Chapter 6
Nutrition in Liver Cirrhosis

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Abstract Nutritional/metabolic disorders such as protein–energy malnutrition are frequently observed with liver cirrhosis. Nutritional therapy prevents complications of liver cirrhosis and improves prognoses as well as quality of life. Branched chain amino acids are key drugs of nutritional therapy for liver cirrhosis, improve hypoalbuminemia, and are useful as a late evening snack for energy malnutrition. Appropriate nutritional therapy must be conducted for liver cirrhosis patients associated with sarcopenia or obesity.

Keywords BCAA · Liver cirrhosis · Nutritional therapy · PEM · Sarcopenia

6.1 Pathology and Nutrition of Liver Cirrhosis

The liver plays a central role in nutritional/energy metabolism control and liver cirrhosis patients with decreased hepatic functional reserve are associated with various nutritional/metabolic disorders. Particularly because protein–energy malnutrition (PEM), which is common in patients with liver cirrhosis, is deeply involved in the prognosis and deterioration of quality of life (QOL) in the same patients, appropriate diagnosis (nutritional assessment) along with early intervention (nutritional therapy) is important [1, 2].

Although the resting energy expenditure of liver cirrhosis patients is elevated, the uptake of glucose into the liver and the ability to synthesize/store glycogen in the liver are decreased as liver parenchymal cells decrease. In particular, as liver cirrhosis progresses, liver cirrhosis patients are frequently associated with abnormal glucose metabolism such as diabetes and postprandial hyperglycemia/hyperinsulinemia because the utilization efficiency of carbohydrates decreases, while the

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utilization efficiency of fat as a physiological energy substrate increases. Patients with cirrhosis show a compromised ability to store glycogen and blunted gluconeogenesis [3, 4].

With liver cirrhosis, a decrease in branched chain amino acids (BCAAs) and an increase in aromatic amino acids along with a decrease in the Fischer ratio, which is a molar ratio of these (amino acid imbalance), are observed. Among BCAAs, leucine in particular promotes protein synthesis through the activation of mTOR signaling. BCAA administration for protein malnutrition raises the serum albumin levels and improves the QOL and survival of patients with liver cirrhosis. BCAAs play an important role in maintaining and increasing skeletal muscle mass and the decline in BCAA in liver cirrhosis patients is deeply involved in the development of hypoalbuminemia and sarcopenia [5–7].

Sarcopenia is a syndrome characterized by reduced skeletal muscle mass and muscle strength. With liver cirrhosis, because BCAAs are more energy efficient than glucose and the substrate burned as an energy source in skeletal muscle is mainly BCAAs, progression of PEM, decline in BCAAs, and the development of sarcopenia are observed as a series of pathological conditions. Moreover, with liver cirrhosis, because ammonia that cannot be treated due to a decline in hepatic detoxification function is metabolized in skeletal muscle in a compensatory manner using BCAAs as a substrate, the BCAA concentration further decreases [8, 9]. The loss of hepatic functional reserve and skeletal muscle mass is also involved in glucose intolerance (Fig. 6.1).

In addition to malnutrition, hypernutrition also exacerbates the prognosis of liver cirrhosis patients. Obesity and diabetes in particular have been reported to increase the risk of hepatocellular carcinoma (HCC), so attention is required. Currently, one-third of liver cirrhosis patients are obese [10]. Moreover, liver cirrhosis with backgrounds of nonalcoholic steatohepatitis related to obesity and lifestyle diseases is also increasing. Based on the fact that the nutritional status of liver cirrhosis patients is shifting from PEM/malnutrition to obesity/hypernutrition, improvements of nutritional therapy, exercise therapy, and lifestyle habits should be promoted.

6.2 Basics of Nutritional Therapy

When starting nutritional therapy of liver cirrhosis, it is important to accurately evaluate the nutritional status of patients, especially PEM. PEM is strongly associated with the severity of hepatic decompensation in the setting of cirrhosis and the Child–Pugh classification is a commonly used tool for measuring the severity of chronic liver failure. Cirrhotic patients with Child–Pugh classes B and C have been shown to be most likely to develop PEM [11]. The subjective global assessment (SGA), an attractive test due to its accuracy, is also used as a standard nutritional evaluation in hospitals. The SGA is simple to execute because it is a questionnaire with two main components, history and physical examination [12]. A biochemical

