

# Two randomized controlled studies comparing the nutritional benefits of branched-chain amino acid (BCAA) granules and a BCAA-enriched nutrient mixture for patients with esophageal varices after endoscopic treatment

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## Abstract

**Background** The usefulness of branched-chain amino acid (BCAA) granules and BCAA-enriched nutrient mixtures for patients with liver cirrhosis is often reported. However, no randomized controlled studies have investigated the usefulness of these supplements in the nutritional intervention of cirrhotic patients receiving endoscopic treatment for esophageal varices.

**Methods** Patients without BCAA before endoscopic treatment were divided into study 1, and those who received BCAA were divided into study 2. In study 1, 44 eligible patients were divided into a control group ( $n = 13$ ), a general liquid nutrient (snack) group ( $n = 15$ ), and a BCAA-enriched nutrient mixture (BCAA-EN) group ( $n = 16$ ). In study 2, 48 eligible patients were divided into a BCAA group ( $n = 24$ ) and a BCAA-EN group ( $n = 24$ ). The nutritional status including non-protein respiratory quotient (NPRQ) levels, weight gain, and albumin were evaluated on days 0, 7, and 50.

**Results** In study 1, the BCAA-EN group showed significant improvement in NPRQ levels on day 7 as compared with the snack group. In study 2, the BCAA-EN group showed significant improvement in NPRQ levels on day 7 and in weight levels on day 50 relative to the BCAA group,

while the BCAA group showed improved serum albumin levels on day 7 compared to the BCAA-EN group.

**Conclusions** The BCAA-enriched nutrient mixture maintained NPRQ and weight in cirrhotic patients. Our findings suggest that supplements including both BCAA and a nutritional energy supplement would be beneficial for cirrhotic patients undergoing endoscopic treatment for esophageal varices.

**Keywords** Liver cirrhosis · Esophageal varices · Nutritional therapy · Endoscopic treatment

## Introduction

Esophageal and gastric varices are common adverse events associated with portal hypertension in cirrhotic patients [1]. Indeed, at the time of diagnosis, 60 % of patients already have esophageal varices of different grades. These varices gradually become larger and eventually start bleeding. Because the acute bleeding is a life-threatening medical emergency, it constitutes a turning point in the severity of the portal hypertension. Additionally, most cirrhotic patients suffer from severe protein energy malnutrition (PEM) [2–4], which has been identified as a predictor of liver cirrhosis adverse events [5].

The nutritional status of cirrhotic patients is even more problematic during treatments for esophageal and gastric varices. In Japan, endoscopic injection sclerotherapy and esophageal variceal ligation are established not only for hemostasis during hematemesis from the esophageal varices, but also as prophylactic treatments [6–8]. However, because dietary intake during these treatments is restricted, there is a high possibility of worsening cirrhotic PEM during the fasting period following treatment [9–11].

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Nagata et al. [11] reported that a significant decrease in body weight occurred during the treatment of esophageal varices, and that the decreased body weight failed to recover after three months. It is thought that malnutrition is prolonged over a long period of time after treatment. Hence, nutritional therapeutic intervention is necessary to maintain and improve nutritional status and hepatic spare ability during treatment of esophageal varices.

For patients with liver cirrhosis, BCAA is reported to offer various benefits: improved hypoalbuminemia [12–15], suppressive effects on the occurrence of adverse events from cirrhosis of the liver [10], suppressive effects on liver cancer [16, 17], and remedial effects on insulin resistance [18, 19]. Additionally, the usefulness of late-evening snacks (LES) is becoming clear [20–22]. However, studies that have found nutritional intervention to be useful after the treatment of esophageal varices are few. Further, there are no previous reports on either prospective controlled studies that included a control group that did not receive nutritional intervention, or on controlled studies that targeted cases where BCAA was introduced. We performed here two different studies to examine the optimal nutritional replenishment therapy for maintaining and improving the nutritional status of patients receiving treatment for esophageal varices.

## Methods

This study was conducted by placing patients who were not receiving BCAA during the treatment of esophageal varices into study 1, and patients who had already received a BCAA preparation for at least a month during treatment into study 2 (Fig. 1a), since nutritional therapy with BCAA could have represented a biasing factor. Endoscopic treatment of the esophageal varices was implemented once per week until the varices vanished.

Study 1 consisted of patients receiving treatment for esophageal varices who had not received a BCAA preparation. Patients in this group were randomly assigned to one of the following groups within the school's liver disease center by the numbered container method: a control group that received no nutritional intervention (normal post-treatment diet only), a snack group that was administered a general liquid nutrient containing only calories (210 kcal of RACOL<sup>®</sup>, Otsuka Pharmaceutical Co., Ltd. Tokyo, Japan, one after eating breakfast and one before sleeping), and a BCAA-EN group that was administered a BCAA-enriched nutrient mixture composed of both BCAA and calories (210 kcal of Aminoleban EN<sup>®</sup>; BCAA: 6 g, Otsuka Pharmaceutical Co., Ltd. Tokyo, Japan, one after eating breakfast and one before sleeping) after endoscopic

treatment. A short-term comparative examination of the nutritional improvement in each group was performed (Fig. 1b).

