World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps
wjg@wjgnet.com
doi:10.3748/wjg.v18.i33.4486

World J Gastroenterol 2012 September 7; 18(33): 4486-4490
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

Toru Ishikawa, MD, *Series Editor*

Early administration of branched-chain amino acid granules

Toru Ishikawa

Toru Ishikawa, Department of Gastroenterology and Hepatology, Saiseikai Niigata Daini Hospital, Niigata 950-1104, Japan
Author contributions: Ishikawa T contributed solely to this review.
Correspondence to: Toru Ishikawa, MD, PhD, 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
Received: March 11, 2012 Revised: May 21, 2012
Accepted: May 26, 2012
Published online: September 7, 2012

Abstract

The effect of malnutrition on survival in patients with decompensated liver cirrhosis has not been well defined. Nutritional intervention with branched-chain amino acid (BCAA) can increase serum albumin concentration in patients with decompensated cirrhosis but its effects on survival are unclear. The BCAA to tyrosine ratio (BTR) is a surrogate marker (the normal range of BTR is between 4.41 and 10.05, and a Fischer's ratio of 1.8 corresponds to a BTR of 3.5) in patients with decompensated liver cirrhosis, and BCAA inhibits hepatic carcinogenesis in patients with compensated cirrhosis. This review discusses data regarding the effect of early administration of BCAA granules based on the ratio of BCAA to BTR on prognosis in patients with cirrhosis.

Key words: Branched-chain amino acid to tyrosine ratio; Branched-chain amino acid granules; Liver cirrhosis; Nutritional intervention; Malnutrition; Quality of life; Albumin; Cancer onset

Peer reviewers: Dr. Richard Parker, Department of Gastroenterology, Sandwell and West Birmingham NHS Trust, Dudley Road, Birmingham B1 2AF, United Kingdom; Ilker Tasci, Department of Internal Medicine, Gulhane School of Medicine, GATA Ic Hastaliklari Bilim Dali, 06018 Etlik, Ankara, Turkey

Ishikawa T. Early administration of branched-chain amino acid granules. *World J Gastroenterol* 2012; 18(33): 4486-4490 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i33/4486.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i33.4486

INTRODUCTION

The liver plays a key role in nutrient metabolism, and patients with cirrhosis may develop various metabolism and nutrition disorders. In fact, many cirrhosis patients suffer from protein-energy malnutrition (PEM)[1], which is particularly pronounced in the decompensated stage. Correction of PEM can improve prognosis in patients with decompensated cirrhosis[2]. Patients with cirrhosis and decreased plasma branched-chain amino acid (BCAA) levels can develop PEM with increased catabolism[3].

PEM is associated with a high morbidity and mortality due to an increased risk of life-threatening complications, resulting in poor survival and poor quality of life (QoL)[4,5].

SIGNIFICANCE OF BCAA SUPPLEMENTATION

BCAAs are a group of essential amino acids, including valine, leucine, and isoleucine. A low plasma level ratio of BCAAs to aromatic amino acids suggests the presence of liver cirrhosis, and BCAA supplementation was originally developed in order to normalize the patient's amino acid profile and nutritional status[6].

This article summarizes the findings of previous studies to determine whether nutritional intervention with a granulated BCAA preparation can contribute to improved prognosis of patients with PEM and cirrhosis. In Japan, oral BCAA preparations are used in nutritional therapy to correct protein and amino acid abnormalities

in patients with cirrhosis. Moreover, enteral nutrition guidelines published by the European Society for Clinical Nutrition and Metabolism list BCAA supplementation as a grade B recommendation in the treatment of advanced cirrhosis[7].

BCAA supplementation effectively increases Fischer's ratio and improves hypoalbuminemia in patients with liver cirrhosis[8]. In addition, not only does BCAA serve as components of albumin, the activation by *L*-leucine of mammalian target of rapamycin in hepatocytes and the subsequent activation of albumin mRNA transcription and protein synthesis in ribosomes are thought to constitute the mechanism for albumin increase[9,10]. This increase in albumin has been verified in various clinical trials to be effective for improving hypoalbuminemia[8,11].

