Review Article

Branched chain amino acid-to-tyrosine ratio: not only an indicator of the amino acid imbalance

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Abstract: Chronic liver diseases induce various metabolic disorders. Amino acid imbalance is known to be associated with the symptoms of hepatic encephalopathy, especially in decompensated cirrhosis. The branched-chain amino acid (BCAA)-to-tyrosine ratio (BTR) was proposed as an easily measurable and inexpensive indicator of the amino acid imbalance. The BTR well correlates with Fischer's ratio and is commonly used in Japan to assess the amino acid imbalance. However, the BTR also reflects various pathophysiological disorders of chronic liver diseases. The BTR decreases in line with the progression of liver fibrosis, and a low BTR is considered as a risk factor for the presence of sarcopenia (decreased skeletal muscle volume), high-risk varices, hypoalbuminemia, and insulin resistance in patients with chronic liver diseases. A low BTR was proposed as a possible predictive marker for undesired cirrhosis-related events and a poor prognosis. Furthermore, the BTR was suggested to be associated with the treatment efficacy and prognosis of patients with hepatocellular carcinoma. It is suggested that long-term BCAA administration can suppress the risk of all fatal events, such as the development of liver cancer, bleeding of esophagogastric varices, and progression of liver failure (encephalopathy, icterus and ascites). Patients with an amino acid imbalance and a decreased BTR are expected to effectively obtain clinical benefits from BCAA treatment, so the BTR may be useful for determining the indication of BCAA treatment.

Keywords: Amino acid imbalance; branched-chain amino acid (BCAA); BCAA-to-tyrosine ratio (BTR)

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Introduction

Chronic liver diseases induce various metabolic disorders. Amino acid imbalance is known to be associated with the symptom of hepatic encephalopathy, especially in patients with advanced cirrhosis (1-4). However, chronic liver diseases gradually progress over several decades (5). In a previous study (6), we showed that amino acid imbalance progresses even before leading to cirrhosis and is also associated with the severity of esophagogastric varices in patients with hepatitis C virus (HCV) infection.

We herein report an overview of the amino acid imbalance in patients with chronic liver diseases. In addition, we discuss the branched chain amino acid (BCAA)-to-tyrosine ratio (BTR) (7), which not only reflects the degree of amino acid imbalance but also is associated with various clinical aspects in patients with chronic liver diseases.

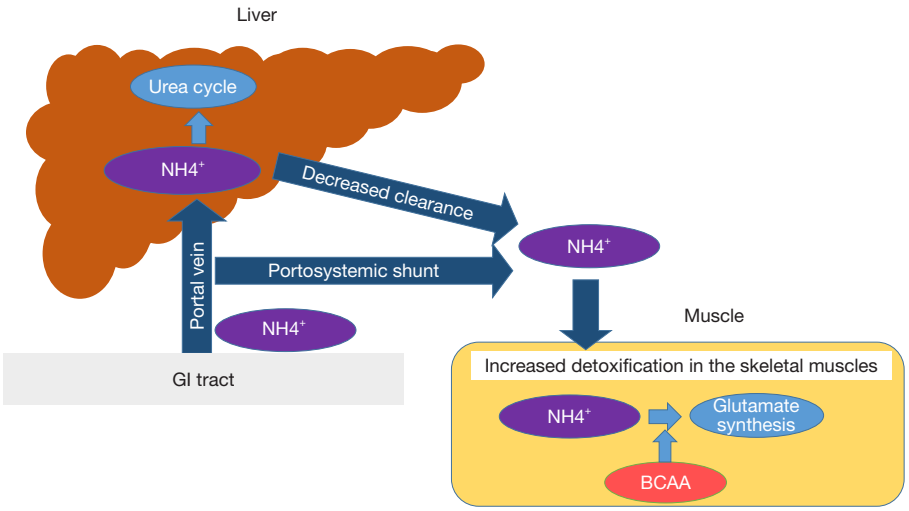

Figure 1 Schematic representation of the ammonia clearance in the liver and skeletal muscles. In patients with liver cirrhosis, because of the decreased metabolic functions in the liver and direct inflow of the ammonia into the circulation system, skeletal muscles play an important role for the clearance of ammonia. Thus, skeletal muscle loss (sarcopenia) is associated with a high risk of developing hyperammonemia and hepatic encephalopathy. Administration of BCAAs is suggested to show favorable effects on hepatic encephalopathy through multiple mechanisms, including the involvement of ammonia detoxification and the increase in skeletal muscle volume. BCAA, branched chain amino acid.

