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TOPIC HIGHLIGHT

Toru Ishikawa, MD, *Series Editor*

Branched-chain amino acids to tyrosine ratio value as a potential prognostic factor for hepatocellular carcinoma

Toru Ishikawa

Toru Ishikawa, Department of Gastroenterology and Hepatology, Saiseikai Niigata Daini Hospital, 280-7 Teraji, Niigata 950-1104, Japan
Author contributions: Ishikawa T contributed solely to this manuscript.
Correspondence to: Toru Ishikawa, MD, Department of Gastroenterology and Hepatology, Saiseikai Niigata Daini Hospital, 280-7 Teraji, Niigata 950-1104, Japan. toruishi@ngt.saiseikai.or.jp
Telephone: +81-25-2336161 Fax: +81-25-2338880
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Abstract

The prognosis of hepatocellular carcinoma (HCC) depends on tumor extension as well as hepatic function. Hepatic functional reserve is recognized as a factor affecting survival in the treatment of HCC; the Child-Pugh classification system is the most extensively used method for assessing hepatic functional reserve in patients with chronic liver disease, using serum albumin level to achieve accurate assessment of the status of protein metabolism. However, insufficient attention has been given to the status of amino acid (AA) metabolism in chronic liver disease and HCC. Fischer's ratio is the molar ratio of branched-chain AAs (BCAAs: leucine, valine, isoleucine) to aromatic AAs (phenylalanine, tyrosine) and is important for assessing liver metabolism, hepatic functional reserve and the severity of liver dysfunction. Although this ratio is difficult to determine in clinical situations, BCAAs/tyrosine molar concentration ratio (BTR) has been proposed as a simpler substitute. BTR correlates with various liver function examinations, including markers of hepatic fibrosis, hepatic blood flow and hepatocyte function, and can thus be considered as reflecting the degree of hepatic impairment. This manuscript examines the literature to clarify whether BTR can serve as a prognostic factor for treatment of HCC.

Key words: Branched-chain amino acids to tyrosine ratio; Fischer's ratio; Prognostic factor; Hepatocellular carcinoma

Peer reviewer: Gabriele Grassi, Associate Professor, Department of Medical, Technological and Translational Sciences, University Hospital of Cattinara, Strada di Fiume 447, 34100 Trieste, Italy

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TREATMENT OF HEPATOCELLULAR CARCINOMA REGARDING RECURRENCE

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide[1]. With advances in imaging diagnostics, together with the understanding of high-risk patients, HCC can now often be detected at an early stage[2]. Furthermore, HCC is associated with severe complications in patients with cirrhosis or chronic hepatitis with severe fibrosis.

In addition to surgical resection as a treatment for HCC, techniques that can be used alone or in combination include transcatheter arterial embolization, transcatheter arterial chemoembolization, percutaneous ethanol injection therapy, percutaneous microwave coagulation therapy, and percutaneous radiofrequency ablation. Thus, local control of HCC can now be achieved in consideration of the location of the tumors, the area occupied and hepatic functional reserve.

Recently, the prognosis of HCC has improved dra-

matically with the identification of high-risk populations and the advancement of diagnostic imaging and treatment. However, recurrence of HCC is frequent in the early post-treatment period even in patients who have undergone radical hepatectomy or radical local treatment including percutaneous treatment, because HCC arises from chronic liver disease. The recurrence rate after treatment of HCC is higher than that of cancer in other organs.

Therefore, despite initial remission of HCC after surgical and interventional treatments, limits are seen on the prolongation of survival. In other words, the therapeutic options available to deal with recurrence determine survival of patients, because risk of recurrence is high even if radical therapy is undertaken.

Treatment tactics may be selected depending on the tumor stage and severity of underlying liver disease.

The reasons for poor survival are that intrahepatic distant recurrence is common and, even more importantly, decompensation occurs due to a decrease in hepatic functional reserve that accompanies progression of chronic liver disease. Therefore, death due to liver failure represents a major problem. In other words, hepatic functional reserve is recognized as a factor affecting survival. However, sufficient research into the effects of the reserve liver function has not been carried out.

BRANCHED-CHAIN AMINO ACIDS TO TYROSINE RATIO AS STATUS OF AMINO ACID METABOLISM

When treating HCC, the Child-Pugh classification system is the most extensively used method worldwide for assessing the hepatic function in patients with chronic liver disease, and represents an important assessment factor. The Child-Pugh classification has been widely used to evaluate hepatic functional reserve in cirrhotic patients, and has a good correlation with prognosis[3], but cannot be used to predict survival in patients with HCC.

In the Child-Pugh classification, the serum albumin level is used to achieve accurate assessment of the status of protein metabolism. However, to date, no attention has been given to the status of amino acid (AA) metabolism in chronic liver disease and HCC.

