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Late evening snacks with branched-chain amino acids improve the Fischer ratio with patients liver cirrhosis at fasting in the next morning

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SUMMARY

Background & aims: A late evening snack (LES) is recommended as a nutritional therapy for liver cirrhosis to minimize early starvation. In patients with liver cirrhosis, the maintenance of the branched-chain amino acid (BCAA) levels is important during muscle synthesis at night. Therefore, we investigated the effects of a LES with BCAAs on the Fischer ratio in patients with liver cirrhosis.

Methods: This study included 10 outpatients with liver cirrhosis who did not consume a LES. Regarding the patient characteristics, the mean age was 73.1 ± 8.9 years, the male:female ratio was 5:5, and the mean body mass index was 23.3 ± 2.4 kg/m^2. The etiology was hepatitis C virus in eight patients and alcoholism in two patients. Amino acid levels were measured in all 10 patients at four time points: before LES (control) and 1 month after the administration of each BCAA. The administration levels included 1) LES: BCAA-enriched enteral nutrition (BCAA-EN) containing BCAAs 6.1 g as a LES; 2) GP-no LES: BCAA-enriched granule product (BCAA-GP) containing 4 g BCAAs per pack, two packs per day, and BCAA-EN until dinner containing BCAAs in total 14.1 g per day; and 3) GP-LES: BCAA-GP, two packs per day, and BCAA-EN as a LES containing BCAAs in total 14.1 g per day. The Friedman nonparametric test with a post-hoc Dunn's multiple comparison was used for statistical analyses.

Results: There were no significant changes in body weight and serum albumin levels between the three types of BCAA administration. Valine significantly increased following LES and GP-LES, isoleucine significantly increased following GP-LES, and tyrosine significantly decreased following LES and GP-LES compared with those in the control. There was no significant difference in the leucine and phenylalanine levels among the groups. The Fischer ratio in the LES (2.2 ± 0.8) and GP-LES (2.3 ± 0.8) groups were significantly higher than that in the control (1.8 ± 0.6), but there was no significant difference compared with the Fischer ratio in the GP-no LES (1.8 ± 0.7) group. Furthermore, the Fischer ratio was significantly higher in the GP-LES group than in the GP-no LES group.

Conclusion: These results suggested that it is not only the amount of BCAAs, but also LES with BCAAs, which is needed to improve the Fischer ratio at fasting.

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1. Introduction

The liver plays a central role in the energy metabolism of all nutrients, including macronutrients. Hepatic function and nutritional metabolism are integrated; therefore, metabolic disorders

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Abbreviations

NAFLD	nonalcoholic fatty liver disease
PEM	protein-energy malnutrition
BCAA	branched-chain amino acid
PS	performance status
LES	late evening snack
QOL	quality of life
npRQ	non-protein respiratory quotient
HCV	hepatitis C virus
BMI	body mass index
GP	granule product
Alb	albumin
TP	total protein
BUN	blood urea nitrogen
CRE	creatinine
T-CHO	total cholesterol
TG	triglyceride
T-bil	total bilirubin
D-bil	direct bilirubin
Glu	glucose
γ-GTP	gamma-glutamyl transpeptidase
ChE	cholinesterase
Na	sodium
K	potassium
Cl	chlorine
AST	aspartate aminotransferase
ALT	alanine aminotransferase
HBA1c	Hemoglobin A1c
WBC	white blood cell count
RBC	red blood cell count
Hct	hematocrit
NH3	ammonia
CRP	C-reactive protein
EN	enteral nutrition
TotalAA	total amino acid
NEAA	non-essential amino acid
EAA	essential amino acid
mTORC1	mammalian target of rapamycin complex 1
BTR	branched-chain amino acid to tyrosine ratio
ESPEN	European Society for Clinical Nutrition and Metabolism