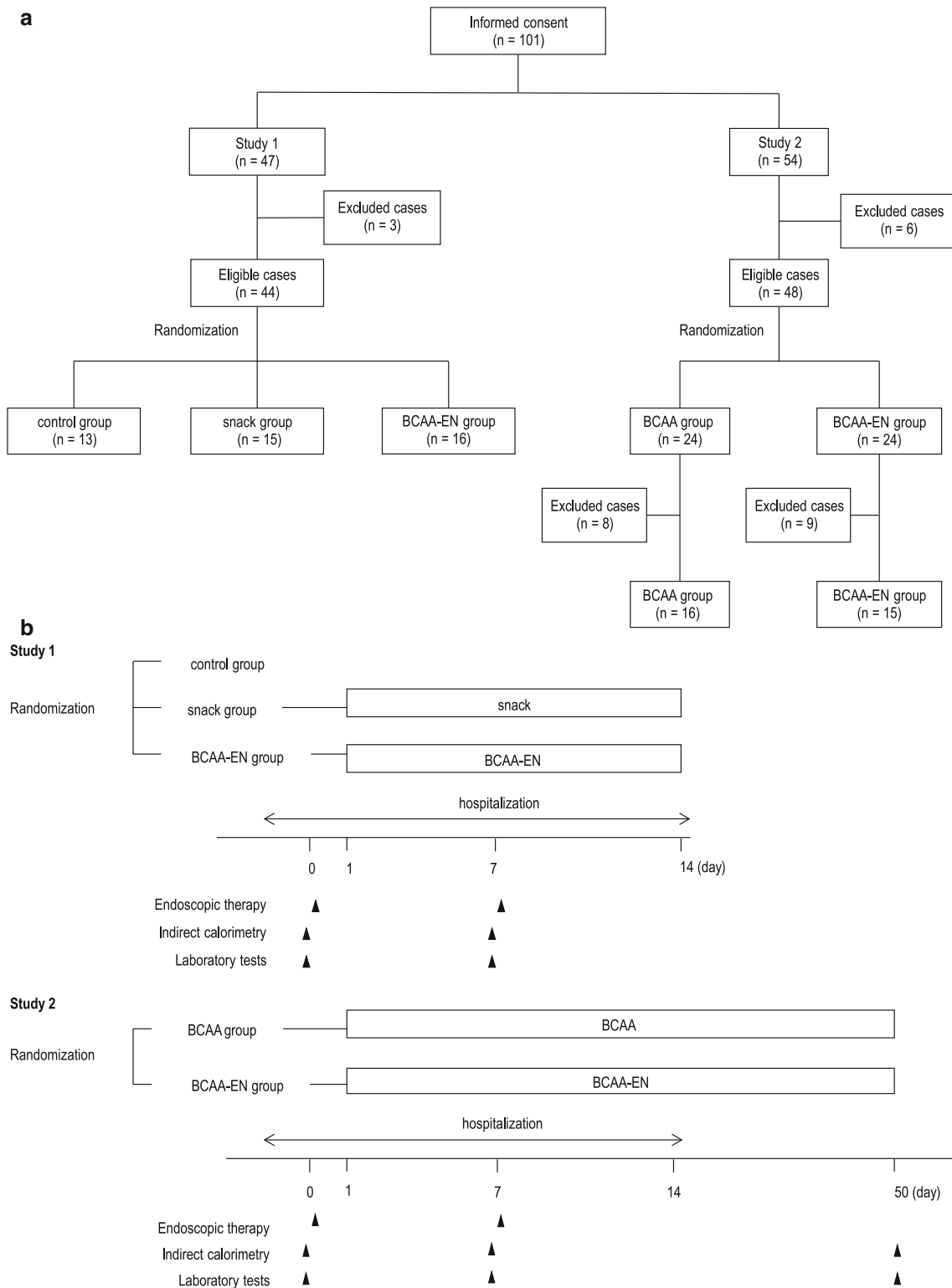
Study 2 consisted of patients receiving treatment for esophageal varices who had already received a BCAA preparation. Discontinuing administration of BCAA to these patients would cause an ethical issue. For this reason, these patients were randomly assigned to one of two groups within the school's liver disease center: a BCAA group that took BCAA-granules containing only BCAA orally (16 kcal of Livact<sup>®</sup>; BCAA: 4 g, Ajinomoto Pharmaceutical Co. Ltd., Tokyo, Japan, one after eating breakfast and two before sleeping), and a BCAA-EN group that was administered a BCAA-enriched nutrient mixture containing both BCAA and calories (210 kcal of Aminoleban EN<sup>®</sup>; BCAA: 6 g; Otsuka Pharmaceutical Co., Ltd. Tokyo, Japan, one after eating breakfast and one before sleeping) after endoscopic treatment. These patients continued this diet after being discharged from the hospital. Short-term and long-term comparative examinations of the nutritional improvement in both groups were performed (Fig. 1b).

From the reports of Nakaya et al. [23] and Katsumi et al. [9], the number of cases can be set based on a significance level of 5 % on one side and a statistical power of 80 %. Referring to the data mentioned above, the estimated number of cases was set at 25 for each group, with a total of 75 cases in study 1 and 50 cases in study 2.

The main assessment for both studies was set as the improvement in the non-protein respiratory quotient (NPRQ), as determined using an indirect calorimeter, and the serological albumin (ALB) levels. The secondary items were the following body measurement levels: body weight (BW), body mass index (BMI), triceps skinfold thickness (% TSF), and arm-muscle circumference (% AMC). Resting energy expenditure/basal metabolic rate (REE/BMR) was set as an indicator of energy metabolism. Pre-albumin (preALB), retinol-binding protein (RBP), and the branched-chain amino acid and tyrosine ratio (BTR) were set as indicators of protein metabolism. Fasting blood sugar (FBS), immunoreactive insulin (IRI), homeostasis model assessment insulin resistance (HOMA-R), and glycoalbumin (G-ALB) were set as glucose metabolism indicators.

Values were measured using an indirect calorimeter, body measurements, and blood tests. Measurements were taken on the day treatment began (day 0) and seven days after the treatment began (day 7). For study 2 only, the assessment was also performed 50 days after treatment began (day 50) in order to assess the degree of long-term improvement.