Amino acid abnormalities are reportedly common even in patients who have liver cirrhosis but no hepatic encephalopathy and in patients with chronic hepatitis[4]. The amino acid molar ratio called Fischer's ratio [branched chain amino acids (BCAAs): leucine, valine, isoleucine/aromatic amino acids (AAAs): phenylalanine, tyrosine] is important for assessing liver metabolism, hepatic functional reserve and the severity of liver dysfunction[5]. Protein malnutrition is a result of amino acid imbalance. Accordingly, to accurately assess the status of protein metabolism in HCC patients with a background of chronic liver disease, determining not only the serum albumin level but also the status of amino acid metabolism is essential.

Proteins contained in biological cells are broken down into amino acids, while at the same time proteins are newly synthesized from free amino acids. Metabolic turnover is achieved when the breakdown and synthetic processes are in balance. The liver is the main organ involved in protein and amino acid metabolism. Hypoalbuminemia and fluctuations in plasma free-amino acid concentrations are usually seen in patients with chronic liver disease. Serum albumin is a protein that is synthesized and secreted by hepatocytes, and is used as an index of hepatic synthetic capacity for protein. This parameter is particularly important for evaluating the severity and prognosis of cirrhosis.

Fluctuations in plasma free-amino acid concentrations are particularly observed in cirrhosis. These changes include marked decreases in BCAAs and increases in AAAs, methionine, and other amino acids. The molar concentration ratio of BCAAs/AAAs (Fischer's ratio) and the BCAAs/tyrosine molar concentration ratio (BTR) decrease with increasing severity of hepatic damage. The Fischer's ratio has long been used for analysis of plasma free-amino acid concentrations, while BTR represents a simplified version of Fischer's ratio[6]. Azuma *et al*[6] proposed the BTR as a substitute for Fischer's ratio as an index of hepatic damage, and later reported that BTR reflected the progression of chronic liver disease.

Fluctuations in plasma free-amino acid concentrations are also seen in compensatory cirrhosis. For that reason, amino acid metabolic abnormalities in the liver become more severe as the state of chronic liver disease worsens.

On the other hand, assessing hepatic functional reserve from the perspective of amino acid metabolism can prove useful in different ways compared with investigations of the degree of hepatic fibrosis, hepatic blood flow and hepatocyte function. BTR correlates with each of the various liver function examinations, including fibrosis markers, which indicate the degree of hepatic fibrosis; indocyanine green retention rate 15 min (ICG R15), which primarily indicates hepatic blood flow; and asialo-scintigraphy, which reflects hepatocyte function. BTR also reportedly shows significant correlations with albumin value and cholinesterase (Ch-E) levels[7]. As a result, BTR can be thought to reflect the degree of hepatic impairment.

BTR offers a significant indicator of reserve liver function. However, to date, no reports have clarified the potential of BTR as a prognostic factor at the time of treating HCC.

RELATIONSHIP BETWEEN BTR AND TREATMENT OF HCC

The significance of amino acid analysis for assessing hepatic functional reserve has not been elucidated in patients with HCC.

In the case of poor nutritional status, BTR decreases in advance of decreases in serum albumin level. For

that reason, early identification of patients at risk of hypoalbuminemia is possible; specifically, determination of BTR enables prediction of changes in the serum albumin level[8], in turn allowing prediction of the need for administration of BCAAs. Moreover, because of the existence of that time-lag, monitoring of BTR separately from albumin is necessary when considering prognostic factors for HCC. A large-scale clinical study has demonstrated the usefulness of administering oral BCAA preparations to patients showing decreased BTR[9]. In other words, there is a strong possibility that determining BTR provides a prognostic factor for HCC.

In this paper, I have undertaken a review of the published literature with regard to whether BTR can serve as a prognostic factor for HCC.

A small number of experimental and clinical studies have examined BTR in terms of amino acid fluctuations following hepatectomy[10-12]. In experimental models, BTR is correlated with the extent of hepatectomy, with the post-operative interval time and with the liver weight when animals are sacrificed. In clinical studies, BTR has been determined on the immediate post-operative day and every day during the first post-operative week[10-12]. In addition, BTR reportedly decreased following hepatectomy, but then recovered on post-operative day 3 with administration of a BCAA-rich amino acid transfusion[13]. In that report, BTR on day 14 was lower than immediately before the hepatectomy, and the significance of improvements in BTR due to administration of a BCAA-rich amino acid transfusion for several days following the surgery was unclear.

In general, total bilirubin level is used as an indicator of hepatic functional reserve following hepatectomy, but in some cases hepatic functional reserve cannot be fully understood on the basis of total bilirubin level alone. For that reason, determination of arterial blood ketone bodies has been recommended[14]. However, no association exists between arterial blood ketone body values and the actual disease state, and thus this measurement cannot be claimed to offer a superior index compared with total bilirubin level. Moreover, substances such as serum albumin, fibrinogen and cholinesterase, which are synthesized in the liver, show high levels of specificity as indicators of hepatic functional reserve. However, levels are modified by aggressive replacement therapy, and thus are not useful in the clinic. A simple indicator that will permit objective assessment of recovery of liver function following hepatectomy is therefore needed. On the other hand, Fischer's ratio (BCAAs/AAAs), which decreases in various diseases such as cirrhosis that are characterized by a decrease in liver function, has been reported to be useful for understanding the status of liver function[15]. However, Fischer's ratio is difficult to determine, and is not commonly used as a test value following procedures such as hepatectomy. Furthermore, BTR has been developed as a simpler assay method and costs less, and is starting to be used clinically instead of Fischer's ratio in recent times[6,16].