are based on the degree of hepatocyte dysfunction. Conventional nutritional management of liver cirrhosis mainly comprises nutritional therapy aimed at improving malnutrition resulting from insufficient intake of each nutrient due to liver dysfunction. Recently, due to the increase in metabolic syndromes and nonalcoholic fatty liver disease, it has become evident that impaired glucose tolerance [1] and abnormal lipid and iron metabolism [2] are involved in the progression of chronic liver disease. The role of a nutritional therapeutic approach for such metabolic abnormalities is important. The nutritional status of liver cirrhosis is protein-energy malnutrition (PEM) [3]. In patients with liver cirrhosis, energy production decreases due to reduced glycogen storage in the liver. Patients with liver cirrhosis reportedly have an increased resting energy expenditure compared with that in healthy individuals, resulting in malnutrition due to energy deficiency [3]. Branched-chain amino acids (BCAAs) and glycogen are supplied as energy sources from skeletal muscles to compensate for this malnutrition due to energy deficiency [4,5]. The ability to metabolize ammonia decreases in patients with liver cirrhosis due to the disruption of the urea cycle, while the amount of ammonia metabolized by the glutamine synthesis system in skeletal muscles increases [5]. In addition, BCAAs are used for energy production and ammonia metabolism in skeletal muscles in patients with liver cirrhosis; therefore, it is thought that the BCAA levels used for protein synthesis in the liver declines, causing malnutrition and sarcopenia [6]. The medical validity of nutritional treatment has been recently demonstrated with the long-term oral administration of BCAAs resulting in improved hypoalbuminemia and complications such as ascites, jaundice, rupture of esophageal varix, and liver carcinogenesis, as well as increased survival rates and quality of life (QOL) [7,8]. Particularly, the effect of a late evening snack (LES) containing BCAAs has attracted attention for patients with liver cirrhosis, owing to the resulting decrease in skeletal muscle mass in these patients. In patients with a non-protein respiratory quotient (npRQ) < 0.85, a snack containing 200 kcal is required before going to bed to minimize early starvation [9]. LES is recommended according to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [7] and in Japan [10]. However, BCAA supplementation is only for cirrhosis patients with hepatic encephalopathy. Therefore, the daily dose of BCAAs, timing of administration of BCAAs, and dose of BCAAs in LES in patients with liver cirrhosis without hepatic encephalopathy are unclear. Therefore, we investigated the effects of LES with BCAAs in patients with liver cirrhosis.

2. Materials and methods

2.1. Patients

This study included 10 outpatients (5 male, 5 female) with liver cirrhosis at the Department of Gastroenterology of Kofu Municipal Hospital between March 2016 and March 2017. The mean age and body mass index (BMI) were 73.1 ± 8.9 years and 23.3 ± 2.4 kg/m^2, respectively. The etiology was hepatitis C virus (HCV) in eight patients and alcoholism in two patients. Patients who underwent chemotherapy or radiotherapy 3 months prior to the start of the study were excluded. Upon implementation of this study, written informed consent was obtained from each patient. The study design was approved by the Ethical Committee of Kofu Municipal Hospital (No.27-14).

2.2. Blood biochemical examination

Blood samples were collected early in the morning of fasting days, during which all food and beverages (except tea and water) were forbidden, at the visiting outpatient department of gastroenterology. Laboratory tests included serum albumin concentration (Alb), total protein (TP), blood urea nitrogen (BUN), creatinine (CRE), total cholesterol (T-CHO), triglyceride (TG), total bilirubin (T-bil), direct bilirubin (D-bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GTP), cholinesterase (ChE), sodium (Na), potassium (K), chlorine (Cl), Glucose Glu), ammonia (NH_3), C-reactive protein (CRP), Hemoglobin A1c (HBA1c), white blood cell count (WBC), red blood cell count (RBC), and hematocrit (Hct) and amino acid analysis (SRL, Inc.) (Table 1, Fig. 2).