As this study was a prospective randomized study, it was registered with UMIN once it began (UMIN000001534, <https://upload.umin.ac.jp/>). Additionally, this research has



**Fig. 1 a** Flow of patients. **b** Study design

been performed in accordance with the ethical guidelines laid down in the 1964 Declaration of Helsinki and its later amendments, and received approval after review from the

Hyogo College of Medicine ethics committee (No. 650). Written consent was obtained from all participating patients.

## Inclusion/exclusion criteria

Both studies targeted patients who were indicated for prophylactic treatment prescribed in the guidelines for the endoscopic treatment of esophageal/gastric varices as published by the Japan Gastroenterological Endoscopy Society. Patients were excluded from this study if they were being administered an albumin preparation at least once per week in a 1-month period, exhibited significant glucose metabolism disorders, experienced conditions associated with renal failure, had congenital amino acid metabolism disorders, or were judged unfit for this study by their attending physicians.

## Meals

All of the patients in both studies were served specialized meals during treatment for their esophageal varices at the Hyogo College of Medicine. The specialized meals were administered according to the schedule shown in Supplementary Table S1. In addition to this diet, nutrients were added the day following treatment (Fig. 1b). The amount of daily ingested energy was adjusted to about 30–35 kcal/kg/day with 1–1.3 g/kg/day of protein (Supplementary Table S1).

## Statistical analysis

The statistical significance of differences between the two groups was evaluated using Student's *t* test or Mann–Whitney *U* test. The data for the comparisons among the three groups were analyzed by ANOVA with a subsequent Bonferroni correction or Kruskal–Wallis *H* test, and a subsequent Mann–Whitney *U* test with Bonferroni correction. Categorical data were analyzed by the Chi-square or Fisher's exact test as appropriate. Statistical significance was defined as  $p < 0.05$  (two-sided). All statistical analyses were performed using JMP version 8.0.2 software (SAS institute, Cary, NC, USA).

## Results

The studies were stopped once a statistical significance was obtained in the principal assessment item (NPRQ) within each group. For this reason, study 1 ended with 47 cases, and study 2 ended with 54 cases.

### Study one

Among the 47 individuals, three were excluded according to our exclusion criteria. Of the remaining 44 participants, 13 were assigned to the control group, 15 to the snack

group, and 16 to the BCAA-EN group. There were no drop-out cases. The patient flow chart is shown in Fig. 1. No statistical significance was seen within the demographic data of the three groups (Table 1).

### Short-term changes in body measurement values

The changes in the ratios of body measurement values at day 7 were compared among the three groups, using the day 0 levels as reference values. As shown in Fig. 2a and b, the BW and BMI levels in the control group were significantly lower than those in the BCAA-EN group ( $-3.0$  vs.  $-1.3$  %;  $p = 0.043$ ,  $-3.0$  vs.  $-1.3$  %;  $p = 0.042$ , respectively). No statistical significance was seen in the % AMC levels. Because a significant difference in the % TSF levels was observed between the control and BCAA-EN groups at day 0, no comparisons were consequently performed.

### Short-term changes in energy metabolism indicators

The changes in the ratio of the energy metabolism indicators at day 7 were compared among the three groups, using the day 0 levels as reference values. As shown in Fig. 2c and d, an improvement in the NPRQ level was seen in the BAA-EN group compared to the control and snack groups ( $-1.5$  vs.  $+6.4$  %,  $p = 0.002$ ;  $-1.9$  vs.  $+6.4$  %,  $p < 0.001$ , respectively). No statistical differences were observed in the REE/BRM levels among the three groups.

### Short-term changes in protein metabolism indicators

The changes in the ratio of the protein metabolism indicators at day 7 were compared among the three groups, using the day 0 levels as reference values. As shown in Fig. 2e and f, the BTR levels were increased in the BCAA-EN group relative to those of the control and general liquid groups ( $+5.6$  vs.  $+34.5$  %,  $p < 0.001$ ;  $-2.0$  vs.  $+34.5$  %,  $p < 0.001$ , respectively). No statistical differences in ALB, preALB, and PRP levels were seen among the three groups.

### Short-term changes in glucose metabolism indicators

The changes in the ratio of the glucose metabolism indicators at day 7 were compared among the three groups, using the day 0 levels as reference values. Regarding FBS, IRI, HOMA-R, and G-ALB levels, no significant differences were seen among the three groups (data not shown).

### Study two

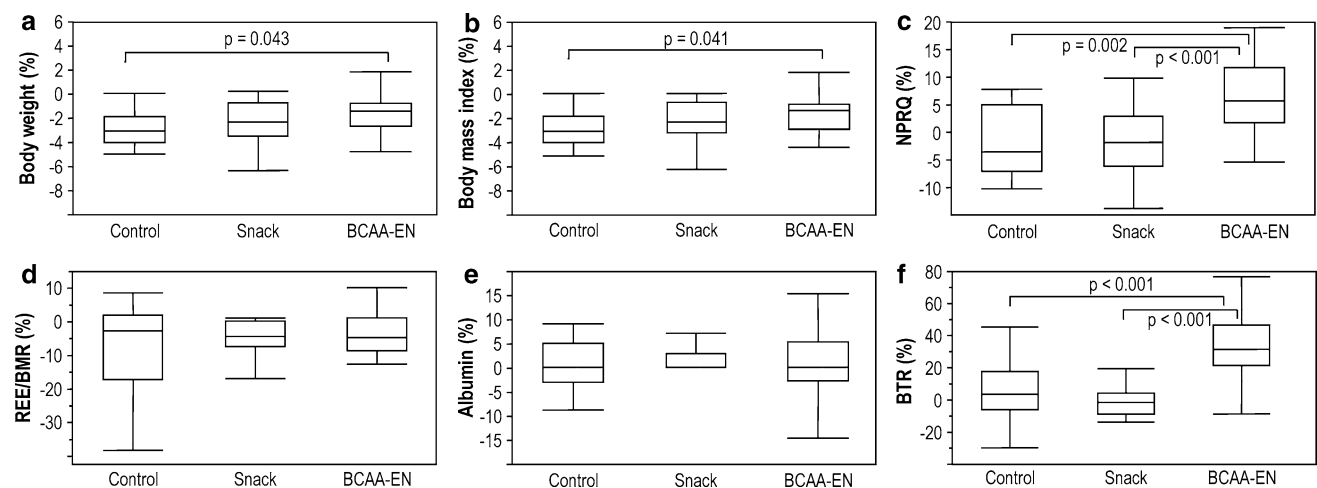
Among the 54 cases in study 2, six patients were excluded according to our exclusion criteria (Fig. 1a).

