Branched-Chain Amino Acid Enriched Supplements as Therapy for Liver Disease\textsuperscript{1–3}

Michael Charlton\textsuperscript{4}

Department of Gastroenterology and Hepatology, Mayo Clinic and Foundation, Rochester, MN

ABSTRACT Altered amino acid metabolism is a hallmark of liver disease, characterized by low levels of circulating BCAAs and elevated levels of circulating aromatic amino acids, and methionine. Although overwhelming evidence indicates that the incidence of complications of liver disease increases with malnutrition, the reported impact of nutritional therapy, specifically BCAA supplementation, on outcomes in patients with liver disease has varied with the indication. Multiple small studies report the beneficial effects of BCAA supplementation, including improved metabolic profiles, as measured by protein sparing and/or normalization of respiratory quotients and clinical improvement of hepatic encephalopathy. Other studies have failed to show a clinical benefit of BCAA supplementation. The data concerning the impact of BCAA supplementation in prophylaxis of long-term morbidity and mortality in patients with cirrhosis is more promising and has been the subject of 2, large randomized controlled trials. In a study of 174 patients with advanced cirrhosis, who were randomized to either BCAA or 1 of 2 control arms, the combined event rates were seen to be significantly reduced in the BCAA supplementation arm, although this was not true for individual complications. In a more recent, larger, randomized controlled trial (\textit{n} = 646) using a more palatable formulation, investigators demonstrated that long-term BCAA supplementation is associated with decreased frequency of hepatic failure and overall complication frequency. Both studies found improved nutritional status associated with BCAA supplementation. On balance, BCAA supplementation appears to be associated with decreased frequency of complications of cirrhosis and improved nutritional status when prescribed as maintenance therapy. Cost and palatability may limit the potential applicability of this treatment modality. J. Nutr. 136: 295S–298S, 2006.

KEY WORDS: • branched-chain amino acids • liver disease

The liver is responsible for the metabolism of many hormones that have discordant effects on protein, carbohydrate, and lipid metabolism, including insulin, the sex hormones, insulin-like growth factors, and glucagon. It is thus not surprising that chronic and acute liver disease can profoundly alter nutritional status and amino acid metabolism.

The prevalence of malnutrition in patients with liver disease varies from 10% to 100%, depending largely on the method of nutritional assessment performed and the population studied. Protein-calorie malnutrition (PCM)\textsuperscript{5} can be observed in all clinical stages but is more frequently seen in advanced stages of liver disease (1). Alcoholic liver disease is the form of liver disease most frequently associated with PCM. Reported prevalences of PCM are between ~20% for patients with compensated alcoholic liver disease in the community and 100% in hospitalized patients with acute alcoholic hepatitis (2). Reliable data based on a detailed nutritional assessment of the prevalence of PCM in patients with nonalcoholic liver disease are relatively scant. In a study by Morgan et al. (3), 40% of patients with primary biliary cirrhosis were found to have evidence of PCM vs. 12% of patients with chronic hepatitis.

The pathophysiology of malnutrition in liver disease is complex and multifactorial. Contributing factors include diminished intake, increased requirements (\textit{e.g.}, due to ascites formation and maldigestion), altered substrate utilization (characterized by lowered respiratory quotients), and altered protein and amino acid metabolism.

When the liver fails acutely, it is the loss of hepatic regulation of protein metabolism that results rapidly in death. The alterations in amino acid metabolism associated with liver disease are characterized by low levels of circulating BCAAs (leucine, isoleucine and valine), elevated levels of circulating aromatic amino acids (phenylalanine, tryptophan and tyrosine), and methionine (4). It is widely believed that the changes

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\textsuperscript{4} To whom correspondence should be addressed. E-mail: charlton.michael@mayo.edu.

\textsuperscript{5} Abbreviations used: PCM, protein calorie malnutrition.
in amino acid metabolism play a role in the pathogenesis of many of the complications of cirrhosis, such as portosystemic encephalopathy. Cirrhosis is often associated with a) increased endogenous leucine flux, an indicator of protein breakdown and leucine oxidation; and b) decreased protein synthesis response to a meal.

The presence of malnutrition has been variably associated with increased short- and long-term mortality in patients with acute and chronic liver diseases (5,6). Preoperative malnutrition has also been reported to be associated with increased operative blood loss, longer lengths of stay in intensive care units, increased mortality, and higher total hospital charges after liver transplantation (7). Furthermore, malnutrition is associated with its own morbidity in patients with acute and chronic liver disease, for example, cognitive dysfunction and dermatological manifestations of zinc deficiency. In this setting, nutritional therapy, particularly BCAA supplementation, is an attractive concept in the prevention and treatment of complications.

