Nutritional Pharmacotherapy of Liver Cirrhosis for Prognosis and Improvement of Quality of Life

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Summary Patients with liver cirrhosis are in a state of protein and energy malnutrition (PEM), and this can lead to patients’ poor prognosis and quality of life. Metabolic abnormalities such as hypermetabolism or decreased glucose level and increased fat oxidation, as measured by indirect calorimetry, might trigger and/or worsen PEM. Supplementation with branched-chain amino acids (BCAA) improves hepatic encephalopathy and protein malnutrition (e.g., increasing the serum albumin level and improving the nitrogen balance), and subsequently improves patients’ prognosis and quality of life. Late evening snack (LES) shortens the starvation period during the night in cirrhosis. Decreased respiratory quotient, suggesting patients’ poor prognosis, was recovered to almost normal by LES. This might help to prevent the reduction of muscle volume and fat tissue, improving energy malnutrition in cirrhosis. Preservation of muscle volume is a critical issue for the patients whose muscle strength is weakened, which contributes to poor quality of life. In future studies, the mechanism of the clinical effects of BCAA and LES should be elucidated for the improvement of PEM in patients with cirrhosis.

Key Words: liver cirrhosis, protein and energy malnutrition, branched-chain amino acids, indirect calorimetry, late evening snack

Patients with liver cirrhosis are in a state of protein and energy malnutrition (PEM). We previously reported that about 80% of inpatients with liver cirrhosis had either protein malnutrition, energy malnutrition, or both [1]. PEM in patients with liver cirrhosis affects their quality of life (QOL) [2] as well as their prognosis [3, 4]. Therefore, the improvement of the malnutrition status is a critical issue for these patients. We herein review the recent reports about malnutrition in liver cirrhosis, and describe 2 types of nutritional

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pharmacotherapy for the patients: branched-chain amino acid (BCAA) therapy, and consumption of a late evening snack (LES).

IMPACT OF MALNUTRITION IN LIVER CIRRHOSIS

The mechanism of malnutrition in liver cirrhosis is not well known. One possible explanation is the hypermetabolism. Indirect calorimetry detected an increase in resting energy expenditure (REE) in liver cirrhosis [5]. Greco and his associates reported that 24-h energy expenditure was significantly increased in Child B cirrhosis [6]. They also showed that energy intake was relatively reduced in cirrhotic patients as compared with that in healthy controls. Therefore, the ratio of energy intake to REE was significantly decreased in cirrhosis compared with that in controls. A reduction in energy intake in cirrhosis is not uncommon, especially when ascites, pleural effusion or hepatocellular carcinoma is present. The reduced energy intake could accelerate the impaired nutrition status in cirrhosis. As a result, the excessive utilization of energy might lead to a weight loss [7] due to the mobilization of muscle and fat tissues for gluconeogenesis as an energy substitute.

The reason for hypermetabolism in cirrhosis is still to be elucidated. Hormones or cytokines could be factors that affect REE. Müller and his associates reported the elevated plasma epinephrine and norepinephrine concentrations in hypermetabolic cirrhotic patients, and found that the differences in REE from the predicted values were positively correlated with the epinephrine concentration [8]. In fact, the administration of propranolol significantly reduced REE in cirrhosis, suggesting that β-adrenergic activity could play an important role in hypermetabolism in cirrhosis [8].

Leptin has been also reported to contribute to hypermetabolism in cirrhotic patients [9]. It exists in 2 different forms in serum, free and bound forms, and the latter seems to be related to hypermetabolism. While free leptin was not elevated in cirrhosis and reflected fat mass in both cirrhosis and controls, bound leptin was significantly increased in cirrhotics compared with controls, and correlated significantly with REE × fat-free mass^{-1} or with the difference between measured and estimated REE. The reason why increased bound leptin leads to the elevation of REE is still not known. One explanation could be the direct stimulation of the sympathetic nervous system by leptin [10].

NUTRITIONAL SUPPORT FOR LIVER CIRRHOSIS

1. **BCAA therapy**

BCAA (valine, leucine, isoleucine) are essential amino acids and are named “branched-chain” because they have branched CHn in their structure. BCAA were found to have various physiological and clinical effects, such as the improvement of hepatic encephalopathy (HE), a protein-sparing effect, or serving as an energy substrate. Commercial products such as BCAA-enriched solution or BCAA granules have been widely used for cirrhotic patients expecting those clinical effects in Japan. However, at the same
time, there is no definitive conclusion as to the clinical effects of BCAA in either Europe or the U.S.A. [11].