**Table 1** Demographic data of the patients in study 1

Characteristics	Control group	Snack group	BCAA-EN group	Analysis
N	13	15	16	n.s
Age (mean ± SD)	64.3 ± 15.2	64.4 ± 9.2	59.1 ± 12.0	n.s
Gender (M/F)	9/4	9/6	11/5	n.s
Diabetes mellitus, n (%)	2 (15.4 %)	3 (20 %)	1 (6.3 %)	n.s
Hepatocellular carcinoma	1 (7.7 %)	3 (20 %)	3 (18.8 %)	n.s
Child-Pugh score	6.4 ± 1.6	5.4 ± 0.7	5.6 ± 1.0	n.s
Varix (EIS/EVL)	11/2	13/3	16/0	n.s
HCV/HBV/nBnC/alcohol/other	5/1/3/2/2	5/1/3/2/4	8/2/2/2/2	n.s
Body weight (kg)	56.9 ± 8.9	55.4 ± 8.5	63.1 ± 16.4	n.s
Body mass index	22.3 ± 2.8	22.0 ± 2.6	23.3 ± 4.8	n.s
% AMC	107.0 ± 7.7	107.8 ± 13.5	109.2 ± 12.0	n.s
% TSF	135.3 ± 76.5	171.9 ± 134.6	196.4 ± 76.0	<i>p</i> < 0.05*
NPRQ	0.83 ± 0.04	0.84 ± 0.05	0.83 ± 0.05	n.s
REE/BMR	1.01 ± 0.19	1.03 ± 0.09	1.07 ± 0.1	n.s
Albumin (g/dl)	3.4 ± 0.4	3.6 ± 0.5	3.5 ± 0.5	n.s
Pre-albumin (mg/dl)	10.4 ± 3.4	11.7 ± 3.5	11.1 ± 4.1	n.s
RBP	1.3 ± 0.4	1.5 ± 0.5	1.3 ± 0.5	n.s
BTR	3.9 ± 1.7	4.3 ± 1.2	3.8 ± 1.0	n.s
FBS (mg/dl)	106.7 ± 19.5	117.4 ± 43.5	105.3 ± 20.3	n.s
IRI	11.9 ± 5.7	12.0 ± 7.5	10.4 ± 4.2	n.s
HOMA-R	3.2 ± 1.8	3.6 ± 2.6	2.7 ± 1.1	n.s
G-ALB (%)	19.1 ± 6.1	19.5 ± 6.8	18.6 ± 4.9	n.s

*Snack* general liquid nutrient, *BCAA-EN* branched-chain amino acid-enriched nutrient mixture, *EIS* endoscopic injection sclerotherapy, *EVL* esophageal variceal ligation, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *nBnC* non-HBV and non-HCV, *AMC* arm-muscle circumference, *TSF* triceps skinfold thickness, *NPRQ* non-protein respiratory quotient, *REE/BMR* resting energy expenditure/basal metabolic rate, *RBP* retinol-binding protein, *BTR* branched-chain amino acid and tyrosine ratio, *FBS* fasting blood sugar, *IRI* immunoreactive insulin, *HOMA-R* homeostasis model assessment-insulin resistance, *G-ALB* glycoalbumin, *n.s* not significant

\* Control vs. BCAA-EN



**Fig. 2** Comparisons of the short-term changes in the ratio of the values on day 7 between the control, snack, and BCAA-EN groups in study 1, with day 0 levels as reference values. **a** BW levels. **b** BMI levels. **c** NPRQ levels. **d** REE/BMR levels. **e** ALB levels. **f** BTR

levels. *BCAA* branched-chain amino acid, *BCAA-EN* branched-chain amino acid-enriched nutrient mixture, *NPRQ* non-protein respiratory quotient, *REE* resting energy expenditure, *BMR* basal metabolic rate, *BTR* molar ratio of branched-chain amino acids to tyrosine

**Table 2** Demographic data of the patients in study 2

Characteristics	BCAA group	BCAA-EN group	Analysis
<i>N</i>	24	24	n.s
Age (mean ± SD)	65.2 ± 11.5	65.9 ± 11.7	n.s
Gender (M/F)	16/8	17/7	n.s
Diabetes mellitus, <i>n</i> (%)	2	3	n.s
Hepatocellular carcinoma	8	5	n.s
Child-Pugh score	6.85 ± 1.03	6.67 ± 1.3	n.s
Varix (EIS/EVL)	22/2	22/2	n.s
HCV/HBV/nBnC/ alcohol/other	14/4/4/2/0	13/2/2/5/2	n.s
Body weight (kg)	59.6 ± 10.3	59.6 ± 10.6	n.s
Body mass index	23.6 ± 3.2	22.0 ± 3.2	n.s
% AMC	90.7 ± 11.7	106.2 ± 7.8	<i>p</i> < 0.01
% TSF	154.6 ± 62.5	97.0 ± 36.4	<i>p</i> < 0.01
NPRQ	0.86 ± 0.08	0.86 ± 0.08	n.s
REE/BMR	0.98 ± 0.1	0.96 ± 0.2	n.s
Albumin (g/dl)	3.2 ± 0.3	3.4 ± 0.4	n.s
Pre-albumin (mg/dl)	8.1 ± 3.6	10.8 ± 6.1	n.s
RBP	1.2 ± 0.4	1.6 ± 1.1	n.s
BTR	3.8 ± 1.6	3.7 ± 1.5	n.s
FBS (mg/dl)	109.4 ± 28.3	103.9 ± 14.5	n.s
IRI	15.1 ± 9.3	14.0 ± 9.3	n.s
HOMA-R	2.7 ± 0.6	2.7 ± 0.5	n.s
G-ALB (%)	18.5 ± 2.5	20.5 ± 6.4	n.s