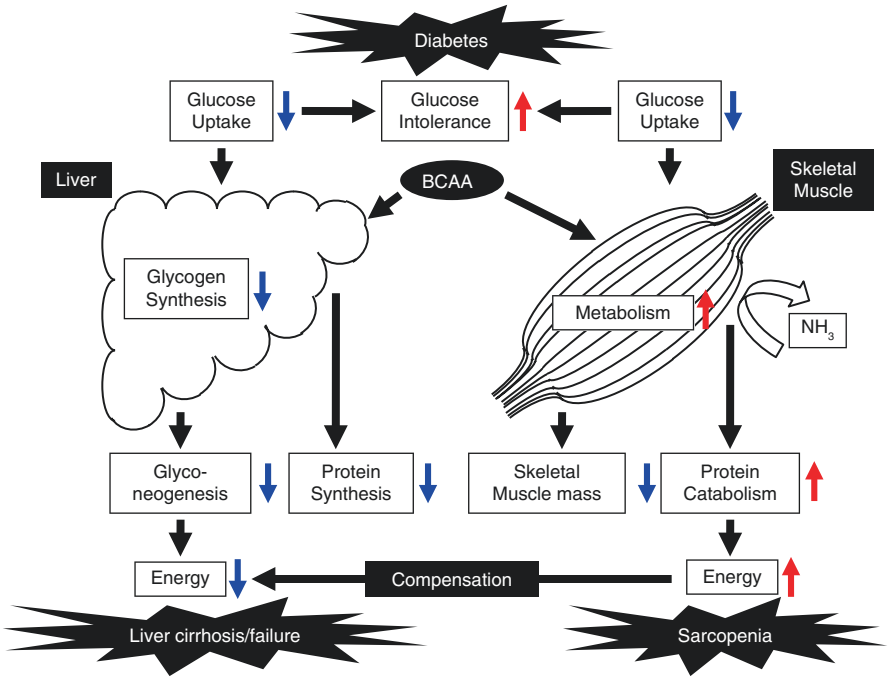

Fig. 6.1 Pathophysiological mechanisms linking metabolic abnormalities, sarcopenia, and glucose intolerance in patients with liver cirrhosis. *BCAA* branched chain amino acids

assessment is commonly performed to evaluate malnutrition and serum albumin is a common tool to measure nutritional status.

In 2015, the Japanese Society of Gastroenterology revised the evidence-based clinical practice guidelines for liver cirrhosis, which is useful to undergo nutritional therapy for such disease [13]. In the guidelines, the protein malnutrition status of liver cirrhosis patients is evaluated using their serum albumin level. A serum albumin level of less than 3.5 g/dL significantly decreases survival rate. In liver cirrhosis patients, serum albumin levels are correlated with BCAA concentrations and are the basis for demonstrating the utility of BCAA replacement therapy for the same patients. Energy malnutrition is evaluated using the nonprotein respiratory quotient, arm muscle circumference length/arm circumference length, and serum free fatty acid levels. For hypoalbuminemia, amino acid imbalance, and energy malnutrition, it is necessary to proactively conduct nutritional therapy [3, 14] (Fig. 6.2).

Diet plays a substantial role in cirrhosis. For liver cirrhosis, a nutritional care plan is prepared by paying attention to complications such as ascites/edema, impaired glucose tolerance, and hepatic encephalopathy/protein intolerance. Physical measurements along with a subjective comprehensive evaluation are conducted and a nutritional assessment is conducted over time according to changes in the pathological conditions. Although the energy requirement is calculated based on the

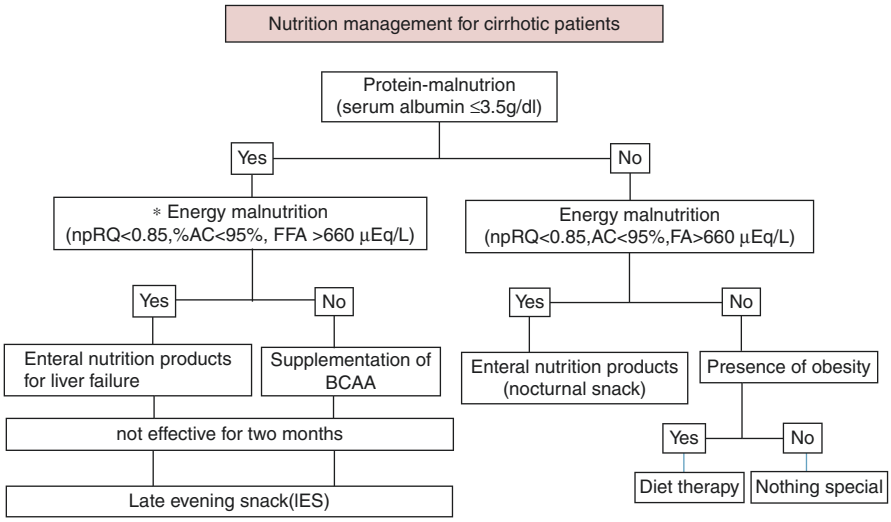

Fig. 6.2 Algorithm for nutritional therapy in patients with liver cirrhosis. *npRQ* nonprotein respiratory quotient, *%AC* percent arm circumference, *FFA* free fatty acid. This figure is referred from [13]