Improvement of hepatic encephalopathy. It was reported that a reduction in the molar ratio (Fischer’s ratio) of plasma BCAA to aromatic amino acid (AAA) is related to the pathogenesis of HE in cirrhosis [12], and infusion of a BCAA-enriched solution was shown to improve HE in such patients [13]. Since then, there have been several affirmative reports as to the effect of BCAA on HE in cirrhosis [14-16]. While BCAA were found to be effective for chronic portosystemic encephalopathy [17], it seemed to be less effective for acute episodic HE [18]. This is probably because events prior to HE, such as infection or gastrointestinal hemorrhage, might severely damage the liver, leading to irreversible coma. Therefore, types of HE should be considered before the administration of BCAA in cases of HE.

Factors such as ammonia, pseudoneurotransmitters, mercaptan, and short-chain fatty acids would be involved in the pathogenesis of HE. BCAA could reduce serum ammonia, and this might be due to increased ammonia metabolism in the muscle. When BCAA are converted to branched-chain α-ketoacids in the muscle, a reaction to form glutamate from α-ketoglutarate is coupled with this conversion. Then, ammonia is fixed to glutamate to synthesize glutamine by glutamine synthetase. This ammonia is thus detoxified in the muscle in the presence of BCAA when the urea cycle is not well functioning due to the liver damage.

Protein-sparing effect. BCAA have a protein-sparing effect on cirrhotics. It was reported that cirrhotic patients have a negative nitrogen balance [19] as well as a plasma amino acid imbalance [20], which could lead to loss of muscle volume and visceral protein. The negative nitrogen balance and amino acid imbalance were corrected by the administration of BCAA in cirrhotics [19]. The correction of the negative nitrogen balance might be achieved either by increased protein synthesis [21, 22], or by a reduction in protein breakdown [21], as shown both in the patients and in rat cirrhotic models.

Patients with cirrhosis suffer from muscle weakness. In alcoholic cirrhosis, muscle weakness is equal to muscle atrophy; and the atrophy is related to the severity of the malnutrition [23]. The mechanism of muscle atrophy is not known, but this could be caused by an increase in protein catabolism rather than the result of a reduction in protein synthesis [24]. BCAA might prevent the muscle catabolism observed in cirrhosis [25].

Albumin is produced by hepatocytes, and one of its important functions is to maintain the plasma osmopressure at the physiological level. Because of the decreased albumin level, peripheral edema, ascites, or pleural effusion is observed in cirrhotic patients. Yoshida et al. found that oral administration of BCAA granules for 6 months or more brought about a significant increase in the plasma BCAA concentration, Fischer’s ratio, and serum albumin, leading to improved cumulative survival rate and patients’ better QOL [26]. The improvement of albumin turnover, or the increase in the rate of albumin synthesis with the administration of BCAA might explain the elevated serum albumin level in cirrhosis [27, 28].

A role as an energy substrate. As mentioned above, patients with liver cirrhosis have an increased energy requirement. To meet this demand, glucose is the first choice as
an energy substrate, although the patients often show hyperglycemia due to insulin resistance. BCAA could be used as an energy substrate more preferentially than glucose or fatty acids in cirrhosis [29], because BCAA are mainly utilized in the muscle rather than in the damaged liver. However, it was also reported that glucose utilization could be elevated, negatively correlated with body mass index and positively correlated with the creatinine-height index in cirrhosis [30]. Therefore, adequate nutritional assessment is needed to choose appropriate energy substrate in cirrhotic patients.

Enhancement of liver regeneration. BCAA might promote liver regeneration. In rat experimental models, BCAA-enriched solution shortened the time course until the peak DNA synthesis in hepatocytes after partial hepatectomy [31]. Among BCAA, a high dose of valine-rich solution increased synthesis in hepatocytes, liver weight, and hepatic protein content in hepatectomized rats [32]. However, there has been so far no evidence for liver regeneration in clinical patients.

In short, BCAA seem to be effective to improve HE and hypoalbuminemia; and there could be some other affirmative effects for cirrhotic patients, such as its function as an energy substrate. These effects might lead to a better patient QOL and prognosis. However, studies should be carried out to find which patients actually respond to BCAA therapy, and long-term control trial is needed to prove these effects in a large-scale patient population.

2. Late evening snack

As mentioned above, cirrhotic patients are in a state of either energy malnutrition, protein malnutrition, or both. Patients with energy malnutrition, due to the shortage of energy intake, suffer from loss of body cell mass and fat tissue, although the level of serum protein such as albumin is maintained in normal range; and patients' prognosis is relatively not poor. In contrast, patients with protein malnutrition, which means the loss of serum protein and relatively well preserved body cell mass and fat tissue, shows poor prognosis [33]. Most cirrhotic patients show mixed malnutrition. Recently, it was shown that the consumption of a late evening snack (LES) was effective to improve cirrhotic patients' energy malnutrition.

