Chapter 19
Conservative Treatment: Nutritional Treatment

Ryujin Endo and Yasuhiro Takikawa

Abstract In liver cirrhosis, the nutritional elements and the energy metabolism are disturbed, resulting in the status of protein-energy malnutrition (PEM). PEM is common in patients with liver cirrhosis and is also a significant predictor of complications and survival in these patients. On the other hand, the bleeding from esophagogastric varices is still a major and severe complication affecting the prognosis of liver cirrhosis. Although endoscopic therapy and interventional radiology therapy have been widely performed as treatments for portal hypertension, the patients often require dietary restriction after these treatments, resulting in the aggravation of PEM. It has recently become evident that late evening snack improved the status of energy malnutrition and long-term oral administration of branched-chain amino acids (BCAA) supplements decreases the progression of hepatic failure and improves the event-free survival and quality of life, as well as the serum albumin concentration, in patients with decompensated liver cirrhosis. In addition, diet with BCAA-enriched nutrient supplementation may prevent the aggravation of nutritional status in patients with liver cirrhosis during the treatment of portal hypertension.

Keywords Protein-energy malnutrition (PEM) · Hepatic encephalopathy · Branched-chain amino acids (BCAA) · Late evening snack (LES) · Liver cirrhosis

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19.1 Introduction

Endoscopic therapy and interventional radiology (IVR) therapy have been widely performed as treatments for portal hypertension, enabling less invasive treatment. However, patiens often develop hepatic encephalopathy and exacerbation of ascites due to the deterioration of nutritional status and liver dysfunction during the perioperative period. Further, esophagogastric varices combined with liver cirrhosis often recur, with the determination regarding whether or not to continue therapy depending on the hepatic reserve. Therefore, it is extremely important to conduct proper nutrition management, taking into consideration the clinical condition based on liver dysfunction, along with the treatment for varices.

In this article, we outline the features of the nutritional metabolism of liver cirrhosis and explain actual nutritional therapy during treatment for portal hypertension.

19.2 Significance of Nutritional Therapy for Liver Cirrhosis

The occurrence of protein-energy malnutrition (PEM) among patients with cirrhosis is high, and patients with remarkable malnutrition are associated with a high occurrence of complications and mortality [1, 2].

Recently, enteral nutrition against liver cirrhosis has been shown to improve liver function and nutritional status, inhibit the development of complications, and improve the survival rate [2]. Furthermore, the oral administration of branched-chain amino acid (BCAA) preparations for the purpose of correcting PEM prolongs the patient's survival duration [3], indicating the medical validity of nutritional therapy.

19.3 Characteristics of Nutritional Metabolic Disorders Related to Liver Cirrhosis

19.3.1 Energy Consumption

In patients with cirrhosis, the resting energy expenditure (REE) is exacerbated [4]. The exacerbation of REE increases with the progress of severity [5], particularly markedly in the event of ascites, spontaneous bacterial peritonitis (SBP), liver cancer, and circulatory dynamic instability accompanying the ruptured esophagus and gastric varices [6, 7]. As a mechanism by which energy consumption becomes exacerbated, it is considered that the respiratory and circulatory systems are in a hyperdynamic state and both hormones and cytokines are involved in the hypermetabolism.

19.3.2 Substrate Utilization

In liver cirrhosis, despite the exacerbation of REE, the glycogen storage capacity is insufficient, and the skeletal muscle mass decreases due to gluconeogenesis from amino acids by degrading the muscle protein, which is in a state of negative nitrogen equilibrium. Moreover, the substrate utilization after overnight fasting is said to be equivalent to the 3-day fasting state of a healthy person, having the characteristics of a significantly reduced respiratory quotient and higher use of endogenous fat than in healthy people [4, 5]. Substrate oxidation rates are known to reflect the severity of the liver dysfunction (Fig. 19.1), with patients having low values of respiratory quotients below 0.85 known to have poor prognoses [8]. A reduction in the amount of glycogen stored in the liver and impaired glucose tolerance (reduction in insulin resistance and glucose utilization) are considered to be factors involved in the change in substrate utilization.