Although there is overwhelming evidence that the incidence of complications of liver disease increases with malnutrition, the impact of BCAA nutritional therapy on outcomes in patients with liver disease has been variable (8–12).

Alcoholic hepatitis

The correlation of malnutrition with mortality and the particularly high prevalence of malnutrition among patients with alcoholic liver disease has led to a relatively large number of clinical trials of nutritional therapies in this group. Despite initial promise, the aggregate of evidence suggests that parenteral or enteral hyperalimentation (with or without BCAA-enriched preparations) does not confer a medium- or long-term survival benefit to patients with acute alcoholic hepatitis (13). It is important to note however, that patients with alcoholic hepatitis who do not achieve a positive nitrogen balance have very poor survival rates. A nitrogen-balance–maintaining diet using standard amino acid mixtures or food preparations, with concomitant replacement of potassium, phosphate, magnesium, and thiamine should be aggressively pursued in hospitalized patients with alcoholic liver disease. An enteric route should be preferentially utilized whenever possible.

Hepatic encephalopathy

Even subclinical hepatic encephalopathy, present in ~75% of patients with cirrhosis, can attenuate quality of life and should be treated. Replacement of zinc, when deficient, and/or lactulose therapy are almost always sufficient treatments (14,15). Protein restriction is rarely necessary in the short term, and never necessary in the medium or long term. For overt hepatic encephalopathy, acute withdrawal of protein from the diet while seeking the precipitating causes of encephalopathy is a cornerstone of therapy.

After successful reversal of hepatic encephalopathy, nitrogen balance–maintaining quantities of standard proteins should be reintroduced into the diet. In the unusual patient who cannot tolerate ≥1.0 g kg⁻¹ d⁻¹ of standard proteins without becoming encephalopathic, despite optimal pharmacological therapy, nutritional supplementation with vegetable proteins and, if necessary, BCAA-enriched formulae should be considered. Both of these agents have been shown to produce clinical improvement in chronic hepatic encephalopathy while allowing adequate amounts protein to be consumed (16,17).

Medium- and long-term protein restriction are contraindicated in patients with cirrhosis.

Fulminant hepatic failure

Fulminant hepatic failure is associated with a 1- to 4-fold increase in rates of protein catabolism, with a concomitant loss of capacity for ammonia removal. In addition, the ability of the liver to effectively metabolize insulin and to release glucose through gluconeogenesis is impaired. The risk of hypoglycemia has been well demonstrated in clinical studies and in animal models (18–20). Unfortunately, the ideal method of preventing hypoglycemia and glucopenic brain injury has not been established. Certainly, following the onset of hypoglycemia, blood glucose levels require frequent monitoring and continuous infusions of 10–20% dextrose. Almost every other facet of nutritional therapy in the setting of fulminant hepatic failure is controversial. Although BCAA-enriched formulae and medium-chain triglycerides offer theoretical advantages over standard amino acid and lipid preparations, there is no proven benefit to administering BCAAs or medium-chain triglycerides either enteraly or parenterally. Indeed, there is no compelling evidence to promote the use nutritional therapy of any kind.

Intuitively, patients with fulminant hepatic failure who require prolonged hospitalization would seem to merit nutritional support, and it is usually given. Such support should, however, always be at the discretion of the practitioner and be provided through the enteric route whenever possible.

Prevention of complications of cirrhosis

An early demonstration of a scientific rationale for BCAA supplementation, an increased molar ratio of BCAAs to aromatic amino acids, in association with an observed clinical benefit (21) has been followed by many attempts to define the role of BCAA supplementation in the management of liver disease. The ease with which a beneficial effect of BCAA supplementation has been demonstrated in rats (22,23) has generated optimism that clinical efficacy would be seen in humans. Indeed, there have been multiple reports of beneficial effects of BCAA supplementation, including improved metabolic profiles, as measured by protein sparing and/or normalization of respiratory quotients (24–27), and clinical improvement of hepatic encephalopathy (27–32). Other studies fail to show a clinical benefit of BCAA supplementation (26,33–35). Fabbri et al. (36) bravely tried to bring clarity to the role of BCAA supplementation in the treatment of chronic hepatic encephalopathy through a meta-analysis of randomized controlled trials. Unfortunately, authors of only 2 (of 9) studies submitted data for the meta-analysis. Fabbri et al. commented, as had the authors of a meta-analysis of intravenous BCAA therapies of hepatic encephalopathy (37), that large, multicenter, long-term studies incorporating important clinical outcomes, were needed.

Two such studies dominate the literature regarding the use of BCAA supplementation for the prophylaxis of complications of cirrhosis.

