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Additional BCAA-enriched nutrient mixture improves the nutritional condition in cirrhotic patients with hypoalbuminemia despite treatment with regular BCAA granules: A pilot study

LIVER

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Original Article

ABSTRACT

Background/Aims: To elucidate the effect of adding branched-chain amino acid (BCAA)-enriched nutrient mixtures in cirrhotic patients with hypoalbuminemia despite the use of BCAA granules.

Materials and Methods: A BCAA-enriched nutrient mixture containing 5.6 g of BCAA and 210 kcal was additionally administered in 40 cirrhotic patients with hypoalbuminemia despite their treatment with BCAA granules containing 12 g of BCAA. Laboratory data were assessed at 6 months before beginning additional therapy, at baseline, and at 6 months after baseline.

Results: Serum albumin levels significantly decreased from 6 months before baseline (3.14±0.47 g/dL) to baseline (2.83±0.46 g/dL), despite the treatment with BCAA granules ($p<0.001$), and tended to increase from baseline to 6 months after baseline (2.95±0.42 g/dL) ($p=0.084$). In the subset of 23 patients without hepatocellular carcinoma treatments, upper gastrointestinal tract bleeding, or albumin infusion, serum albumin levels significantly increased from baseline (2.93±0.38 g/dL) to 6 months after baseline (3.15±0.34 g/dL) ($p=0.014$).

Conclusion: Additional therapy with BCAA-enriched nutrient mixtures increased serum albumin levels of the cirrhotic patients with hypoalbuminemia despite the treatment with BCAA granules and without hepatocellular carcinoma treatment, upper gastrointestinal tract bleeding, or albumin infusion.

Keywords: Liver cirrhosis, amino acid, branched-chain, hypoalbuminemia

INTRODUCTION

It is common knowledge that protein-energy malnutrition (PEM) occurs in cirrhotic patients and leads to high morbidity and mortality (1). PEM is generally described as decreased serum albumin and muscle volume (2). PEM affects the outcome of cirrhotic patients by disturbing both their quality of life (QOL) and survival (1,3). Thus, the treatment of PEM is an important approach in the management of liver cirrhosis.

Advanced cirrhotic patients have a low serum concentration of branched-chain amino acids (BCAA) (4). This is caused by their enhanced consumption in skeletal muscle for ammonia detoxification and energy production and results in the reduction of biosynthesis and secretion of albumin in hepatocytes (5).

Serum albumin level is an important indicator of prognosis in cirrhotic patients. The survival rate of cirrhotic patients with hypoalbuminemia (below 3.5 g/dL) was significantly lower than that in cirrhotic patients with a normal albumin concentration (more than 3.5 g/dL) (3). Therefore, it is important in advanced cirrhotic patients for serum albumin levels to be maintained above 3.5 g/dL by intervention involving nutritional treatment with BCAA nutrients.

After an overnight fast, cirrhotic patients show a metabolic profile comparable to that of normal subjects who have undergone 2–3 days of starvation (6). A late evening snack (LES) with 200 kcal has been recommended to diminish nocturnal starvation caused by overnight fasting in cirrhotic patients (7,8). Therefore, both the

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American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines and the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend late evening snacks with energy supplements to counter nocturnal starvation (9,10).

Oral supplementation containing BCAA has been reported to improve PEM status and QOL and decrease the frequency of complications in liver cirrhosis and prolong event-free survival in patients with decompensated cirrhosis (11-13). Recently, LES with BCAA was reported to enhance protein synthesis and improve nitrogen balance (14).

In Japan, there are two types of BCAA-containing medicines for cirrhotic patients: oral BCAA granules and oral BCAA-enriched nutrient mixtures. BCAA granules (LIVACT granules) at a regular dosage (three packs a day) contain 12 g of BCAA and 48 kcal of energy a day and no carbohydrate or fat. On the other hand, a BCAA-enriched nutrient mixture (Aminoleban EN) contains 5562 mg of BCAA, 13.5 g of total protein, 31.1 g of carbohydrate, 3.5 g of fat, and 210 kcal of energy in one pack (Table 1). BCAA granules are used to supply only BCAA for cirrhotic patients with hypoalbuminemia, whereas BCAA-enriched nutrient mixtures are used to supply both energy and BCAA for cirrhotic patients with poor dietary intake. Therefore, the two medicines are generally not used in combination.

The amount of energy used for LES was recommended to be approximately 200 kcal at one time (7). One pack of a BCAA-enriched nutrient mixture (210 kcal) is thus specifically suitable for LES. It is often difficult in patients with decompensated cirrhosis for their serum albumin levels to be maintained above 3.5 g/dL by the administration of BCAA granules. It was reported that approximately 30% of patients with decompensated cirrhosis achieved an increase of serum albumin levels of 0.4 g/dL or more with BCAA granules for 3 months (15). The remaining 70% of patients did not achieve sufficient effects with the single use of BCAA granules.

The purpose of this pilot study was to clarify the effect of an additional therapy with BCAA-enriched nutrient mixtures for patients with hypoalbuminemia despite treatment with BCAA granules.

