, Oliver J, Baggs G, Choe Y, How CH, Chow WL, Tan CYL, Kwan SC, Husain FS, Low YL, Huynh DTT, Tey SL. Impact of specialized oral nutritional supplement on clinical, nutritional, and functional outcomes: A randomized, placebo-controlled trial in community-dwelling older adults at risk of malnutrition. *Clin Nutr* 2021; **40**: 1879-1892 [PMID: 33268143 DOI: 10.1016/j.clnu.2020.10.015]

51 **Holeček M**, Vodeničarovová M. Effects of beta-hydroxy-beta-methylbutyrate supplementation on skeletal muscle in healthy and cirrhotic rats. *Int J Exp Pathol* 2019; **100**: 175-183 [PMID: 31321841 DOI: 10.1111/iep.12322]

52 **Lai JC**, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, Feng S. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. *Hepatology* 2017; **66**: 564-574 [PMID: 28422306 DOI: 10.1002/hep.29219]

53 **Lattanzi B**, Bruni A, Di Cola S, Molfino A, De Santis A, Muscaritoli M, Merli M. The Effects of 12-Week Beta-Hydroxy-Beta-Methylbutyrate Supplementation in Patients with Liver Cirrhosis: Results from a Randomized Controlled Single-Blind Pilot Study. *Nutrients* 2021; **13** [PMID: 34371806 DOI: 10.3390/nu13072296]

54 **Espina S**, Sanz-Paris A, Gonzalez-Irazabal Y, Pérez-Matute P, Andrade F, Garcia-Rodriguez B, Carpéné C, Zakaroff A, Bernal-Monterde V, Fuentes-Olmo J, Arbones-Mainar JM. Randomized Clinical Trial: Effects of β-Hydroxy-β-Methylbutyrate (HMB)-Enriched vs. HMB-Free Oral Nutritional Supplementation in Malnourished Cirrhotic Patients. *Nutrients* 2022; **14** [PMID: 35684144 DOI: 10.3390/nu14112344]

55 **Leoni G**, Rosato A, Perozzi G, Murgia C. Zinc proteome interaction network as a model to identify nutrient-affected pathways in human pathologies. *Genes Nutr* 2014; **9**: 436 [PMID: 25367142 DOI: 10.1007/s12263-014-0436-0]

56 **Katayama K**. Zinc and protein metabolism in chronic liver diseases. *Nutr Res* 2020; **74**: 1-9 [PMID: 31891865 DOI: 10.1016/j.nutres.2019.11.009]

57 **Katayama K**, Kawaguchi T, Shiraishi K, Ito T, Suzuki K, Koreeda C, Ohtake T, Iwasa M, Tokumoto Y, Endo R, Kawamura N, Shiraki M, Hanai T, Habu D, Tsuruta S, Sakai H, Miwa Y, Kawada N, Kato A, Takei Y, Mine T, Kohgo Y, Seki T, Sata M, Ito Y, Fukui K, Nishiguchi S, Moriwaki H, Suzuki K. The Prevalence and Implication of Zinc Deficiency in Patients With Chronic Liver Disease. *J Clin Med Res* 2018; **10**: 437-444 [PMID: 29581807 DOI: 10.14740/jocmr3374w]

58 **Cousins RJ**. Gastrointestinal factors influencing zinc absorption and homeostasis. *Int J Vitam Nutr Res* 2010; **80**: 243-248 [PMID: 21462106 DOI: 10.1024/0300-9831/a000030]

59 **Chiba M**, Katayama K, Takeda R, Morita R, Iwahashi K, Onishi Y, Kita H, Nishio A, Kanno T, Saito T, Maeda K, Naito M, Michida T, Ito T. Diuretics aggravate zinc deficiency in patients with liver cirrhosis by increasing zinc excretion in urine. *Hepatol Res* 2013; **43**: 365-373 [PMID: 22994500 DOI: 10.1111/j.1872-034X.2012.01093.x]