Table 1
Laboratory data.

n = 10		Con		LES		BCAA-noLES		BCAA-LES	
BMI	(kg/m²)	28.2	(28.0–29.5)	27.8	(27.1–29.1)	27.7	(27.1–28.8)	27.9	(27.4–28.7)
Body Weight	(kg)	57.7	(52.4–65.6)	56.8	(53.4–62.9)	56.6	(53.1–62.3)	56.9	(53.1–62.4)
Albumin	(g/dl)	3.7	(3.5–4.0)	3.6	(3.5–4.0)	3.6	(3.6–4.0)	3.6	(3.4–3.8)
Total Protein	(g/dl)	7.6	(7.1–7.8)	7.6	(7.4–7.8)	7.6	(7.4–7.8)	7.5	(7.2–7.7)
BUN	(mg/dl)	18	(14–23)	19	(15–22)	18	(14–22)	19	(16–21)
Creatinine	(mg/dl)	0.89	(0.64–1.11)	0.89	(0.70–1.06)	0.89	(0.68–1.06)	0.89	(0.68–1.12)
T-cho	(mg/dl)	165	(137–213)	161	(126–193)	157	(124–186)	157	(123–183)
TG	(mg/dl)	78	(50–76)	69	(54–69)	80	(57–82)	81	(54–82)
Total-bil	(mg/dl)	1.2	(0.9–1.4)	1	(0.7–1.2)	1	(0.7–1.1)	0.9	(0.7–1.3)
Direct-bil	(mg/dl)	0.3	(0.2–0.5)	0.3	(0.2–0.4)	0.3	(0.1–0.4)	0.3	(0.1–0.3)
AST	(IU/l)	41	(28–47)	44	(31–43)	40	(31–47)	41	(28–59)
ALT	(IU/l)	27	(18–36)	30	(18–34)	28	(15–31)	26	(18–35)
γ-GTP	(IU/l)	43	(20–39)	40	(22–34)	36	(20–32)	73	(22–38)
Che	(IU/l)	201	(123–240)	199	(128–244)	200	(131–251)	198	(120–244)
Na	(mEq/l)	141	(140–142)	140	(138–141)	140	(140-140)	140	(138–142)
K	(mEq/l)	4.2	(3.9–4.4)	4	(4.2–4.5)	4.4	(4.2–4.5)	4.5	(4.2–4.6)*
Cl	(mEq/l)	108	(106–110)	108	(107–109)	108	(106–109)	108	(107–111)
Glucose	(mg/dl)	110	(104–113)	113	(99–123)	113	(100–123)	123	(98–128)
NH3	(μg/dl)	59	(32–91)	57	(29–114)	62	(26–92)	67	(33–71)
CRP	(mg/dl)	0.1	(0.0–0.1)	0.1	(0.0–0.1)	0.1	(0.0–0.1)	0.1	(0.0–0.1)
HbA1c (NGSP)	(%)	5.8	(5.4–6.0)	5.8	(5.3–6.1)	5.8	(5.3–6.0)	5.8	(5.4–6.1)
WBC	(/μl)	4650	(3975–5450)	4760	(3850–5400)	4750	(3925–5550)	4650	(3575–5550)
RBC	(10^4/μl)	421	(380–460)	430	(391–465)	426	(408–446)	426	(400–466)
Hct	(%)	36.9	(33.7–40.0)	37.6	(33.4–40.7)	37.2	(34.2–39.2)	37.3	(34.3–40.9)

Con, control; LES, late evening snack; GP-no LES, branched-chain amino acid without late evening snack; GP-LES, branched-chain amino acid with late evening snack; BMI, body mass index; Alb, albumin concentration; TP, total protein; BUN, Blood urea nitrogen; CRE, creatinine; T-CHO, total cholesterol; TG, Triglyceride; T-bil, total bilirubin; D-bil, direct bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma-glutamyl transpeptidase; ChE, cholinesterase; Na, sodium; K, potassium; Cl, chlorine; NH_3, ammonia; CRP, C-reactive protein; HbA1c (NGSP), Hemoglobin A1c (National Glycohemoglobin Standardization Program); WBC, white blood cell count; RBC, red blood cell count; Hct, hematocrit.
Values are means with interquartile range.
*$p < 0.05$ compared with control value.
* significant difference from control.

2.3. Content of branched-chain amino acid products

BCAA enriched enteral nutrition contains13.5 g protein including 6.1 g BCAA (6.5 g as peptides, 6.5 g as amino acids and 0.5 g casein), 31.05 g of carbohydrate, 3.5 g of fat, and trace amounts of minerals and vitamins which produce 210 kcal. Fisher ratio of this product is approximately 38 (Aminoleban® EN; Otsuka Pharmaceuticals Co., Ltd., Tokyo, Japan).