BCAA branched-chain amino acid, BCAA-EN branched-chain amino acid-enriched nutrient mixture, EIS endoscopic injection sclerotherapy, EVL esophageal variceal ligation, HCV hepatitis C virus, HBV hepatitis B virus, nBnC non-HBV and non-HCV, AMC arm-muscle circumference, TSF triceps skinfold thickness, NPRQ non-protein respiratory quotient, REE/BMR resting energy expenditure/basal metabolic rate, RBP retinol-binding protein, BTR branched-chain amino acid and tyrosine ratio, FBS fasting blood sugar, IRI immunoreactive insulin, HOMA-R homeostasis model assessment-insulin resistance, G-ALB glycoalbumin, n.s not significant

Of the remaining 48 cases, the patients were equally divided between the BCAA and BCAA-EN groups. There were no drop-out cases by day 7. However, by day 50, some patients either had difficulties arriving to the hospital or failed to make their appointments. Hence, eight and nine drop-out cases occurred in the BCAA and BCAA-EN groups, respectively. No statistical significance was seen within the demographic data of the two groups (Table 2).

#### Short-term changes in body measurements

The changes in the ratio of the body measurement values at 7 day were compared between the groups, using the day 0 levels as reference values (Fig. 3a, b). No statistically

significant differences were seen among the BW or BMI levels for the two groups. Since a statistical difference in the % TSF and % AMC levels was seen between the BCAA and BCAA-EN groups at day 0, no comparisons were consequently performed.

#### Short-term changes in energy metabolism indicators

The changes in the ratio of the energy metabolism indicators at day 7 were compared between each group, using the day 0 levels as reference values. As shown in Figs. 3c and d, the NPRQ level in the BCAA group was lower than that in the BCAA-EN group (−4.8 vs. +0.5 %, *p* = 0.007). No significant differences were seen between the two groups in regards to REE/BMR.

#### Short-term changes in protein metabolism indicators

The changes in the ratios of the protein metabolism indicators at day 7 were compared between the groups, using the day 0 levels as reference values. As shown in Figs. 3e and f, the BCAA group showed increased ALB levels compared to the BCAA-EN group (+4.5 vs. +0.3 %, *p* = 0.038). No statistical differences in the preALB, RBP, and BTR levels were seen between the two groups.

#### Short-term changes in glucose metabolism indicators

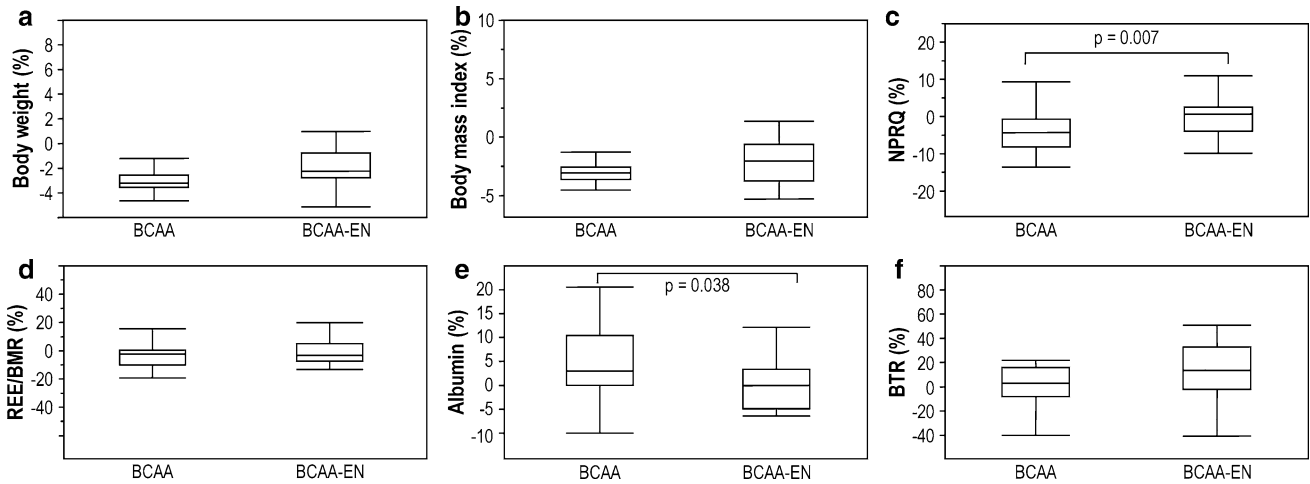
The changes in the ratios of the protein metabolism indicators at day 7 were compared between the groups, using the day 0 levels as reference values. No statistically significant differences in FBS, IRI, HOMA-R, and G-ALB levels were observed between the two groups for either indicator (data not shown).