Amino acid imbalance and the BTR

Cirrhotic patients are known to show specific changes in the serum levels of amino acids, which are characterized by a decrease in BCAAs (valine, leucine and isoleucine) and increase in aromatic amino acids (AAAs). Thus, a low BCAA-to-AAA ratio (Fisher's ratio) is generally recognized to reflect amino acid imbalance (2,3). Hyperammonemia and hepatic encephalopathy are well-known events associated with amino acid imbalance, and the improvement of hyperammonemia with BCAA treatment has been reported in various studies (8-10). Currently, in the Japanese guidelines for the management of liver cirrhosis, the supplementation of BCAA is described as a standard treatment option for hepatic encephalopathy (11,12).

Fischer's ratio is known to be a well-established indicator for assessing the amino acid imbalance and hepatic encephalopathy. However, a total amino acid analysis is laborious and costly to perform, so the BTR was proposed (7). The BTR correlates well with Fischer's ratio and is commonly used in Japan to evaluate the amino acid imbalance (13-16). In a previous study (6), we investigated the relationship between the liver fibrosis stage and BTR in HCV-positive patients and showed that the BTR gradually decreased in line with the severity of liver fibrosis, even during non-cirrhotic stages (6). Therefore, the amino acid imbalance occurs at an early stage of chronic liver disease, before changes in the general indicators of the hepatic function, such as prothrombin time and bilirubin, are observed. Michitaka *et al.* (16) showed that the tyrosine level increased during non-cirrhotic stages, whereas a decrease in BCAA levels was mainly found in the cirrhotic stage. Thus, an increase in AAAs rather than a decrease in BCAAs was suggested to relate to the early symptom of amino acid imbalance. Although the BTR is not a pure fibrosis marker, it appears to be an indicator that widely reflects the pathophysiology progression of chronic liver diseases.

BTR in cirrhotic patients

BTR and skeletal muscles

In cirrhotic patients, ammonia clearance in the liver is decreased, and the skeletal muscle plays an important role in ammonia metabolism (17,18) (*Figure 1*). In skeletal muscle cells, BCAAs are consumed for the clearance of

ammonia, so supplementation of BCAAs may help control hyperammonemia.

As the skeletal muscle plays a significant role in ammonia detoxification in cirrhotic patients, reduced muscle mass can lead to hyperammonemia. However, liver cirrhosis is known to be associated with a high risk of a decreased muscle mass (sarcopenia) (19,20). In addition, it is assumed that hyperammonemia itself causes the muscle volume loss, thus further exacerbating the faulty ammonia clearance. BCAA supplementation is suggested to increase the muscle mass (21,22), and the administration of BCAAs is expected to cease such a vicious cycle by not only improving the amino acid imbalance but also increasing the muscle mass.

A low BTR is not only an indicator of amino acid imbalance, which is caused by the metabolism of BCAAs and AAAs, but also a significant predictive factor for a decreased skeletal muscle mass (23). Thus, BCAA administration is considered particularly beneficial for such patients.

BTR and albumin production

Cirrhotic patients frequently develop malnutrition, which may be related to a poor prognosis, and those with a low level of serum albumin (≤3.5 g/dL) are considered to have "protein malnutrition" (24,25). In addition to improving the amino acid imbalance, BCAA administration is known to increase the serum albumin level (26,27). BCAAs have been found to not only be useful as a material for albumin synthesis but also function as a physiologically active substance that promotes albumin synthesis in hepatocytes (28). BCAA administration was suggested to activate the signal pathway of the mammalian/mechanistic target of rapamycin (mTOR) and stimulate albumin synthesis (29). In addition, BCAA metabolites, including branched-chain α-keto acids (BCKA), β-hydroxy-β-methyl butyrate (HMB) and glutamate, also activate mTOR pathways and contribute to protein synthesis (30).