19.3.3 Metabolic Disorders of Protein/Amino Acids

Protein metabolic disorders related to liver cirrhosis occur as hypoalbuminemia, and patients with serum albumin levels less than 3.5 g/dL have a significantly lower survival rate [9]. In addition, BCAA in plasma decreases because the use of BCAA as an energy substrate for ammoniation in the skeletal muscles and gluconeogenesis is enhanced, while aromatic amino acids (AAA) and methionine which are metabolized in the liver increase as the severity of cirrhosis worsens. These metabolic disorders of amino acids are characterized by a decrease in the Fischer ratio

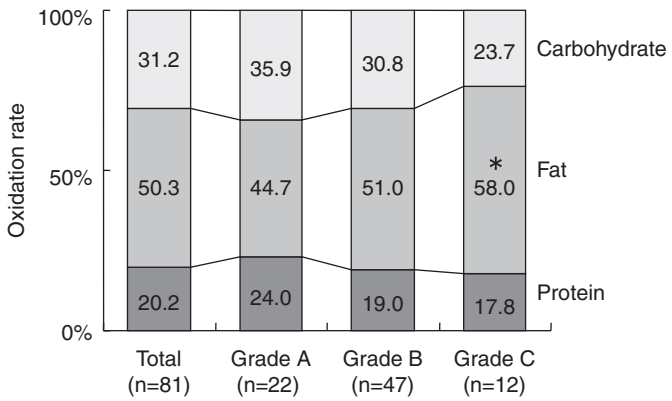

Fig. 19.1 Substrate oxidation rates of glucose, fat, and protein using indirect calorimetry in patients with liver cirrhosis. Seventy cirrhotic patients who were admitted to Iwate Medical University Hospital were investigated. Energy metabolism was measured using indirect calorimetry (Deltatrac-II Metabolic Monitor, Datax Division Inst. Corp., Helsinki, Finland) in the morning after overnight fasting. Each value is shown as the mean. *$P < 0.05$ (compared to grade A). n, number of patients with liver cirrhosis

(BCAA/tyrosine + phenylalanine) and BTR (BCAA/tyrosine ratio). A decrease in BCAA promotes the brain migration of AAA, resulting in an increase in false neurotransmitters, which is a cause of hepatic encephalopathy.

19.3.4 Characteristics of Complicated Hepatic Encephalopathy

Hepatic encephalopathy is a neuropsychiatric symptom centered on consciousness disorders caused by severe hepatic disorder, ranging widely from mild symptoms such as decreased orientation and abnormal behavior to a deep coma with no response whatsoever even if a stimulus is applied. Encephalopathy seen in cirrhosis is classified into a type with a strong factor of portal systemic shunt (chronic recurrent type) and another type with a strong factor of hepatocellular disorder (end-stage type). Determination of the severity of the liver dysfunction is important because the treatment effect and prognosis depend on it. As toxic substances such as ammonia generated in the intestinal tract are often derived from dietary proteins. Cirrhotic patients with portal systemic shunt are in a clinical condition which easily causes hepatic encephalopathy due to an excessive intake of protein (protein intolerance).

19.4 Nutritional Therapy

19.4.1 Basic Policy

We examined the following items to make a nutritional therapy plan, including the subjective global assessment (SGA) and biochemical parameters of nutritional status, clinical stage (compensatory or non-compensatory), presence or absence of hepatic encephalopathy, degree of coma, and the occurrence of complicated diabetes mellitus (Table 19.1) [10].

As the clinical condition of patients with a high level of ascites retention and edemas changes constantly with treatment, it is important to conduct nutritional assessments over time. If esophageal varices are present, the nutritional administration routes need to be flexible in accordance with individual cases [2, 11].

19.4.2 Measures for Energy Metabolism Abnormality

In order to compensate for the energy supply from dinner to the next morning for cirrhosis patients in a state similar to hunger at night, we divided approximately 200 kcal from the target total calories and fed it as a snack before going to bed, which is a method called late evening snack (LES) that has been recommended in clinical practice guidelines in Japan and Western countries [1, 2, 10, 12]. According

Table 19.1 Recommendations for nutritional management of liver cirrhosis

I. Assessment before nutrition and diet therapy
1. Evaluate clinical stage (compensated or decompensated liver cirrhosis) and the severity of liver damage (i.e., Child-Pugh classification) as well as presence of portal systemic shunt
2. Perform subjective global assessment (SGA) and anthropometry
3. Evaluate impaired glucose tolerance, insulin resistance, and postprandial hyperglycemia
4. Evaluate oxidative stress conditions
5. Examine dietary intake using a questionnaire
6. Perform indirect calorimetry and trace element measurement
II. Nutrition and diet therapy
1. Energy requirements 25–35 kcal/kg (ideal body weight)/day, based on standards for dietary intake (2010 edition, Recommended Dietary Allowance According to Intensity of Daily Activity) If any abnormalities are seen in glucose tolerance, intake should be 25 kcal/kg (ideal body weight)/day
2. Required protein intake If there is no protein intolerance: 1.0–1.5 g/kg/day (including oral BCAA granules) If there is protein intolerance: 0.5–0.7 g/kg/day + BCAA-enriched enteral nutrient mixture
3. Required fat intake: lipid energy ratio 20–25%
4. Sodium chloride: ≤6 g/day, and <5 g/day if there are ascites and/or edema
5. Iron: ≤7 mg/day if serum ferritin levels are above the upper limit of the reference interval
6. Others: zinc supplementation, adequate intake of vitamins and dietary fiber (vegetables, fruits, potatoes)
7. Late evening snack (LES) as a divided meal (4 times per day) (amounts to 200 kcal)