#### Long-term changes in body measurements

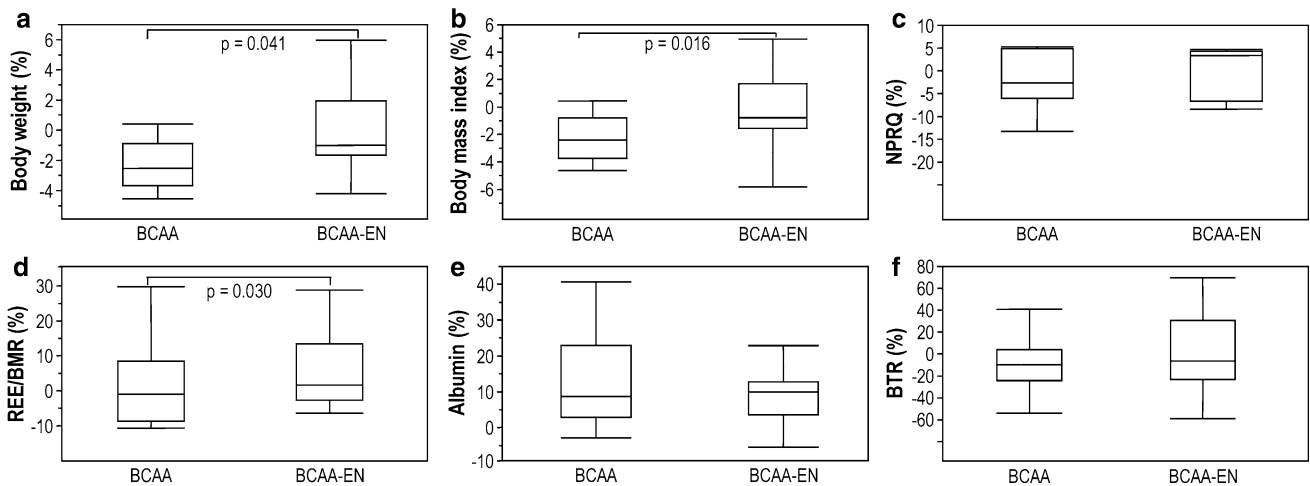
The changes in the ratio of the body measurement values at day 50 were compared between the groups, using the day 0 levels as reference values. As shown in Figs. 4a and b, The BW and BMI levels were lower in the BCAA group than those in the BCAA-EN group (−2.0 vs. +0.0 %, *p* = 0.041, −2.3 vs. −0.2 %, *p* = 0.016, respectively).

#### Long-term changes in energy metabolism indicators

The changes in the ratio of the energy metabolism indicators at day 50 were compared between the groups, using the day 0 levels as reference values. As shown in Figs. 4c and d, the BCAA group showed lower REE/BMR levels than the BCAA-EN group (−2.4 vs. +8.2 %, *p* = 0.030). However, the NPRQ levels were not significantly different between the two groups.



**Fig. 3** Comparisons of the short-term changes in the ratio of the values on day 7 between the BCAA and BCAA-EN groups in study 2, with day 0 levels as reference values. **a** BW levels. **b** BMI levels. **c** NPRQ levels. **d** REE/BMR levels. **e** ALB levels. **f** BTR levels



**Fig. 4** Comparisons of the long-term changes in the ratio of the values on day 50 between the BCAA and BCAA-EN groups in study 2, with day 0 levels as reference values. **a** BW levels. **b** BMI levels. **c** NPRQ levels. **d** REE/BMR levels. **e** ALB levels. **f** BTR levels

*Long-term changes in protein metabolism indicators*

The changes in the ratio of the protein metabolism indicators at day 50 were compared between the groups, using the day 0 levels as reference values (Figs. 4e, f). No difference of statistical significance was seen between the two groups for ALB, preALB, RBP, and BTR.

*Long-term changes in glucose metabolism indicators*

The changes in the ratio of the glucose metabolism indicators at day 50 were compared between the groups, using the day 0 levels as reference values. No differences of statistical significance in FBS, IRI, HOMA-R, and G-ALB levels were seen between the two groups for any of the indicators (data not shown).

**Discussion**

Cirrhosis of the liver is the terminal form of liver disease and is accompanied by multiple nutritional deficiencies [24, 25]. Patients targeted for this study had cirrhosis of the liver and had received endoscopic treatment of esophageal varices. Patients had nutritional deficiencies from cirrhosis of the liver, but there were no cases of emergency hemostasis after hematemesis. Hence, the effect on nutritional indicators of hematemesis can be excluded from this study.

Cases targeted for study 1 were those in which the patients had not received a BCAA preparation prior to participation in the study. The study 1 findings showed no statistically significant differences in NPRQ levels between the control and snack groups. For the BCAA-EN group, a significant increase in NPRQ levels was seen on day 7

(Supplementary Figure S1), as compared with the control and snack groups (Fig. 2c). The usefulness of LES is becoming clear, and Nakaya et al. [20] reported that BCAA-EN as an LES is better than a snack in terms of energy metabolism for patients with cirrhosis. Study 1 showed the same results during the treatment of esophageal varices. Additionally, a snack as an LES has been reported to improve NPRQ levels in patients with cirrhosis [26]. However, in study 1, the snack as an LES did not improve energy metabolism during the treatment of esophageal varices. These findings of study 1 suggest that the ingestion of calories alone is not sufficient to improve NPRQ levels during the treatment of esophageal varices and that combined calorie/BCAA ingestion is necessary.