Long-term administration of BCAAs has been shown to improve serum albumin levels (26,27). In Japan, BCAA granules are commonly used to improve the hypoalbuminemia in cirrhotic patients. However, even among patients with compensated cirrhosis, there are some who develop the mild amino acid imbalance, and early administration of BCAAs to such patients has been shown to prevent the decrease in serum albumin values (31,32). A decreased BTR was reported to not only relate to the presence of hypoalbuminemia but also to be a useful predictive marker for the development of hypoalbuminemia (33).

BTR and insulin resistance

Dysregulation of glucose metabolism is frequently observed in patients with chronic HCV infection (34). In patients with chronic liver diseases, BCAAs are suggested to function in various organs and improve the insulin resistance (28). In the skeletal muscle, BCAA treatment accelerates the glucose uptake through the activation of two pathways: the phosphatidylinositol 3-kinase (PI3K)-protein kinase C (PKC) pathway and the peroxisome proliferator-activated receptor α (PPARα) pathway. In the adipose tissue, BCAA administration activates the Akt-mTOR signal pathway, and the glucose uptake increases. In the liver, BCAA treatment increases the glucose uptake through the activation of the liver X receptor α (LXRα)/sterol regulatory element binding protein-1c (SREBP1-c) pathway and the PPARα pathway (28). A randomized, controlled, crossover trial showed that BCAA treatment decreased the HbA1c values in HCV-infected patients with insulin resistance (35). Thus, amino acid imbalance, represented by a low BTR, is suggested to closely relate to insulin resistance.

BTR and invasive treatments

As mentioned above, oral administration of BCAAs has been used to treat protein malnutrition (36). In the endoscopic treatment of gastroesophageal varices, dietary restriction is generally included in the treatment protocol, but it may deteriorate the nutritional status. In patients with liver cirrhosis, oral intake of a late evening snack (LES) is recognized as an effective nutritional therapy (37,38). BCAA treatment has been suggested to provide some benefits to patients who receive invasive treatments (39).

We suspected that BCAA administration might exert some favorable effects on the maintenance of the nutritious status after endoscopic treatment and assessed the nutrition of cirrhotic patients who received endoscopic therapy for varices (40). BCAA alone was effective in preventing a decrease in the albumin value, whereas BCAA-containing nutritional supplement showed favorable effects on protein and energy malnutrition (40). These findings suggest that supplementing calories may help BCAAs exert their effects

on improving the nutritious status.

However, despite similar results having been reported elsewhere as well (41,42), we should pay attention to the fact that the BTR in patients with esophageal varices, particularly in those with high-risk varices, tends to be low (6). Therefore, the nutritious benefits provided by BCAA administration may be associated with the enrolled patients having a low BTR. It is therefore still necessary to determine whether or not the BTR is associated with the efficacy of BCAA treatment in patients receiving invasive treatments.

BTR and the treatment efficacy of BCAA administration

Long-term BCAA administration has been shown to suppress the risk of all fatal events, such as the development of liver cancer, bleeding of esophagogastric varices, and progression of liver failure (encephalopathy, icterus and ascites) (43). BCAA administration showed particularly favorable effects on patients with HCV-related cirrhosis compared with patients with other etiologies (43,44). It was also shown that the administration of BCAA reduced the incidence of liver cancer in patients with HCV-related cirrhosis and obesity, whose body mass index (BMI) was ≥25 kg/m^2 (44).

As mentioned above, BCAA was suggested to increase muscle mass and contribute to lower serum ammonia levels (21,22). The presence of sarcopenia, a decreased muscle mass, is known to lead to several adverse effects and worsen the prognosis of liver disease; however, BCAA treatment was suggested to exert favorable effects on cirrhotic patients with sarcopenia (45,46). Therefore, BCAA administration may improve the prognosis through various mechanisms in addition to the correction of hyperammonemia and hypoalbuminemia.