BCAA enriched granule product contains 4 g of BCAA; 952 mg of L-isoleucine, 1904 mg of L-leucine, and 1144 mg of L-valine which produce 12 kcal (LIVACT Granules®; AY Pharmaceuticals Co., Ltd., Tokyo, Japan) (Table 2).

2.4. Branched-chain amino acid administration

Prior to BCAA administration, baseline measures were made for all 10 patients as the control group. The first level of BCAA administration was LES, which included BCAA-enriched enteral nutrition (BCAA-EN) containing 210 kcal, 13.5 g protein, and 6.1 g BCAA (LES group). The amount of BCAA was then increased to 14.1 g per day by administering two BCAA-enriched granule product (BCAA-GP) packs (one in the morning and one at lunch) containing 4 g BCAA per pack, in addition to the BCAA-EN provided during the day to be consumed before 17:00 (GP-no LES group). Finally, the BCAA-GP was administered in the morning and at lunch (two packs per day), as well as one pack of BCAA-EN as a LES for a total BCAA of 14.1 g (GP-LES group) (Fig. 1). After continuing each protocol for 1 month, amino acid analysis was conducted.

2.5. Dietary record and counseling

A 1-day dietary record that included nutritional products was provided by the patients or their family on the day before amino acid analysis, and a registered dietician calculated the food intake using the Standard Tables of Food Composition in Japan, 2015 (7th Revised Version). In this study, nutritional counseling was conducted once a month by a registered dietician at the time of LES introduction.

2.6. Statistical analysis

Data were expressed as mean with interquartile range. Regarding the results of physical examination, blood biochemical examinations, and amino acid analyses, Dunn's test of multiple comparisons, which is a nonparametric post-hoc test, was used to compare 39 amino acids, Total amino acid (TotalAA), non-essential amino acid (NEAA), essential amino acid (EAA), BCAA, EAA/NEAA, BCAA/TotalAA, and the Fischer ratio. Statistical analysis was performed using Graph Pad Prism 7. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Physical and blood biochemical examination findings

There was no change in the body weight and BMI during the follow-up observation period, and there were no significant changes in the liver and renal functions and TP and albumin levels. However, the mean potassium level significantly increased in the GP-LES group than in the control group.

3.2. Amino acid analysis

The mean valine and isoleucine levels were significantly higher in the GP-LES group than in the control and GP-no LES groups, whereas the mean tyrosine level was significantly lower in the LES

Group	Control	LES	GP-noLES	GP-LES
Period	1 month	1 month	1 month	1 month
Total BCAA(g)	0	6.1	14.1	14.1
Intraday digestion	-	-	BCAA-GP 2Pack BCAA enriched EN 1 Pack	BCAA-GP 2Pack
LES	-	BCAA-enriched EN 1Pack	-	BCAA-enriched EN 1Pack

LES, late evening snack; BCAA-GP, branched-chain amino acid-enriched granule product; BCAA-EN, branched-chain amino acid-enriched enteral nutrition

Fig. 1. Sampling design of the different branched amino acid (BCAA) products administered. Control, without BCAA products; LES, BCAA-enriched enteral nutrition (BCAA-EN) as the LES containing 6.1 g BCAA; GP-no LES, two BCAA-enriched granule product (BCAA-GP) packs a day and BCAA-EN until dinner for a total of 14.1 g BCAA; GP-LES, two BCAA-GP packs a day and BCAA-EN as LES for a total of 14.1 g BCAA.

and GP-LES groups. The mean lysine level was significantly lower in the LES group than in the control groups. Furthermore, the mean ornithine level was significantly higher in the GP-LES group than in the GP-no LES group. There was no significant change in the leucine or phenylalanine levels among all four groups. The Fischer ratio was significantly higher in the LES (2.2 ± 0.8) and GP-LES (2.3 ± 0.8) groups than in the control group (1.8 ± 0.6). Furthermore, the Fischer ratio was significantly lower in the GP-no LES group (1.8 ± 0.7) than in the LES and GP-LES groups. The BCAA level was significantly higher in the GP-LES group than in the control and GP-noLES groups. The BCAA/TotalAA levels were significantly higher in the LES and GP-LES groups than in the control group. No other significant changes were observed in this study.