60 **Riggio O**, Merli M, Capocaccia L, Caschera M, Zullo A, Pinto G, Gaudio E, Franchitto A, Spagnoli R, D'Aquilino E. Zinc supplementation reduces blood ammonia and increases liver ornithine transcarbamylase activity in experimental cirrhosis. *Hepatology* 1992; **16**: 785-789 [PMID: 1505922 DOI: 10.1002/HEP.1840160326]

61 **Katayama K**, Saito M, Kawaguchi T, Endo R, Sawara K, Nishiguchi S, Kato A, Kohgo H, Suzuki K, Sakaida I, Ueno Y, Habu D, Ito T, Moriwaki H, Suzuki K. Effect of zinc on liver cirrhosis with hyperammonemia: a preliminary randomized, placebo-controlled double-blind trial. *Nutrition* 2014; **30**: 1409-1414 [PMID: 25280421 DOI: 10.1016/j.nut.2014.04.018]

62 **Holecek M**. Ammonia and amino acid profiles in liver cirrhosis: effects of variables leading to hepatic encephalopathy. *Nutrition* 2015; **31**: 14-20 [PMID: 25220875 DOI: 10.1016/j.nut.2014.03.016]

63 **Grüngreiff K**, Reinhold D, Wedemeyer H. The role of zinc in liver cirrhosis. *Ann Hepatol* 2016; **15**: 7-16 [PMID: 26626635 DOI: 10.5604/16652681.1184191]

64 **Stewart-Knox BJ**, Simpson EE, Parr H, Rae G, Polito A, Intorre F, Meunier N, Andriollo-Sanchez M, O'Connor JM, Coudray C, Strain JJ. Zinc status and taste acuity in older Europeans: the ZENITH study. *Eur J Clin Nutr* 2005; **59** Suppl 2: S31-S36 [PMID: 16254578 DOI: 10.1038/SJ.EJCN.1602295]

65 **Park JG**, Tak WY, Park SY, Kweon YO, Chung WJ, Jang BK, Bae SH, Lee HJ, Jang JY, Suk KT, Oh MJ, Heo J, Woo HY, Jang SY, Lee YR, Lee JS, Kim DY, Kim SH, Suh JI, Kim IH, Kang MK, Lee WK. Effects of Branched-Chain Amino Acid (BCAA) Supplementation on the Progression of Advanced Liver Disease: A Korean Nationwide, Multicenter, Prospective, Observational, Cohort Study. *Nutrients* 2020; **12** [PMID: 32429077 DOI: 10.3390/nu12051429]

66 **Morihara D**, Iwata K, Hanano T, Kunimoto H, Kuno S, Fukunaga A, Yotsumoto K, Takata K, Tanaka T, Sakurai K, Iwashita H, Ueda S, Hirano G, Yokoyama K, Nakane H, Nishizawa S, Yoshikane M, Anan A, Takeyama Y, Kakumitsu S, Kitamura Y, Sakamoto M, Irie M, Shakado S, Sohda T, Watanabe H, Sakisaka S. Late-evening snack with branched-chain amino acids improves liver function after radiofrequency ablation for hepatocellular carcinoma. *Hepatol Res* 2012; **42**: 658-667 [PMID: 22380706 DOI: 10.1111/j.1872-034X.2012.00969.x]

67 **Kanekawa T**, Nagai H, Kanayama M, Sumino Y. Importance of branched-chain amino acids in patients with liver cirrhosis and advanced hepatocellular carcinoma receiving hepatic arterial infusion chemotherapy. *Cancer Chemother Pharmacol* 2014; **74**: 899-909 [PMID: 25138286 DOI: 10.1007/s00280-014-2564-z]