BCAA branched-chain amino acid (based on Suzuki et al. [10])

to the Japanese Society of Gastroenterology, cases of nonprotein respiratory quotient <0.85 are indicated for LES [12].

Ordinary food or general enteral nutrients may be used. However, by using BCAA-enriched nutrient mixture (e.g., Aminoleban® EN, 210 kcal; Hepan ED®, 310 kcal), the serum albumin concentration increases, and the oxidation rates for nutrients (carbohydrate, fat) after overnight fasting is improved. Therefore, maintenance of nitrogen balance, improvement of energy metabolic disorders, and impaired glucose tolerance can be expected through the long-term oral supplementation with a BCAA-enriched mixture use in LES [10, 12–14]. In addition, when LES is performed, it is important that the total daily calorie intake does not increase because LES leads to potential obesity and deterioration of impaired glucose tolerance by simply adding it to the previous meals.

19.4.3 Measures for Metabolic Disorders of Protein/Amino Acids

Dietary therapy centered on BCAA substitution therapy occupies the central position of nutritional treatment aimed at the correction of amino acid imbalance and negative nitrogen equilibrium along with the synthesis promoting effect of albumin,

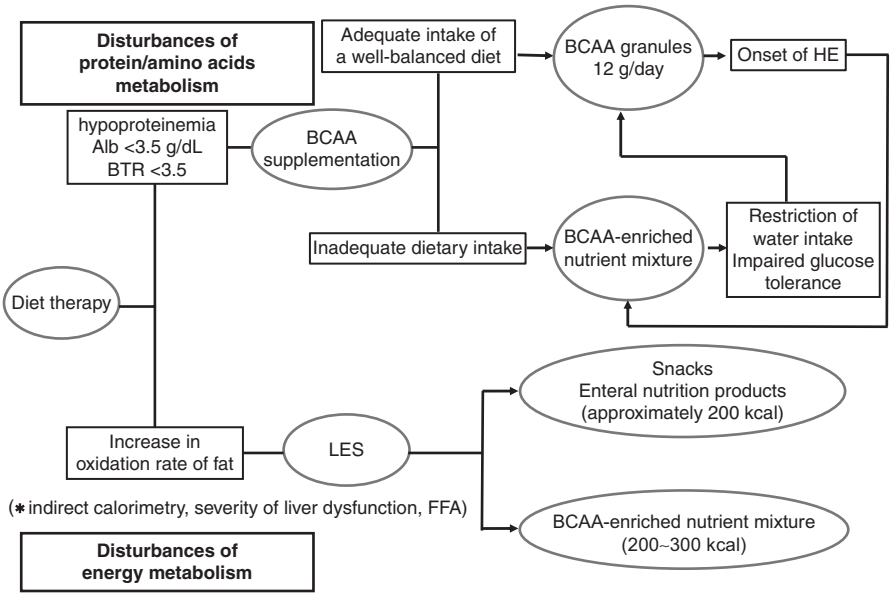

Fig. 19.2 Nutritional treatment for PEM in patients with liver cirrhosis. *PEM* protein-energy malnutrition, *BCAA* branched-chain amino acid (valine + leucine + isoleucine), *BTR* BCAA/tyrosine ratio, *LES* late evening snack, *HE* encephalopathy, *FFA* free fatty acid. Asterisk—indirect calorimeters are available, measurement of resting energy expenditure, nonprotein respiratory quotient (npRQ), and oxidation rates for various nutrients (carbohydrate, fat, protein) after overnight fasting is useful in evaluating protein-energy malnutrition. Serum free fatty acid levels are useful indexes for npRQ during routine care

which is also recommended in the clinical practice guidelines in Japan and Western countries [2, 10, 12].