Improvement of energy malnutrition. As a characteristic of energy malnutrition, patients with liver cirrhosis exhibit abnormal fuel metabolism, namely, increased fat and decreased glucose oxidation [5]. This abnormal fuel metabolism means energy exhaustion in the body, leading to the reduction of fat tissue and muscle mass. Therefore, an adequate amount of energy intake is necessary to maintain the energy homeostasis. For malnourished cirrhotic patients, even 1 month of a regular oral diet could improve abnormal fuel metabolism, and subsequently nutritional status was also improved, as evidenced by muscular midarm circumference, creatinine-height index, triceps skinfold thickness, and fat mass [34].

However, only the amount of energy intake in 3 meals a day may not be adequate to correct the malnutrition status in liver cirrhosis. It is well known that even a single night of fasting could lead to metabolic starvation in cirrhosis, which is similar to the condition observed in normal healthy subjects after 2–3 days of fasting. One main reason for this
starvation is the reduced glycogen storage both in the liver and muscle. Glucose intolerance, which is observed in up to 80% of cirrhotic patients, could also be a cause of the reduced glucose oxidation [35].

Advantages of frequent meals were previously reported in healthy subjects. Compared with a 3-meal diet, frequent meals (17 snacks a day) reduced fasting serum total cholesterol, low-density lipoprotein cholesterol, and apolipoprotein B [36]. Furthermore, the serum insulin level was also decreased. This result suggests that frequent meals have an effect to stabilize the metabolic status in healthy subjects. So is the case in cirrhosis. In a randomized crossover study, Swart et al. showed the improvement of nitrogen balance with 4 to 6 meals a day in cirrhotic patients as compared to 3 meals a day [37]. It was also reported, based on indirect calorimetry, that a ‘nibbling pattern’ (7 meals daily) increased carbohydrate oxidation in cirrhosis as compared to the ‘gorging pattern’ (2 meals daily) [38]. However, comparison of ‘gorging’ with ‘nibbling’ could be impractical, because most cirrhotic patients might take 3 meals a day rather than 2 meals. Even taking 3 meals could not prevent increased fat oxidation in cirrhosis, and the addition of an LES (50 g of carbohydrate) improved such catabolism [39]. However, caution should be employed in giving additional energy intake to cirrhotic individuals because it may induce obesity, and because excess intake of energy could also lead to steatosis, which is contributory to fibrosis in patients with chronic hepatitis C [40]. We previously reported improved fuel metabolism with 3 regular meals plus LES without a change in total energy or nitrogen intake [41]. Our results confirmed that the frequency of meals rather than the total amount of energy is important to improve abnormal fuel metabolism in cirrhosis and also that it could be beneficial for patients not to take excessive energy.

It has been shown that a reduced respiratory quotient (RQ) in cirrhosis affects patient prognosis; namely, patients with an RQ of more than 0.85 have a better prognosis than those with one below 0.85 [1]. Therefore the improvement of RQ with LES possibly leads to better prognosis in cirrhotic patients.

Improvement of protein malnutrition. LES may well be efficient to improve protein malnutrition in cirrhosis. Zillikens et al. showed that cirrhotic patients exhibited increased protein turnover rates (measured with 15N-glycine) [42]. After nocturnal oral administration of glucose, protein turnover rates were decreased with the improvement of nitrogen balance by 36%. This could mean that LES improves protein malnutrition as well as energy malnutrition. The reduction in muscle volume and serum protein might be prevented with LES by supplying cirrhotic patients with sufficient energy without catabolizing muscle and protein during the starvation period at night.

Which substrate should be administered for LES needs to be considered. As mentioned above, BCAA have a protein-sparing effect in cirrhosis. Moreover, it was reported that overnight BCAA infusion caused a sustained decline in the levels of most plasma amino acids and in net forearm release of phenylalanine, effects attributable to a sustained suppression of whole body and muscle proteolysis in healthy volunteers [43]. Whether or not nocturnal BCAA supplementation would further improve protein malnutrition in cirrhosis needs to be examined.

Although several studies showed the short-term effects of LES on protein and energy
metabolism in cirrhosis, long-term trial of LES is still under way. Frequency of meals, the ratio of each substrate in LES, and the ratio of each meal in terms of daily total calories should be considered in future studies.

*Nutritional pharmacotherapy for the future.* Improvement of PEM by BCAA has gradually become approved by clinicians. The reason for the skepticism about the clinical effects of BCAA could be the unknown mechanism behind the effects. The molecular target of BCAA is still not known, but some candidates (e.g. amino acid sensor protein [44]) have been already suggested. To find which components of BCAA actually have clinical effects and which tissue or cells could be the target will be the next step to classify BCAA as a therapeutical option in cirrhosis.

It is well described that LES shortens the starvation period, leading to possible preservation of muscle volume and fat tissue. However, the metabolic effect of LES with respect to the severity of liver disease has not yet been clarified. Moreover, LES might worsen glucose intolerance, especially in cirrhotic patients complicated with diabetes. The usefulness of LES should be evaluated by a long-term trial of LES in patients with cirrhosis.

REFERENCES