MATERIALS AND METHODS

Patients

One pack of a BCAA-enriched nutrient mixture was additionally administered as LES in 40 cirrhotic patients with hypoalbuminemia (serum albumin levels were less than 3.5 g/dL) despite treatment with regular BCAA granules from June 2004 to March 2014, and their clinical data were retrospectively studied (Table 2). Patients with kidney dysfunction were excluded from this study because this can influence the serum albumin levels.

Study drugs

BCAA granules (LIVACT Granules; Ajinomoto Co., Inc., Tokyo, Japan) containing 1144 mg of L-valine, 1904 mg of L-leucine, and 952 mg of L-isoleucine per packet were orally administered daily at a regular dosage of one packet three times a day (after meals). A BCAA-enriched nutrient mixture (Aminoleban EN; Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) containing 210 kcal of energy, 13.5 g of protein, 3.5 g of fat, and a little amount of minerals and vitamins, in addition to 1602 mg of L-valine, 2037 mg of L-leucine, and 1923 mg of L-isoleucine, was orally administered at one pack per day as LES (before bedtime). The adherence of each patient to the treatment was maintained at a sufficient level, and the dietary intake of each patient did not change in the study period.

Study design

Laboratory data were collected at three points as follows: 6 months before baseline, at baseline (beginning of additional therapy), and 6 months after baseline.

Hepatocellular carcinoma (HCC) treatment such as radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), or hepatectomy and upper gastrointestinal tract

Table 1. Contents of BCAA-containing medicines

	3 packs of BCAA granules	1 pack of BCAA-enriched nutrient mixture	Combination of 3 packs of BCAA granules and 1 pack of BCAA-enriched nutrient mixture
Total protein (g/day)	12.0	13.5	25.5
Total BCAA (mg/day)	12000	5562	17562
L-valine (mg/day)	1144	1602	3746
L-leucine (mg/day)	1904	2037	3941
L-isoleucine (mg/day)	952	1923	2875
Carbohydrate (g/day)	-	31.1	31.1
Fat (g/day)	-	3.5	3.5
Total calories (kcal/day)	48	210	258

BCAA: branched-chain amino acid

Table 2. Clinical characteristics and laboratory values of the patients at baseline

	All patients	HCC treatment, upper gastrointestinal tract bleeding and/or albumin infusion		p value
		(-)	(+)	
No. of subjects	**40**	**23**	**17**	**(-) vs (+)**
Sex (male/female)	29/11	17/6	12/5	NS
Age (years)	64.9±11.7	65.2±11.9	64.6±11.5	NS
Height (cm)	161.3±10.6	160.0±11.3	162.9±9.2	NS
Body weight (kg)	61.0±14.3	58.9±14.2	64.1±13.9	NS
Body mass index (kg/m^2)	23.3±3.8	22.9±3.8	23.8±3.8	NS
Etiology of liver disease				
Hepatitis B	2	2	0	NS
Hepatitis C	21	11	10	
Alcoholic liver injury	11	7	4	
Primary Biliary Cirrhosis	2	1	1	
Autoimmune hepatitis	1	1	0	
Non-alcoholic steatohepatitis	2	1	1	
Idiopathic portal hypertension	1	0	1	
Child-Pugh grade (A/B/C)	8/22/10	7/14/2	1/8/8	0.011
HCC (+/-)	16/24	4/19	12/5	0.001
Stage of HCC (I/II/III/IV)	6/5/5/0	2/0/2/0	4/5/3/0	NS
HCC treatment (RFA/TACE/hepatectomy) in the study period	10	0	10	-
Upper gastrointestinal tract bleeding in the study period	2	0	2	-
Albumin infusion	5	0	5	-
Concurrent diabetes mellitus (+/-)	14/26	10/13	4/13	NS
White blood cell counts (/μL)	4113±1764	4217±2248	3971±775	NS
Total lymphocyte counts (/μL)	1095±534	1206±601	950±404	NS
Red blood cell counts (×10^6/μL)	3.58±0.71	3.60±0.74	355±0.69	NS
Platelets (×10^4/μL)	8.37±5.77	9.27±7.20	7.15±2.66	NS
Hemoglobin A1c (%)	5.43±0.97	5.48±0.94	5.32±1.10	NS
Total protein (g/dL)	6.96±0.89	7.02±0.83	6.87±0.99	NS
Serum albumin (g/dL)	2.83±0.46	2.93±0.38	2.69±0.52	NS
Total bilirubin (mg/dL)	1.95±1.68	1.36±0.79	2.75±2.19	0.006
Aspartate aminotransferase (IU/L)	52.3±19.4	50.1±20.5	55.3±17.9	NS
Alanine aminotransferase (IU/L)	34.6±15.7	31.0±14.2	39.5±16.6	NS
Total cholesterol (mg/dL)	131±34	136±36	125±32	NS
Triglycerides (mg/dL)	90±46	101±54	75±31	NS
Cholinesterase (IU/L)	111±68	125±80	93±41	NS
Serum creatinine (mg/dL)	0.92±0.39	0.94±0.34	0.89±0.44	NS
C-reactive protein (mg/dL)	0.6±1.0	0.8±1.0	0.6±0.9	NS