Study 2 investigated cases where a BCAA preparation had already been administered prior to entry in the study. Patients in these cases had decompensated cirrhosis with ALB levels of 3.5 g/dl or lower, and at the very least, a decline in Fisher's ratio was confirmed once BCAA preparations were begun. According to the Japanese BCAA indication criteria, the use of BCAA was considered to be applicable in these cases. For this reason, a protocol was drafted to continue BCAA administration in both groups because of the ethical issue that would have resulted had BCAA administration been stopped. Study 2 provided the opportunity to compare the effects of ingesting calories in addition to BCAA from the early stage on to nutritional indicators during the treatment period of this study. Although a few reports have compared the effects of BCAA and BCAA-EN [27, 28], no previous studies have compared their effects during the treatment of esophageal varices. The study 2 findings showed that in comparison with the BCAA group, the BCAA-EN group both showed and maintained a statistically significant difference for NPRQ levels on day 7 (Fig. 3c), although BCAA as an LES has been reported to result in improved NPRQ levels in patients with cirrhosis [29]. Moreover, the administration of BCAA as an energy substrate for cirrhotic patients has been shown to have better energy efficiency when compared with other nutrients [30]. For this reason, when BCAA alone is prescribed in situations where dietary restrictions have been added, it is consumed as energy and may not function as BCAA. However, if calories and BCAA are both prescribed, BCAA is not consumed as energy, suggesting that it could be effective in improving metabolism. No statistical significance was noted in the differences between the NPRQ levels of the two groups on day 50. However, it is thought that this is because BCAA functioned as intended in both the BCAA and BCAA-EN groups, as BCAA was ingested while patients consumed a sufficient number of calories after hospital discharge. During this study, cirrhotic patients undergoing stress that accompanied therapeutic intervention were able to avoid

decreased body mass by day 50 through ingesting both calories and BCAA. However, those patients that ingested only BCAA were not able to avoid decreased body mass (Fig. 4a). This also suggests the possibility that maintaining NPRQ levels on day 7 through short-term nutritional intervention had an effect on body weight maintenance on day 50. Thus, these findings suggest that nutritional intervention is even more necessary when stress and dietary restrictions are introduced, even in cases where a BCAA preparation has already been introduced.

The liver cirrhosis practice guidelines published by the Japanese Society of Gastroenterology recommend ingestion of a BCAA-enriched nutrient mixture in cases of protein malnutrition (ALB <3.5 g/dl) or in cases of energy malnutrition (NPRQ <0.85). Among the 44 cases in study 1, only 13 cases (30 %) showed protein malnutrition (ALB <3.5 g/dl) and energy malnutrition (NPRQ <0.85): six cases in the control group, three cases in the snack group, and four in the BCAA-EN group. However many cases (25/44; 57 %) showed energy malnutrition. Indeed, the BCAA-EN group showed significant improvement in energy metabolism over both the control group and the snack group (Fig. 2c), thus suggesting the usefulness of nutritional support. To improve energy metabolism when stress and dietary restrictions are introduced, calorie ingestion alone is insufficient. This suggests that enteral nutrients rich in BCAA that provide adequate calories are necessary. Among the 48 cases in study 2 that were already receiving a BCAA preparation, 14 (29 %) showed a state of protein malnutrition (ALB <3.5 g/dl) and a state of energy malnutrition (NPRQ <0.85): nine cases in the BCAA group and five cases in the BCAA-EN group. Even in study 2, a maintained improvement in energy metabolism was seen in the BCAA-EN group when compared with the BCAA group (Fig. 3c). These findings suggest that nutritional intervention is even more necessary when stress and dietary restrictions are introduced, even for cases where a BCAA preparation has already been introduced.

In both studies 1 and 2, the BCAA-EN group saw a significant maintained improvement in NPRQ levels, which acted as an energy metabolism indicator and cirrhotic long-term prognosis indicator. Merli et al. [31] reported that decreased body weight during physical measurements was one adverse prognostic factor. However, in study 1, a significant decrease in body weight was seen in the control group when compared with the BCAA-EN groups. In study 2, a significant reduction in body weight was seen in the BCAA group when compared with the BCAA-EN group. Regarding % TSF and % AMC levels, study 1 did not show a statistical significance in any group for % TSF levels before treatment, although a slight difference was observed. In study 2, a statistical significance was noted in the % TSF and AMC levels between both



groups before treatment. Because measurement errors can easily occur when examining % TSF and AMC levels, and because no differences of statistical significance were seen in this study between the groups in measuring target patient height, weight, and BMI, interpretation of the % TSF and AMC values must be carried out with the utmost care.

Regarding protein metabolism, no statistical significance in albumin level variance was seen between the groups in study 1. However, in study 2, a significant increase was noted on day 7 in the BCAA group when compared with the BCAA-EN group. BCAAs have been reported to activate mTOR and subsequently increase the levels of proteins that upregulate albumin synthesis [32]. Moreover, Sato et al. (LIV-EN study) reported that BCAA was not inferior to BCAA-EN in terms of serum albumin in patients with decompensated liver cirrhosis who have hepatic encephalopathy [28]. Study 2 showed that BCAA alone is also beneficial with respect to serum albumin levels in a short-term assessment. However, no statistical significance was seen in differences in either preALB or RBP. Additionally, on day 50, no statistically significant difference was noted between the two groups, so that the clinical meaning is unclear. No statistically significant differences were seen in glucose tolerance between any groups in either study 1 or study 2. There was no change on day 7 in the study 1 snack group. In contrast, a reduction in early morning blood sugar and HOMA-R was seen in both the control and BCAA-EN groups on day 7. An abnormal reduction due to calorie insufficiency is suspected in the control group. However, an improvement effect on glucose tolerance [33] due to BCAA in the BCAA-EN group of study 1 is suggested. Glucose tolerance in the BCAA and BCAA-EN groups in study 2 did not improve, possibly because the patients had already been receiving BCAA.

Finally, although maintained improvement in the cirrhotic patients' respiratory quotient and body weight was possible during treatment through enteral nutrients rich in BCAA, it was unable to be maintained using either BCAA or calories alone. This suggests that ingesting both BCAA and calories is beneficial in the treatment of these patients.

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**Conflict of interest** The authors declare that they have no conflict of interest.