Marchesini et al. (38) reported the results of a large multicenter, randomized controlled trial comparing outcomes after 1 y of nutritional support with BCAA-enriched dietary supplements vs. lactoalbumin or maldodextrin dietary supplementation. The principal finding was that the primary outcome (i.e., a composite of death, frequency of hospital admission, and duration of hospital stay) was significantly lower in the BCAA arm of the study than in the lactoalbumin arm (odds ratio 0.51; 95% CI, 0.19–0.96, P = 0.039). There was a trend for the superiority of BCAA over maldodextrin (P = 0.108). This
study had a high frequency of participant withdrawal, with regular follow-up in only 115 of 174 patients, thus reducing the power of the study. Perhaps because of this, in intention to treat analysis, the time course of events was not different between groups. A benefit of BCAA supplementation could only be seen when nonliver-related deaths were excluded from the analysis. The higher than expected number of participants withdrawing from the study was most commonly due to noncompliance and/or the side effects of therapy (withdrawal of consent due to poor palatability and intolerance of required water intake).

The authors included a rigorous analysis of portosystemic encephalopathy and nutritional status in their study. Perhaps surprisingly, no significant differences in encephalopathy test scores, including Reitan testing, were seen among treatment groups. Participants in the BCAA arm did, however, experience significant improvement in nutritional status in contrast to the deterioration that occurred in the malodextrin and lactoalbumin groups. An improvement in nutritional status is likely to have contributed to the observed differences in hospitalization, as severity of malnutrition has been shown to correlate with the progression of cirrhosis and the development of complications (5,6). BCAAs have been shown to stimulate hepatic regeneration, perhaps further contributing to the benefits seen in the study by Marchesini et al. (39), such as improved biochemical profiles and Child-Pugh scores.

The study by Marchesini et al. (38) was a potent demonstration of one of the primary limitations of BCAA supplementation: poor palatability.

Another recent study incorporating a more palatable granular formulation of leucine, isoleucine, and valine (Livact, Ajinomoto) has been completed. In what is by far the largest study in this setting, Muto et al. (40) conducted a multicenter, randomized, and nutrient-intake-controlled trial on the comparative effects of BCAA orally administered at 12 g/d for 2 y versus non-BCAA-supplemented diet therapy. Daily food intake was 1.0–1.4 g protein kg⁻¹ d⁻¹ including BCAA preparation and 25–35 kcal kg⁻¹ d⁻¹. The study was conducted in 646 patients with cirrhosis. The primary end point was a composite of death by any cause, development of liver cancer, rupture of esophageal varices, or progress of hepatic failure (event-free survival). The secondary end points were serum albumin concentration and health-related quality of life (QOL) measured by Short Form-36 questionnaire (41). The incidence of events comprising the primary end point decreased in the BCAA group compared with the diet group (hazard ratio, 0.67; 95% confidence interval, 0.49–0.93; P = 0.015; median observation period, 445 d). Serum albumin concentration increased in the BCAA group compared with the diet group (P = 0.018). The general health perception measure in Short Form-36 was also improved (P = 0.003).

The study by Muto et al. (40) provides important new evidence of a therapeutic benefit to BCAA supplementation in the prevention of complications of cirrhosis. Having apparently largely resolved the issue of poor palatability of BCAA supplements for patients by incorporating the BCAA into granules and thus limiting interaction with ungrateful taste buds, should we expect wider application of BCAA supplementation? There is competition to the results of the studies by Marchesini et al. and Muto et al. that could limit the recommendations for expanding BCAA use by the Journal of Parenteral and Enteral Nutrition (JPEN) and American Society of Parenteral and Enteral Nutrition (ASPEN). For example, there are other means to ameliorate muscle wasting and/or negative nitrogen balance in patients with cirrhosis. A late evening meal has been shown to have a positive effect on nitrogen balance in patients with cirrhosis when compared with an equicaloric diet without a late evening meal (42). Uptake of BCAA therapy might also be limited by the fact that lactulose is cheap and effective in the treatment of acute and chronic encephalopathy, presumably a common cause of hospital admissions in both studies. Prophylaxis of spontaneous bacterial peritonitis and variceal hemorrhage, other likely causes of hospital admissions, can also be achieved by alternative simple pharmacological means. The most compelling basis for a more widespread prescription of BCAA supplements to patients with cirrhosis is the potential to avert general hepatic decompensation and subsequent death and liver transplantation: direct data for which are lacking. Making palatable the spending of precious healthcare resources today for a possible benefit tomorrow is likely to remain a Sisyphean challenge.

LITERATURE CITED