Oral BCAA preparations come in two dosage forms: enteral nutrition formulas (or elemental diet products) for liver failure and oral BCAA granules. In 1996, an oral BCAA granule product containing valine, leucine, and isoleucine (Val, Leu, Ile) in a composition ratio of 1:2:1.2 was marketed in Japan (Livact®, Ajinomoto Pharmaceuticals, Tokyo, Japan). This product is indicated for decompensated cirrhosis patients who have hypoalbuminemia despite adequate dietary intake.

IMPROVEMENT OF PROGNOSIS AND INHIBITION OF HEPATOCAR-CINOGENESIS

An Italian research group reported a multicenter randomized trial in which a total of 174 patients with advanced liver cirrhosis were given BCAA as a supplement for 1 year and its effects were compared with administration of lactalbumin or maltodextrin[12]. Long-term use of a BCAA granule preparation has been reported to increase serum albumin and to inhibit the incidence of events related to poor prognosis[8,12].

Moreover, Marchesini *et al*[12] analyzed whether oral BCAA might prevent progressive liver failure and improve nutritional parameters and quality of life.

They conclude that long-term nutritional supplementation with oral BCAA is useful to prevent progressive hepatic failure and to improve health status ,and recommend that new formulas are needed to increase compliance. An oral BCAA granule (Livact®, Ajinomoto Pharmaceuticals, Tokyo, Japan) is the form of small uniform granules, which reduces BCAA-induced stimulation of taste buds and contributes to improve compliance.

Kobayashi *et al*[13] conducted a study of patients with compensated cirrhosis caused by hepatitis C. After a mean follow-up of 3.2 years, the authors reported that the incidence of hepatocellular carcinoma (HCC) among men with a baseline serum albumin level of 3.6 to 4.0 g/dL tended to be lower in the BCAA granule treatment group than in the control group. A large-scale postmarketing clinical study conducted at 89 sites in Japan to determine the effects of BCAA granules on the prognosis of cirrhosis patients [Long-term Survival Study (LOTUS)] demonstrated that the onset of complications associated with poor prognosis (i.e., liver failure, ruptured esophageal varices, HCC, and death) was significantly lower among patients in the BCAA granule treatment group than in the dietary therapy group (hazard ratio: 0.67; 95% CI: 0.49-0.93)[8]. Furthermore, stratified analysis of the LOTUS study for groups at high risk for HCC, specifically, patients with a body mass index $\geqslant$ 25 kg/m^2 or elevated alpha-fetoprotein, showed that BCAA granules had an inhibitory effect on the incidence of HCC[14]. Meanwhile, a study by Tsuchiya *et al*[15] on radical therapy for HCC patients reported that long-term treatment with BCAA granules reduced the rate of the third and subsequent relapses of HCC and improved the cumulative rate of survival in patients with baseline serum albumin $\leqslant$ 3.5 g/dL. Sato *et al*[16] undertook a comparative study of dietary control protocols and found that a BCAA granule product and an enteral nutrient for liver failure (or an elemental diet product) had similar effects in terms of improving or maintaining serum albumin and preventing the onset of hepatic encephalopathy. The authors reported that, despite control of the total dietary energy intake, an increase in glycosylated hemoglobin and other markers of abnormal glucose tolerance occurred in the enteral nutrient group, whereas these unfavorable changes were not observed in the BCAA granule treatment group[16].

Moreover, Hayaishi *et al*[17] reported that Oral BCAA supplementation is associated with reduced incidence of HCC in patients with cirrhosis.

Based on these findings, a BCAA granule preparation (Livact®) has been now recommended in the guidelines for the treatment of liver cirrhosis by the Study Group for the Standardization of Treatment of Viral Hepatitis Including from the Ministry of Health, Labour and Welfare in Japan in order to increase serum albumin in cirrhosis patients with the aim of reducing the onset of cancer[18] (Table 1).