With regard to assessing liver function from the perspective of amino acid metabolism, BTR (BCAAs/tyrosine) has been shown to be useful in different ways compared with such liver function investigations as determining the degree of hepatic fibrosis, hepatic blood flow or hepatocyte function. However, our preliminary experience suggests that BTR can be considered a survival factor in Stage Ⅰ / Ⅱ HCC (data not shown). Thus, overall survival in the high BTR group (4.5 or higher) was significantly longer than in the low BTR groups (4.4 or lower) regardless of serum albumin value, respectively. BTR may represent a contributing factor for hepatic functional reserve and survival at the time of HCC treatment. In the future, closer investigations of this issue in a large number of HCC cases will be needed.

In addition, prospective studies will be required to investigate various aspects, including whether maintenance of hepatic functional reserve by administration of BCAA preparations, as indicated by the BTR, is useful in improving the prognosis of HCC.

CONCLUSION

Nutritional management plays an important role in the treatment of HCC, particularly in patients with chronic liver disease. With the objective of improving protein metabolism in patients with cirrhosis, supplemental therapy using oral BCAA preparations is administered to patients with decreased BTR. We can hope that this approach will be found to improve the prognosis of HCC, and that BTR will be thought to be useful as an indicator of such improvement. In the future, it will be necessary to carry out a large-scale prospective study designed to elucidate these points.

REFERENCES

1 **Okuda K**. Hepatocellular carcinoma. *J Hepatol* 2000; **32**: 225-237
2 **Shiratori Y**, Yoshida H, Omata M. Management of hepatocellular carcinoma: advances in diagnosis, treatment and prevention. *Expert Rev Anticancer Ther* 2001; **1**: 277-290
3 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649
4 **Morgan MY**, Marshall AW, Milsom JP, Sherlock S. Plasma amino-acid patterns in liver disease. *Gut* 1982; **23**: 362-370
5 **Soeters PB**, Fischer JE. Insulin, glucagon, aminoacid imbalance, and hepatic encephalopathy. *Lancet* 1976; **2**: 880-882
6 **Azuma Y**, Maekawa M, Kuwabara Y, Nakajima T, Taniguchi K, Kanno T. Determination of branched-chain amino acids and tyrosine in serum of patients with various hepatic diseases, and its clinical usefulness. *Clin Chem* 1989; **35**: 1399-1403
7 **Dudrick SJ**, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. *Surgery* 1968; **64**: 134-142
8 **Suzuki K**, Suzuki K, Koizumi K, Ichimura H, Oka S, Takada H, Kuwayama H. Measurement of serum branched-chain amino acids to tyrosine ratio level is useful in a prediction of a change of serum albumin level in chronic liver disease. *Hepatol Res* 2008; **38**: 267-272

9 **Muto Y**, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, Kato M, Nakamura T, Higuchi K, Nishiguchi S, Kumada H. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. *Clin Gastroenterol Hepatol* 2005; **3**: 705-713
10 **Nagasue N**, Kanashima R, Inokuchi K. Alteration in plasma amino acid concentrations following subtotal hepatectomy in dogs. *Ann Chir Gynaecol* 1981; **70**: 50-55
11 **Nagasue N**, Yukaya H, Sasaki Y, Ogawa Y, Hirose S. Infusion of branched chain amino acids after partial hepatectomy in man. *Nutr Cancer* 1984; **6**: 32-39
12 **Joyeux H**, Matias J, Saint-Aubert B, Astre C, Gouttebel MC, Vedrenne JB, Deneux L. [Serum marker of the functional hepatic mass after extensive hepatectomy. The branched/aromatic amino acid ratio. Experimental and clinical studies]. *Chirurgie* 1994; **120**: 283-288
13 **Niguma T**, Yumura M, Yamasita Y, Maeda K, Kimura T, Yamamura M, Kodani J. Ratio of branched chain amino acid to tyrosine after hepatectomy. *Surg Today* 1999; **29**: 825-827
14 **Ozawa K**, Aoyama H, Yasuda K, Shimahara Y, Nakatani T, Tanaka J, Yamamoto M, Kamiyama Y, Tobe T. Metabolic abnormalities associated with postoperative organ failure. A redox theory. *Arch Surg* 1983; **118**: 1245-1251
15 **Fischer JE**, Rosen HM, Ebeid AM, James JH, Keane JM, Soeters PB. The effect of normalization of plasma amino acids on hepatic encephalopathy in man. *Surgery* 1976; **80**: 77-91
16 **Shimizu H**, Taniguchi K, Sugiyama M, Kanno T. Rapid enzymatic analysis of plasma for tyrosine. *Clin Chem* 1990; **36**: 32-35

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