4. Discussion

The present study showed that the tyrosine level significantly decreased following GP-LES administration, which contained 14.1 g BCAA [of which the LES contributed to 6.1 g of BCAA (210 kcal)], at fasting in the next morning. No significant differences in other aromatic amino acid levels were observed following GP-LES administration. It has been previously reported that the tyrosine level decreased and the BCAA to tyrosine ratio (BTR) increased when BCAAs were administered as a LES to patients with liver cirrhosis [11]. The tyrosine and phenylalanine levels decreased after an intravenous injection of BCAAs in rat models [12]. Zhang et al. reported that the methionine and aromatic amino acid (tyrosine, phenylalanine, and tryptophan) levels decreased due to administration of BCAAs in young men [13]. In the present study, the valine and isoleucine levels were significantly higher in the GP-LES group than in the control group following fasting. However, GP-LES administration did not result in increased leucine levels compared with that in the control. The decrease in tyrosine, combined with the increase in valine and isoleucine, may have improved the Fischer ratio in this group. Blood amino acid levels are important for protein assimilation [14]. Among them, leucine is essential for muscle synthesis, which is associated with appetite and insulin secretion [15]. Previous studies have reported that leucine is especially necessary for muscle synthesis at night [16–18]. The lack of increased leucine levels at fasting in the next morning in the present study may be due to the utilization of leucine for muscle synthesis at night. Leucine is very important for anabolism, and valine and isoleucine in BCAA supplements have been shown to interact with each other; therefore the composition of BCAAs for patients with liver cirrhosis is important. One study has reported the proportions of leucine, isoleucine, and valine, whereby a ratio of 2:1:1.2 was adequate for the patients with chronic liver disease [19], but the optimal proportion is unknown. Tsien et al. reported that 15 g/day BCAA administration (7.5 g L-leucine, 3.75 g L-isoleucine, and 3.75 g L-valine) improved the mammalian target of rapamycin complex 1 (mTORC1) signaling and autophagy in the skeletal muscle of alcoholic cirrhotic patients [20]. However, the optimal dose of BCAA in LES, the optimal dosage of BCAA per day, and the upper limit of BCAA administration are still unclear. In patients with liver cirrhosis, glycogen storage decreases during fasting, whereas catabolism is accelerated in the muscle and adipose tissue. Therefore, the use of a substrate for patients with cirrhosis must correspond to the 3-day fasting state of a healthy individual [21]. In patients with liver cirrhosis, the nitrogen balance reportedly improves when the number of meals is increased from three ordinary times to four up to six times [8]. The split administration of BCAAs, including the nighttime administration of an LES, may also be effective. Furthermore, the importance of avoiding fasting conditions over a long period of time is suggested. LES is used to improve energy metabolism abnormalities in patients with liver cirrhosis; moreover, LES is recommended by ESPEN [7] and in Japan [10]. It is thought that a LES containing approximately 200 kcal is appropriate for Japanese patients [9,22]. The patients in our study received nutritional guidance by a dietitian once a month when the nutritional therapy was changed because if the body weight increases due to LES administration, there is a risk of obesity and insulin resistance, as shown by the relationship between obesity and carcinogenesis [23] and higher mortality rates compared with those in individuals with a normal BMI [24]. In our study, weight gain due to LES administration was not observed throughout the study period. In the present study, the administration of EN containing BCAA as LES improved the Fischer ratio at fasting in the next morning. Improvements in the Fischer ratio is expected to have a therapeutic effect by reducing tryptophan uptake in the brain, with reports showing a decreased risk of hepatic encephalopathy [25,26] and improved symptoms [27]. It is thereby considered beneficial in terms of prevention of hepatic encephalopathy and maintaining a positive nitrogen balance; hence, we have chosen the Fischer ratio as the primary outcome of this study. The present study showed that not only a daily dose of BCAAs but also the administration of BCAAs as LES is necessary to achieve this result. LES administration for 1 day [28] or 1 week [9] reportedly improves the respiratory quotient. Moreover, Okamoto et el. reported improvements in the BTR and glucose pattern after administering a BCAA-enriched LES for a week [29]. Harima et al. observed improvements in the BTR and pre-Alb and ALT levels after BCAA-enriched LES administration for five weeks [30].