Oral BCAA preparations include BCAA granules (Livact® Granules) and enteral nutrients for liver failure (e.g., Aminoleban® EN, Hepan ED®), which are selected depending on the severity of energy malnutrition and the presence or absence of hepatic encephalopathy (Fig. 19.2). The former is indicated for patients with hypoalbuminemia (3.5 g/dL or less) despite adequate amounts of a well-balanced diet intake, while the latter is indicated for those after awakening from hepatic encephalopathy or having a history thereof, involving chronic liver failure accompanied by protein intolerance. Even with a history of encephalopathy, the granule preparation can be administered as long as a balanced diet is sufficiently ingested and ammonia is under control. On the other hand, even with no history of encephalopathy, if dietary intake is insufficient, it is also effective to select enteral nutrients from the viewpoint of improving nutritional metabolism [15]. Therefore, in choosing an oral BCAA preparation, it is important to sufficiently grasp the decrease in intake amount and the presence or absence of bias in nutritional balance via a dietary survey.

19.5 Nutrition Management in the Treatment of Esophagogastric Varices

19.5.1 Nutrition Management during Emergency Hemostasis

19.5.1.1 Nutrition Administration Routes and Basic Infusion

In the case of bleeding of the esophagogastric varices, because liver failure advances due to a decrease in the circulating plasma volume, we strive to stabilize the circulatory dynamics. As a basic infusion, an extracellular solution replenisher, such as bicarbonate Ringer's solution (e.g., Bicarbon®, Bikanate®) or glucose-added acetate Ringer's solution (e.g., Veen-D®), is administered from the peripheral vein, switching to saccharification maintenance infusion (no amino acid) centering on glucose after hemostasis to control the general condition. For patients whose circulation dynamics are stable and oral intake is expected to be possible at a relatively early stage (within 1–2 weeks), peripheral parenteral nutrition (PPN) is often selected because they have some degree of calorie deficiency and should start oral intake as soon as possible. The indication for total parenteral nutrition (TPN) is limited to cases such as cardiorenal disease requiring water restriction and those requiring long-term fasting, etc.

19.5.1.2 Strategies for Treatment of Hepatic Encephalopathy

In the case of gastrointestinal bleeding, blood stored in the intestinal tract is decomposed, with ammonia produced by bacterial urease, consequently often resulting in hyperammonemia. The basis of treatment is the removal of toxic substances centering on ammonia and correction of metabolic abnormalities including amino acids, with drug therapy and infusion carried out along with the elimination of incentives and systemic management. Depending on the clinical condition of the patient, in the event of overt encephalopathy (grade II or higher) or in order to improve hyperammonemia, the enema administration of synthetic disaccharides (lactulose syrup) (not covered by insurance) is carried out, or BCAA enriched amino acid solution (e.g. Aminoleban®, Morihepamin®) is administered [11, 13].

BCAA-enriched amino acid solution should be intravenously infused usually within the range of 200–500 mL/day, taking into consideration the nitrogen treatment capacity of the patient. Fasting is continued in the far-advanced stage of comas in which oral intake is difficult, monitoring the extent of conscious awareness and blood ammonia values with the infusion basically containing BCAA and glucose. By using a BCAA infusion, the awakening effect can be obtained at an early stage chronic recurrent type cases, while in end-stage type cases in which the hepatic reserve capacity has declined, hyperammonemia and encephalopathy may be aggravated. Therefore, it is necessary to avoid excessive administration. Further, since it

may cause hypoglycemia after administration, it is also important to monitor blood sugar levels and use glucose solutions in combination (or coinjection).

When patients recover from encephalopathy and oral intake becomes possible, we switch to one to two packs/day of enteral nutrients for the patients with liver failure as soon as possible, gradually adding a low-protein diet [2]. However, it is noteworthy that unnecessary protein restriction tends to make nitrogen equilibrium negative, further promoting PEM. Nutritional therapy should be started with the total energy within the range of 25–35 kcal/kg/day, concurrently using a low-protein diet (0.5–0.7 g/kg/day) and enteral nutrition for patients with liver failure (e.g., one or two packs/day of Aminoleban EN® or Hepan ED®), so that the body constituents can be maintained [10].

19.5.2 Nutritional Management During Preventive/Palliative Treatment

During preventive and palliative endoscopic therapy, we tried to improve the nutritional status, control ascites and hepatic encephalopathy, and correct blood glucose and electrolytes as much as possible prior to surgery.

In the perioperative period of treatment, patients are often forced to fast, which is a concern that PEM may be further exacerbated. Therefore, we have patients who start oral intake as soon as possible after treatment. In this process, for cases involving malnutrition or with a history of hepatic encephalopathy, it is also effective to combine the use of enteral nutrients for liver failure (one to two packs) as LES for the improvement of the respiratory quotient and nitrogen balance as well as the maintenance of serum albumin values [16].

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