intensity of daily activity, particularly in the event of impaired glucose tolerance, attention must be paid to avoid excessive caloric intake (25–35 kcal/kg ideal body weight/day as a guide). The recommendation for carbohydrates is 50–70% of daily calories; however, simple sugar, especially fructose, should be avoided as much as possible [15]. A low salt diet is effective against ascites/edema; however, excessive sodium restrictions require attention because they reduce appetite and deteriorate nutritional status.

Protein restriction is no more a recommended strategy unless contraindicated by clinical complications, such as hepatic encephalopathy. Because protein deficiency is a significant problem in malnutrition, the required protein intake in cirrhotic patients is 1.0–1.5 g/kg/day if there is no protein intolerance [16]. Although protein intake is useful as a countermeasure to sarcopenia, because excessive protein load may induce hepatic encephalopathy, particularly in the event of protein intolerance, low protein diet (0.5–0.7 g/kg/day) or enteral nutrients for liver failure including BCAAs is used. Fat requirements are set to 20–25% in terms of energy ratio. It is also important to supplement zinc and take appropriate amounts of vitamins and dietary fiber (measures for constipation). There should be an increased emphasis on BCAA and fiber with decreased ammonia when the patients suffer from hepatic encephalopathy (Table 6.1).

It should be emphasized that total nutritional management, including both diet and nutritional supplements, is important in order to prevent the progression of chronic liver disease and onset of HCC. In 2012, the Japanese Nutritional Study Group for Liver Cirrhosis published the guidelines on nutritional management in

Table 6.1 Recommendation for nutritional management of liver cirrhosis

1. Daily calories
25–35 kcal/kg ideal body weight/day
If any abnormalities are seen in glucose tolerance, intake should be 25 kcal/kg ideal body weight/day
2. Proteins
If there is no protein intolerance:
1.0–1.5 g/kg/day (including BCAA granules)
If there is protein intolerance:
0.5–0.7 g/kg/day (low protein diet) + BCAA-enriched enteral nutrient mixture
3. Carbohydrates
50–70% of daily calories with decreased simple sugar, especially fructose
4. Lipids
20–25% of daily calories
5. Sodium chloride
If there is ascites and/or edema: 5–7 g/day
6. Divided meal (4–6 times/day) and/or LES (amounts to 200 kcal)

cirrhotic patients from the perspective of preventing HCC [17]. This guideline is useful for the actual nutritional management of patients with liver cirrhosis.

6.3 Nutritional Therapy Using BCAA

To improve hypoalbuminemia and amino acid imbalance, oral BCAA preparations are useful. Although oral BCAA preparations include BCAA granules and enteral nutrients for liver failure, they need to be properly used depending on the energy malnutrition state or the presence of hepatic encephalopathy. While supplemental administration of BCAA granular preparation maintains/increases the serum albumin concentration in decompensated liver cirrhosis patients, it prevents adverse events of liver cirrhosis and improves vital prognosis as well as QOL. A multicenter, randomized, and nutrient intake-controlled trial has revealed that long-term oral BCAA granules supplementation (12 g/day) improves event-free survival (death by any cause, development of HCC, rupture of esophageal varices, or progress of hepatic failure), increases serum albumin levels, and improves QOL in patients with decompensated liver cirrhosis with hypoalbuminemia [5]. The mean annual changes in the model for end-stage liver disease score and Child–Pugh score were smaller and the incidence of overall major cirrhotic complications, such as ascites, was lower in cirrhotic patients taking BCAA granules, which suggests that early interventional oral BCAA administration may prolong the liver transplant waiting period by preserving hepatic reserve in cirrhosis [18]. BCAA supplementation relieves minimal hepatic encephalopathy and increases muscle mass [19]. More

importantly, BCAA supplementation is also involved in reduced incidence of HCC in patients with cirrhosis [20–22].