Improving and maintaining daily metabolism may lead to improvements in nutritional status. Therefore, long-term use of LESs is recommended to improve serum albumin and metabolic disorders.

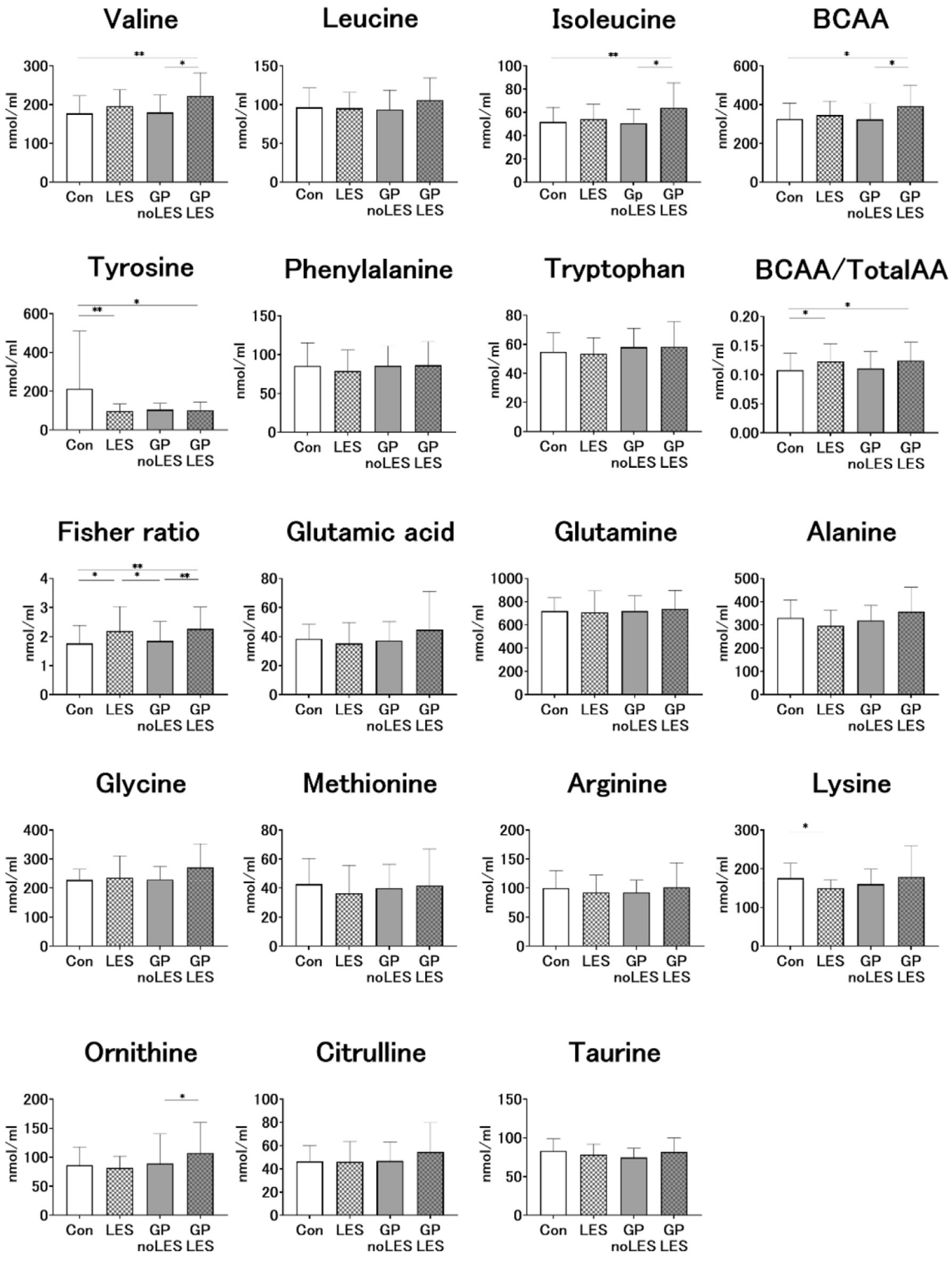

Fig. 2. Comparison of amino acid levels between the different branched amino acid (BCAA) products administered. The Friedman nonparametric test with a post-hoc Dunn's multiple comparison was used for statistical analysis. Graphs for valine, leucine, isoleucine, tyrosine, phenylalanine, tryptophan, glutamic acid, glutamine, alanine, glycine, methionine, arginine, lysine, ornithine, citrulline, taurine, BCAA, BCAA/Total amino acid, branched-chain amino acid/Total amino acid, and Fischer ratio are shown. $^{*}p < 0.05$ and $^{**}p < 0.01$ compared with the control value.

Table 2
Description of the content of BCAA products.

BCAA enriched enteral nutrition		BCAA enriched granule product	
Energy	210 kcal	Energy	16 kcal
Protein	13.5 g	Protein	4 g
BCAA	6.1 g	BCAA	4 g

Abbreviations: BCAA, branched-chain amino acid.

As a long-term effect of BCAA administration, severe liver cirrhosis complications were significantly suppressed compared with those in the group treated with diet only [8], and liver carcinogenesis was significantly suppressed in patients with a BMI > 25 kg/m^2 compared with that of the diet treatment group [31]. Regardless of dietary energy and protein, the albumin enhancement effect by BCAA products is recognized [32]. In particular, improved nitrogen balance and glucose tolerability and suppression of protein degradation at night were reported following LES administration [22,33–35]. In addition, the promotion of appetite and assimilation of food [36], as well as the improvement of insulin resistance and inhibition of sarcopenia progression [5], have been reported. Hence, there has been increasing attention to the role of BCAAs as pharmacological nutrients that have various biological effects. However, we could not evaluate sarcopenia in this study; we will do it in the future.

This study has a few limitations. First, clinically it did not randomize and has no washout period. Second, the number of the patients are small. Body composition and muscle mass were not evaluated in this study. The potassium level significantly increased in the GP-LES group compared with the control group. We assumed that this potassium difference can hardly influence BCAA and that this difference should