IMPORTANCE OF CONTINUED ADMINISTRATION

On the other hand, because some patients do not exhibit any increase in serum albumin after taking BCAA granules, further research has been conducted on the dietary intake and baseline characteristics of these patients. Yatsuhashi *et al*[19] reported that the anti-hypoalbuminemic effect of BCAA granules was not influenced by dietary intake and that continued use of BCAA significantly reduced the incidence of ascites and edema even in patients whose serum albumin did not respond to BCAA granule treatment.

One possible explanation for the significant decline in ascites and edema in the unchanged serum albumin group could be that the BCAA granules improved albumin quality. The sulfhydryl group of the cysteine 34 residue in human serum albumin can exist in a reduced state (reduced albumin) or oxidized state (oxidized albumin). In patients with chronic liver disease, however, the pro-

Table 1 Studies of outcome by branched-chain amino acid administration for cirrhotic patients

Authors	No. of cases	Study time	Outcome
Muto *et al*[8]	646	2 yr	Improving event-free survival, serum albumin concentration, and QoL
Kobayashi *et al*[13]	40	168 wk	Inhibiting hepatic carcinogenesis
Muto *et al*[14]	646	2 yr	Reducing the risk for liver cancer
Fukushima *et al*[21]	7	8 wk	Improving the oxidized/reduced state of serum albumin

QoL: Quality of life .

portion of oxidized albumin increases as the condition progresses[20]; this is associated with body fluid retention, such as ascites and edema. Furthermore, BCAA granules reduce the ratio of oxidized albumin in decompensated cirrhosis patients[21]. These findings suggest that the use of BCAA granules is important in maintaining serum albumin and that its continued use can improve the prognosis of patients with decompensated cirrhosis[22-25].

BCAA TO TYROSINE RATIO VALUE, AN IMPORTANT INDICATOR IN EARLY ADMINISTRATION OF BCAA GRANULES

However, the therapeutic effects of BCAA granules can take longer to appear in patients with advanced decompensated cirrhosis, making it important to determine the optimal timing for administration. After examining the biochemical test results of decompensated cirrhosis patients, Kato *et al*[26] identified the following four characteristics of uncompensated cirrhosis, and thus, the proper time to begin administration of BCAA granule preparations: (1) serum albumin $\leqslant$ 3.5 g/dL; (2) BCAA to tyrosine ratio (BTR) $\leqslant$ 3.5; (3) prothrombin activity $\leqslant$ 60%; and (4) platelet count of $\leqslant$ 100 000/mm^3. This in turn led to the search for markers of cirrhosis in order help facilitate determination of the optimal timing to initiate treatment with BCAA granules.

Cirrhosis patients exhibit shifts in their plasma free amino acid concentration, marked declines in BCAA (Val, Leu, Ile), and increases in aromatic amino acids (AAA; tyrosine, phenylalanine) and methionine, whereas their Fischer's ratio (ratio of molar concentrations of BCAA: AAA) or BTR declines in conjunction with disease severity. Fischer's ratio has long been used to analyze plasma free amino acids[27], but the BTR is a simpler method. Azuma *et al*[28] reported that the BTR based on an enzymatic method serves as an alternative to Fischer's ratio and is a potential indicator of liver disorders as well as subsequent chronic liver disease progression.

In the event of malnutrition, the BTR also declines before the serum albumin declines; therefore, determining the BTR is useful for the early detection of potential hypoalbuminemia. In other words, calculating the BTR enables the prediction of serum albumin level changes[29] and therefore allows determination of the appropriate time to administer BCAA granules. Given this time lag between decreases in serum albumin and BTR, monitoring of BTR needs to be done separately from that of albumin when considering prognostic factors for decompensated cirrhosis. The benefits of administering an oral BCAA preparation in patients with decreased BTR have already been reported in a large-scale clinical study[8]. This also implies that the BTR has considerable potential as a prognostic factor of HCC in decompensated cirrhosis patients. In fact, many reports performed the usefulness of BCAA for the treatment of hepatocellular carcinoma[30-39]. So, BTR may be useful as an indicator of prognosis in patients with HCC[40]. Early administration of BCAA granules based on the ratio of BCAA to tyrosine can improve the prognosis of decompensated cirrhosis.