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## References

- Ashkenazi E, Kovalev Y, Zuckerman E. Evaluation and treatment of esophageal varices in the cirrhotic patient. *Isr Med Assoc J*. 2013;15:109–15.
- Lautz HU, Selberg O, Körber J, et al. Protein-calorie malnutrition in liver cirrhosis. *Clin Invest*. 1992;70:478–86.
- Caregaro L, Alberino F, Amodio P, et al. Malnutrition in alcoholic and virus-related cirrhosis. *Am J Clin Nutr*. 1996;63:602–9.
- Tajika M, Kato M, Mohri H, et al. Prognostic value of energy metabolism in patients with viral liver cirrhosis. *Nutrition*. 2002;18:229–34.
- Huisman EJ, Trip EJ, Siersema PD, et al. Protein energy malnutrition predicts complications in liver cirrhosis. *Eur J Gastroenterol Hepatol*. 2011;23:982–9.
- Singh P, Pooran N, Indaram A, et al. Combined ligation and sclerotherapy versus ligation alone for secondary prophylaxis of esophageal variceal bleeding: a meta-analysis. *Am J Gastroenterol*. 2002;97:623–9.
- Svoboda P, Kantorová I, Ochmann J, et al. A prospective randomized controlled trial of sclerotherapy vs ligation in the prophylactic treatment of high-risk esophageal varices. *Surg Endosc*. 1999;13:580–4.
- Iso Y, Kawanaka H, Tomikawa M, et al. Repeated injection sclerotherapy is preferable to combined therapy with variceal ligation to avoid recurrence of esophageal varices. *Hepatogastroenterology*. 1997;44:467–71.
- Katsumi N, Kawamura N, Yamaguchi Y, et al. Effect of oral branched chain amino acid-rich nutrient administered during endoscopic sclerotherapy of cirrhotic patients. *Hepatol Res*. 2005;32:158–62.
- Shibata N, Matsui H, Onji M, et al. Usefulness of BCAA-enriched nutrient mixture for nutritional treatment undergoing endoscopic treatment for esophageal varices. *J Jpn Soc Gastroenterol*. 2005;32:158–62.
- Nagata N, Numata M, Hirose S, et al. Nutritional assessment after treatment of esophageal varices in patients with Cirrhosis. *Jpn J Portal Hypertens*. 2008;14:201–5.
- Muto Y, Sato S, Watanabe A, et al. Effect of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. *Clin Gastroenterol Hepatol*. 2005;3:705–13.
- Yoshida T, Muto Y, Moriwaki H, et al. Effect of long-term oral supplementation with branched-chain amino acid granules on the prognosis of liver cirrhosis. *Gastroenterol Jpn*. 1989;24:692–8.
- Habu D, Nishiguchi S, Nakatani S, et al. 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;25:312–8.
- Muto Y, Yoshida T, Kato M, et al. Effect of oral supplementation with BCAA-G on the prognosis of liver cirrhosis. *JJPN*. 1995;17:1135–43.
- Muto Y, Sato S, Watanabe A, et al. 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;35:204–14.
- Kobayashi M, Ikeda K, Arase Y, et al. 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.
- Kawaguchi T, Yamagishi S, Sata M. Branched-chain amino acid and pigment epithelium-derived factor: novel therapeutic agents for hepatitis c virus-associated insulin resistance. *Curr Med Chem*. 2009;16:4843–57.

19. Tsuchiya M, Sakaida I, Okamoto M, et al. The effect of a late evening snack in patients with liver cirrhosis. *Hepatol Res.* 2005;31:95–103.
20. Nakaya Y, Okita K, Suzuki K, et al. BCAA-enriched snack improves nutritional stage of cirrhosis. *Nutrition.* 2007;23:113–20.
21. Yamanaka-Okumura H, Nakamura T, Takeuchi H, et al. Effect of late evening snack with rice ball on energy metabolism in liver cirrhosis. *Eur J Clin Nutr.* 2006;60:1067–72.
22. Aoyama K, Tsuchiya M, Mori K, et al. Effect of a late evening snack on outpatients with liver cirrhosis. *Hepatol Res.* 2007;37:608–14.
23. Nakaya Y, Harada N, Kakui S, et al. Severe catabolic state after prolonged fasting in cirrhotic patients: effect of oral branched-chain amino-acid-enriched nutrient mixture. *J Gastroenterol.* 2002;37:531–6.
24. Alberino F, Gatta A, Amodio P, et al. Nutrition and survival in patients with liver cirrhosis. *Nutrition.* 2001;17:445–50.
25. Müller MJ. Malnutrition in cirrhosis. *J Hepatol.* 1995;23(Suppl 1):31–5.
26. Miwa Y, Shiraki M, Kato M, et al. Improvement of fuel metabolism by nocturnal energy supplementation in patients with liver cirrhosis. *Hepatol Res.* 2000;18:184–9.
27. Hidaka H, Nakazawa T, Kutsukake S, et al. The efficacy of nocturnal administration of branched-chain amino acid granules to improve quality of life in patients with cirrhosis. *J Gastroenterol.* 2013;48:269–76.
28. Sato S, Watanabe A, Muto Y, et al. 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;31:232–40.
29. Urata Y, Okita K, Korenaga K, et al. The effect of supplementation with branched-chain amino acids in patients with liver cirrhosis. *Hepatol Res.* 2007;37:510–6.
30. Kato M, Miwa Y, Tajika M, et al. Preferential use of branched-chain amino acids as an energy substrate in patients with liver cirrhosis. *Intern Med.* 1998;37:429–34.
31. Merli M, Riggio R, Dally L. Does malnutrition affect survival in cirrhosis? PINC (Policentrica Italiana Nutrizione Cirrosi). *Hepatology.* 1996;23:1041–6.
32. Ijichi C, Matsumura T, Tsuji T, et al. Branched-chain amino acids promote albumin synthesis in rat primary hepatocytes through the mTOR signal transduction system. *Biochem Biophys Res Commun.* 2003;303:59–64.
33. Owen OE, Reichle FA, Mozzoli MA, et al. Hepatic, gut, and renal substrate flux rates in patients with hepatic cirrhosis. *J Clin Invest.* 1981;68:240–52.