It should be noted that undue BCAA administration may exacerbate nitrogen overload and deteriorate hyperammonemia (18). In addition, a recent study suggested that excessive BCAA administration might increase the risk of cancer development (47), so unnecessary administration should be avoided. In the current guideline of the European Society for Clinical Nutrition and Metabolism (48), BCAA therapy is considered to improve the event-free survival and quality of life in advanced cirrhotic patients, but routine administration to cirrhotic patients is not recommended.

In a previous study (49), Ishikawa *et al.* assessed the associations of the BTR with cirrhosis-related events (death, worsening of esophageal and/or gastric varices, hepatocellular carcinoma, and liver failure). They also compared the event-free survival between patients with BTR ≥4 and BTR <4, and a low BTR was suggested to be a predictive marker of undesired cirrhosis-related events and a poor prognosis. The BTR was also suggested to be associated with the treatment efficacy and prognosis of patients with hepatocellular carcinoma (50,51).

Hiraoka *et al.* assessed the usefulness of the newly developed albumin-bilirubin (ALBI) score as a possible alternative method of determining the BTR in patients with treatment-naïve hepatocellular carcinoma (14). They showed that a high ALBI score (≥–2.588) was a predictor of a low BTR (≤4.4), suggesting that advanced cirrhotic patients with a modified ALBI of at least 2b (≥–2.27) might be regarded as having an amino acid imbalance.

Therefore, patients with an amino acid imbalance and a decreased BTR may effectively obtain clinical benefits from BCAA treatment (31,32,43). The BTR, which was originally developed as an inexpensive and easily measurable index of the amino acid imbalance, may be useful for determining the indication of BCAA treatment. However, in previous reports, cut-off values ranging from 4.0 to 5.0 were used to define "low BTR", so a further study to clarify the optimal cut-off value in order to determine the indication of BCAA administration will be needed. In addition, it would be interesting to investigate the associations of the BTR values with non-hepatic clinical characteristics, such as sex, age and ethnicity.

Conclusions

BCAA treatment is suggested to suppress cirrhosis-related adverse events and improve the prognosis in patients with advanced cirrhosis (52), although such benefits are not directly specified in the current guidelines.

The BTR was originally reported as an inexpensive and easily measurable indicator for amino acid imbalance. However, a low BTR is suggested to reflect various pathophysiological disorders of chronic liver diseases (*Table 1*). In addition, the BTR may also be an index for determining patients who are expected to benefit from BCAA therapy. Determining the optimal cut-off value of the BTR would allow appropriate and early supplementation of BCAA to cirrhotic patients.

Table 1 The BTR in various clinical features

Clinical features	Findings	Reference
Amino acid imbalance	BTR correlates with Fisher's ratio and can be an indicator of the amino acid imbalance	(6,7,13-16)
Liver fibrosis	BTR decreases in line with the progression of liver fibrosis	(6)
Esophagogastric varices	BTR decreases in line with the severity of varices. In particular, patients with high-risk varices show a low BTR	(6)
Sarcopenia	A low BTR is a risk factor for the presence of sarcopenia	(23)
Hypoalbuminemia	A low BTR is a risk factor for the presence of hypoalbuminemia	(28,31,32)
Insulin resistance	A low BTR is suggested to relate to insulin resistance in patients with chronic liver diseases, particularly in HCV-infected patients	(28,35)
Overall cirrhosis-related events	A low BTR was suggested to be a predictive marker for undesired cirrhosis-related events and a poor prognosis	(49)
Hepatocellular carcinoma	The BTR was suggested to be associated with the treatment efficacy and prognosis of patients with hepatocellular carcinoma	(50,51)

BTR, branched chain amino acid-to-tyrosine ratio; HCV, hepatitis C virus.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-29/coif). HE serves as an unpaid editorial board member of *Digestive Medicine Research* from November 2021 to October 2023. HS serves as an unpaid editorial board member of *Digestive Medicine Research* from August 2022 to July 2024. HI received research grants from Otsuka Pharmaceutical Co., Ltd. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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