For energy malnutrition, divided meals and late evening snacks (LES), such as rice ball, liquid nutrients, and BCAA-enriched supplementation, are recommended. Approximately 200 kcal is divided from the target total daily calories and taken as a snack/energy before going to bed to improve nighttime starvation. LES improves nutritional status, increases body protein content, and diminishes fat and protein oxidation in patients with liver cirrhosis [23, 24]. LES is associated with suppression of serum free fatty acid levels, recovery of energy metabolism, and improvement of health-related QOL [25, 26]. In patients with cirrhosis, divided meals with LES fortified with BCAA prevented hypoglycemia and led to increased nutrition due to reduced catabolism overnight [27]. As divided meals/LES need to be continued, one which is easy to prepare and ingest is preferred. Specifically, 1 pack (approximately 200–300 kcal) of enteral nutrition for liver failure containing mostly BCAA is used. BCAAs are a key drug in nutritional therapy of liver cirrhosis patients (Table 6.1 and Fig. 6.3).

Low level of serum BCAA predicts sarcopenia in patients with liver cirrhosis [28]. In a retrospective study of liver cirrhosis patients with sarcopenia, the oral administration group of a BCAA preparation has been reported as having a significantly better prognosis compared to the non-oral administration group [8]. A leucine-enriched BCAA diet is able to reduce the elevated whole-body protein breakdown in patients with cirrhosis [29]. A recent clinical trial has revealed that combination of BCAA supplementation and walking exercise is effective for improving muscle volume and strength in liver cirrhosis patients [30]. As preven-

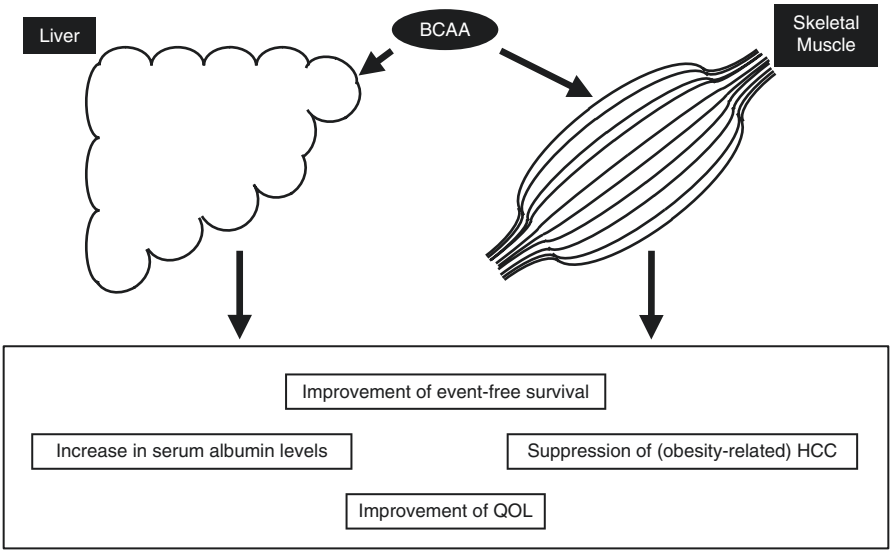

Fig. 6.3 Beneficial impacts of BCAA in patients with liver cirrhosis

tion/treatment of sarcopenia in liver cirrhosis patients, the usefulness of nutritional therapy mainly including BCAAs as well as exercise therapy is anticipated.

6.4 Liver Cirrhosis and Obesity

It has recently been revealed that the nutritional status of liver cirrhosis patients is shifting from PEM/malnutrition to obesity/hypernutrition. Currently, one-third of liver cirrhosis patients exhibit a BMI of 25 or more and liver cirrhosis with a background of obesity and nonalcoholic steatohepatitis is increasing [10]. Obesity exacerbates the prognosis of liver cirrhosis patients and increases the risk of HCC; however, replacement therapy of oral BCAA preparations has been reported to suppress liver carcinogenesis in patients with hepatitis C and cirrhosis who are obese [21]. The beneficial effects of BCAA supplementation on the regulation of glucose metabolism have been reported in recent clinical and experimental studies, which suggest that BCAA may suppress liver carcinogenesis in obese patients with liver cirrhosis, at least in part, by improving insulin resistance [7, 31]. It is necessary to practice nutritional therapy aimed at improvement of the long-term prognosis of liver cirrhosis patients associated with obesity as well as suppression of liver failure and HCC.

6.5 Conclusion

PEM is a serious problem, especially in cirrhotic patients. Appropriately evaluating nutritional/metabolic disorders in liver cirrhosis patients and proactively conducting nutritional therapy lead to the prevention of complications and improved prognoses/QOL. Nutritional therapy for liver cirrhosis should make sure the patients reach the recommended daily calories and nutrients by increasing oral intake or by using other measures, such as oral supplementation, divided meal, and LES. It is also necessary to conduct nutritional therapy including measures for sarcopenia and obesity in coordination with registered dietitians.

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