be considered by increasing the number of cases. In the present study, LES did not improve nutritional indices such as albumin, body weight, and BMI in patients with liver cirrhosis. Such improvements may be possible by continuing long-term EN with BCAA as the LES; however, each protocol was only continued for 1 month in this research design, which may explain the lack of improvement in the nutritional indicators. The strength of this study is that most of the patients had liver cirrhosis from hepatitis C and the nutritional effects of alcohol consumption should not be considered. In our study, the administration of LES with BCAA improves the Fischer ratio, which is considered as an attribute of BCAA as LES administration a day prior rather than an effect of administration period. The reason for that was the Fisher ratio increased when the first LES group was administered for 1 month; however, the GP-noLES group which contains the daily amount of BCAA to 14.1 g, it declined after the same period. Furthermore, the Fisher ratio significantly increased again when GP-LES group which contains the daily amount of BCAA of 14.1 g with LES including 6.1 g of BCAA after its administration for 1 month. We regularly provide nutritional guidance once a month from the introduction of LES, daily total calories to be constant. Thus, only the amount and timing of BCAA are changed in each protocol without daily calories intake in this study. Therefore, it is considered that the result is an effect of BCAA as LES. Research an optimum composition of LES is still lacking. The effect of a LES on the long-term nutritional indices and optimal composition of LES and dose of BCAA based on the severity of disease and patient body weight should be investigated in the future.

Author contributions

Hiroki Maki analyzed the data and wrote the manuscript. Hisami Yamanaka-Okumura designed the research protocol and contributed to the organization. Fumitake Amemiya provided useful advice and conducted all blood sampling tests. Takafumi Katayama provided useful statistical advice. Naomi Kurata and Akihito Hosoda also provided useful advice. Yuka Ozawa provided nutritional guidance for the patients with liver cirrhosis. All authors have participated in the work, take public responsibility for the content of the paper, and have read and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.01.003.

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