In conclusion, BCAA supplementation for liver disorders may be expected not only to increase serum albumin, but also to exert other effects, such as prolongation of survival among liver cirrhosis patients, prevention of liver cancer, and enhancement of QoL. However, in cases of severe decompensated liver cirrhosis, determination of the timing of administration is also an important issue because BCAA granules take time to take effect. The decrease in BTR precedes reductions in serum albumin. While early therapeutic intervention with BCAA granules can help improve the prognosis of patients with decompensated cirrhosis and low BTR, more research and analysis are needed to fully explore the novel effects of BCAA granule preparations.

REFERENCES

1 **Tajika M**, Kato M, Mohri H, Miwa Y, Kato T, Ohnishi H, Moriwaki H. Prognostic value of energy metabolism in patients with viral liver cirrhosis. *Nutrition* 2002; **18**: 229-234
2 **Cabré E**, Gassull MA. Nutritional support in liver disease. *Eur J Gastroenterol Hepatol* 1995; **7**: 528-532
3 **Lautz HU**, Selberg O, Körber J, Bürger M, Müller MJ. Protein-calorie malnutrition in liver cirrhosis. *Clin Investig* 1992; **70**: 478-486
4 Nutritional status in cirrhosis. Italian Multicentre Cooperative Project on Nutrition in Liver Cirrhosis. *J Hepatol* 1994; **21**: 317-325
5 **Moriwaki H**, Miwa Y, Tajika M, Kato M, Fukushima H, Shiraki M. Branched-chain amino acids as a protein- and energy-source in liver cirrhosis. *Biochem Biophys Res Commun* 2004; **313**: 405-409
6 **Kawaguchi T**, Izumi N, Charlton MR, Sata M. Branched-chain amino acids as pharmacological nutrients in chronic liver disease. *Hepatology* 2011; **54**: 1063-1070
7 **Plauth M**, Cabré E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, Ferenci P, Holm E, Vom Dahl S, Müller MJ, Nolte W. ESPEN Guidelines on Enteral Nutrition: Liver disease. *Clin Nutr* 2006; **25**: 285-294
8 **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

9 **Matsumura T**, Morinaga Y, Fujitani S, Takehana K, Nishitani S, Sonaka I. Oral administration of branched-chain amino acids activates the mTOR signal in cirrhotic rat liver. *Hepatol Res* 2005; **33**: 27-32

10 **Nishitani S**, Ijichi C, Takehana K, Fujitani S, Sonaka I. Pharmacological activities of branched-chain amino acids: specificity of tissue and signal transduction. *Biochem Biophys Res Commun* 2004; **313**: 387-389

11 **Habu D**, Nishiguchi S, Nakatani S, Kawamura E, Lee C, Enomoto M, Tamori A, Takeda T, Tanaka T, Shiomi S. Effect of oral supplementation with branched-chain amino acid granules on serum albumin level in the early stage of cirrhosis: a randomized pilot trial. *Hepatol Res* 2003; **25**: 312-318

12 **Marchesini G**, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, Rossi Fanelli F, Abbiati R. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. *Gastroenterology* 2003; **124**: 1792-1801

13 **Kobayashi M**, Ikeda K, Arase Y, Suzuki Y, Suzuki F, Akuta N, Hosaka T, Murashima N, Saitoh S, Someya T, Tsubota A, Kumada H. Inhibitory effect of branched-chain amino acid granules on progression of compensated liver cirrhosis due to hepatitis C virus. *J Gastroenterol* 2008; **43**: 63-70