**Footnotes**

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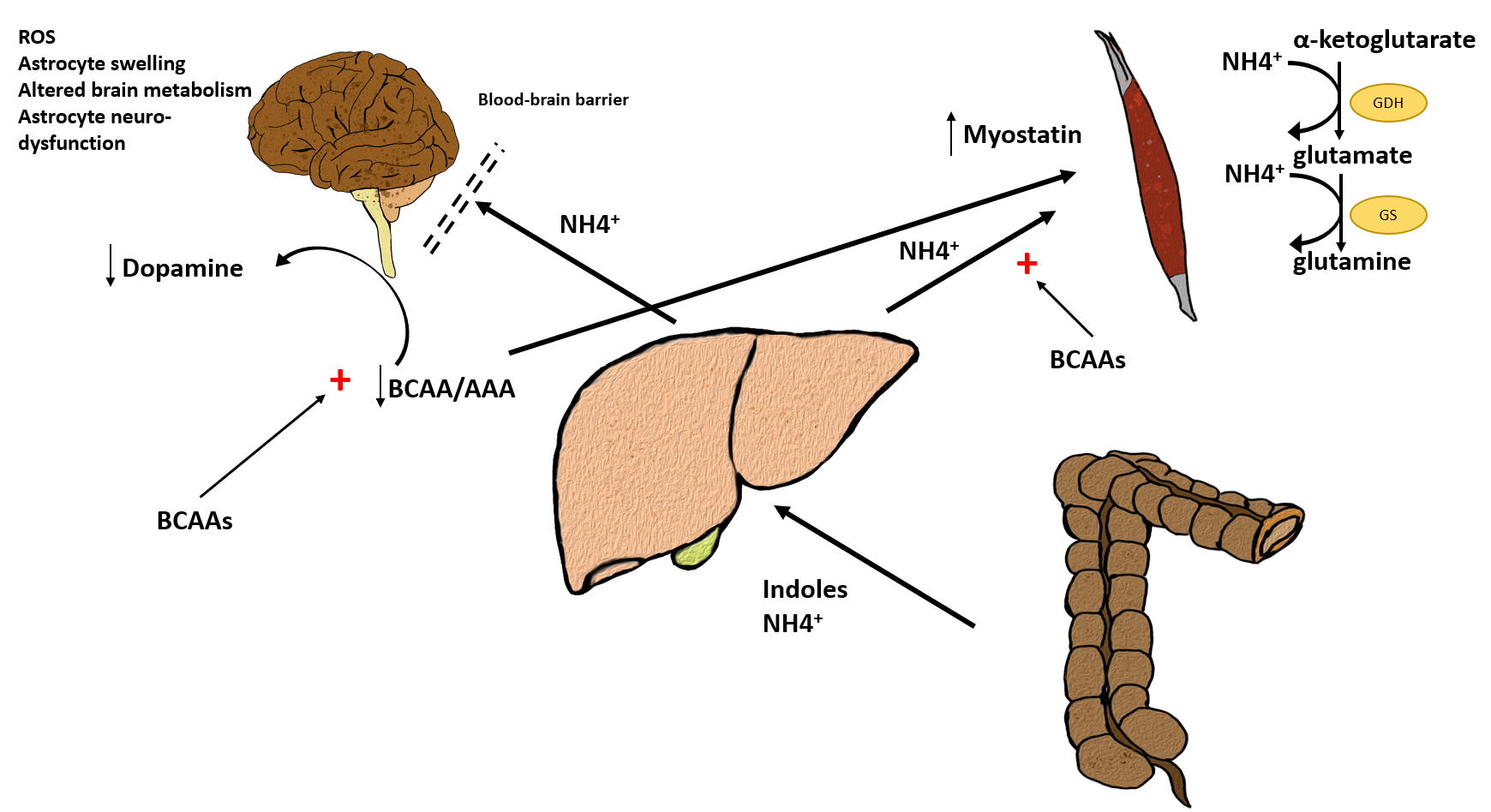
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**Figure Legends**



**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.

**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, nutritional  status, 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.