14 **Muto Y**, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, Kato M, Nakamura T, Higuchi K, Nishiguchi S, Kumada H, Ohashi Y. Overweight and obesity increase the risk for liver cancer in patients with liver cirrhosis and long-term oral supplementation with branched-chain amino acid granules inhibits liver carcinogenesis in heavier patients with liver cirrhosis. *Hepatol Res* 2006; **35**: 204-214

15 **Tsuchiya K**, Asahina Y, Izumi N. [Long time oral supplementation with branched-chain amino acids improves survival and decreases recurrences in patients with hepatocellular carcinoma]. *Nihon Shokakibyo Gakkai Zasshi* 2008; **105**: 808-816

16 **Sato S**, Watanabe A, Muto Y, Suzuki K, Kato A, Moriwaki H, Kato M, Nakamura T. Clinical comparison of branched-chain amino acid (l-Leucine, l-Isoleucine, l-Valine) granules and oral nutrition for hepatic insufficiency in patients with decompensated liver cirrhosis (LIV-EN study). *Hepatol Res* 2005; **31**: 232-240

17 **Hayaishi S**, Chung H, Kudo M, Ishikawa E, Takita M, Ueda T, Kitai S, Inoue T, Yada N, Hagiwara S, Minami Y, Ueshima K. Oral branched-chain amino acid granules reduce the incidence of hepatocellular carcinoma and improve event-free survival in patients with liver cirrhosis. *Dig Dis* 2011; **29**: 326-332

18 **Kumada H**, Okanoue T, Onji M, Moriwaki H, Izumi N, Tanaka E, Chayama K, Sakisaka S, Takehara T, Oketani M, Suzuki F, Toyota J, Nomura H, Yoshioka K, Seike M, Yotsuyanagi H, Ueno Y. Guidelines for the treatment of chronic hepatitis and cirrhosis due to hepatitis C virus infection for the fiscal year 2008 in Japan. *Hepatol Res* 2010; **40**: 8-13

19 **Yatsuhashi H,** Ohnishi Y, Nakayama S, Iwase H, Nakamura T, Imawari M. Anti-hypoalbuminemic effect of branched-chain amino acid granules in patients with liver cirrhosis is independent of dietary energy and protein intake. *Hepatol Res* 2011; **41**: 1027-1035

20 **Watanabe A**, Matsuzaki S, Moriwaki H, Suzuki K, Nishiguchi S. Problems in serum albumin measurement and clinical significance of albumin microheterogeneity in cirrhotics. *Nutrition* 2004; **20**: 351-357

21 **Fukushima H**, Miwa Y, Shiraki M, Gomi I, Toda K, Kuriyama S, Nakamura H, Wakahara T, Era S, Moriwaki H. Oral branched-chain amino acid supplementation improves the oxidized/reduced albumin ratio in patients with liver cirrhosis. *Hepatol Res* 2007; **37**: 765-770

22 **Yoshida T**, Muto Y, Moriwaki H, Yamato M. Effect of long-term oral supplementation with branched-chain amino acid granules on the prognosis of liver cirrhosis. *Gastroenterol Jpn* 1989; **24**: 692-698

23 **Mascarenhas R**, Mobarhan S. New support for branched-chain amino acid supplementation in advanced hepatic failure. *Nutr Rev* 2004; **62**: 33-38

24 **Charlton M**. Branched-chain amino acid enriched supplements as therapy for liver disease. *J Nutr* 2006; **136**: 295S-298S

25 **Holecek M**. Three targets of branched-chain amino acid supplementation in the treatment of liver disease. *Nutrition* 2010; **26**: 482-490

26 **Kato A**, Suzuki K. How to select BCAA preparations. *Hepatol Res* 2004; **30S**: 30-35

27 **Soeters PB**, Fischer JE. Insulin, glucagon, aminoacid imbalance, and hepatic encephalopathy. *Lancet* 1976; **2**: 880-882

28 **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

29 **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

30 **Morihara D**, Iwata K, Hanano T, Kunimoto H, Kuno S, Fukunaga A, Yotsumoto K, Takata K, Tanaka T, Sakurai K, Iwashita H, Ueda S, Hirano G, Yokoyama K, Nakane H, Nishizawa S, Yoshikane M, Anan A, Takeyama Y, Kakumitsu S, Kitamura Y, Sakamoto M, Irie M, Shakado S, Sohda T, Watanabe H, Sakisaka S. Late-evening snack with branched-chain amino acids improves liver function after radiofrequency ablation for hepatocellular carcinoma. *Hepatol Res* 2012; **42**: 658-667

31 **Nishikawa H**, Osaki Y, Inuzuka T, Takeda H, Nakajima J, Matsuda F, Henmi S, Sakamoto A, Ishikawa T, Saito S, Kita R, Kimura T. Branched-chain amino acid treatment before transcatheter arterial chemoembolization for hepatocellular carcinoma. *World J Gastroenterol* 2012; **18**: 1379-1384

32 **Ishikawa Y**, Yoshida H, Mamada Y, Taniai N, Matsumoto S, Bando K, Mizuguchi Y, Kakinuma D, Kanda T, Tajiri T. Prospective randomized controlled study of short-term perioperative oral nutrition with branched chain amino acids in patients undergoing liver surgery. *Hepatogastroenterology* 2010; **57**: 583-590

33 **Takeshita S**, Ichikawa T, Nakao K, Miyaaki H, Shibata H, Matsuzaki T, Muraoka T, Honda T, Otani M, Akiyama M, Miuma S, Ozawa E, Fujimito M, Eguchi K. A snack enriched with oral branched-chain amino acids prevents a fall in albumin in patients with liver cirrhosis undergoing chemoembolization for hepatocellular carcinoma. *Nutr Res* 2009; **29**: 89-93

34 **Poon RT**, Yu WC, Fan ST, Wong J. Long-term oral branched chain amino acids in patients undergoing chemoembolization for hepatocellular carcinoma: a randomized trial. *Aliment Pharmacol Ther* 2004; **19**: 779-788

35 **Lee IJ**, Seong J, Bae JI, You SH, Rhee Y, Lee JH. Effect of Oral Supplementation with Branched-chain Amino Acid (BCAA) during Radiotherapy in Patients with Hepatocellular Carcinoma: A Double-Blind Randomized Study. *Cancer Res Treat* 2011; **43**: 24-31

36 **Kuroda H**, Ushio A, Miyamoto Y, Sawara K, Oikawa K, Kasai K, Endo R, Takikawa Y, Kato A, Suzuki K. Effects of branched-chain amino acid-enriched nutrient for patients with hepatocellular carcinoma following radiofrequency ablation: a one-year prospective trial. *J Gastroenterol Hepatol* 2010; **25**: 1550-1555

37 **Harima Y**, Yamasaki T, Hamabe S, Saeki I, Okita K, Terai S, Sakaida I. Effect of a late evening snack using branched-chain amino acid-enriched nutrients in patients undergoing

hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma. *Hepatol Res* 2010; **40**: 574-584

38 **Inoue H**, Ito T, Siraki K, Sugimoto K, Sakai T, Oomori S, Takase K, Nakano T. Effect of segmental transcatheter arterial chemoembolization on branched chain amino acids and tyrosine ratio in patients with hepatocellular carcinoma. *Int J Oncol* 2000; **17**: 977-980

39 **Ishikawa T**, Michitaka I, Kamimura H, Higuchi K, Kubota T, Seki K, Ohta H, Yoshida T, Kamimura T. Oral branched-chain amino acids administration improves impaired liver dysfunction after radiofrequency ablation therapy for hepatocellular carcinoma. *Hepatogastroenterology* 2009; **56**: 1491-1495

40 **Ishikawa T**. Branched-chain amino acids to tyrosine ratio value as a potential prognostic factor for hepatocellular carcinoma. *World J Gastroenterol* 2012; **18**: 2005-2008

S- Editor Gou SX **L- Editor** A **E- Editor** Li JY