HCC: hepatocellular carcinoma; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization
Data are presented as number of patients or means±SD.
Statistical analysis was performed by $\chi 2$ test or Mann-Whitney U test. NS: not significant

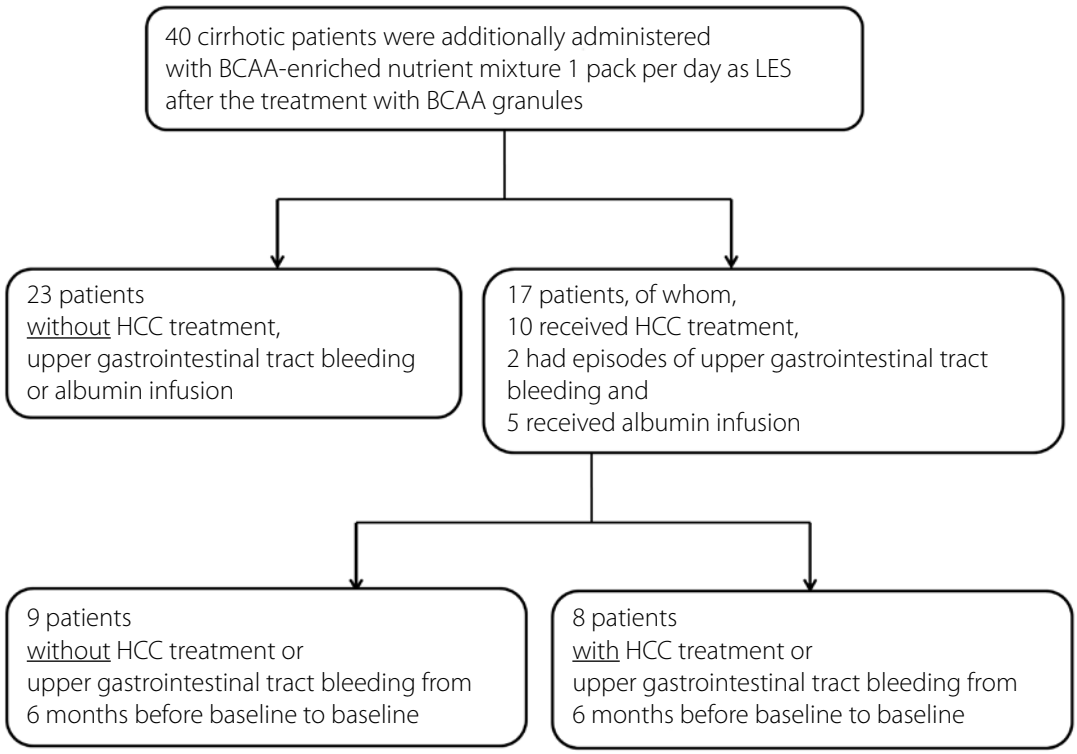

Figure 1. Composition of patients included in the analyses.

bleeding often diminish liver function and decrease serum albumin level in cirrhotic patients. Albumin infusion also influences serum albumin level. Therefore, subset analysis was performed with the patients with or without HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion. Additional analyses were performed in 17 patients according to the presence of HCC treatment or upper gastrointestinal tract bleeding from 6 months before baseline to baseline (Figure 1).

In addition, the patients were divided into three groups based on Child–Pugh grades, and the difference of the effect of BCAA-enriched nutrient mixtures due to liver function was examined.

Research ethics

This study conformed to Japanese Good Clinical Practice and the Declaration of Helsinki and was approved by the institutional ethical review board of our hospital.

Informed Consent

Informed consent was obtained from patients who participated in this study.

Statistical analysis

Differences in the two groups with respect to clinical characteristics and laboratory values at baseline were analyzed using the χ^2 test or Mann–Whitney U test. Differences between the two points of laboratory values were analyzed using Wilcoxon's signed-rank test. Differences were judged as significant for $p<0.05$ (two-tailed). All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) software (SPSS Statistics Version 20.0; IBM Co., Armonk, NY, USA).

RESULTS

Effect of BCAA-enriched nutrient mixture on serum albumin in all patients

Serum albumin levels significantly decreased from 6 months before baseline (3.14±0.47 g/dL) to baseline (2.83±0.46 g/dL) despite the treatment with BCAA granules in all 40 patients ($p<0.001$) and tended to increase from baseline to 6 months after baseline (2.95±0.42 g/dL) with the administration of BCAA-enriched nutrient ($p=0.084$) (Figure 2).

Subset analyses according to the presence of HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion

Subset analyses were performed in 23 patients without HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion during the study period and in 17 patients with HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion during the study period (Table 2). The Child–Pugh grades and total bilirubin levels were significantly poor in patients with HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion compared with those in patients without these criteria ($p=0.011$ and $p=0.006$, respectively).

In the subset of 23 patients without HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion, serum albumin levels significantly decreased from 6 months before baseline

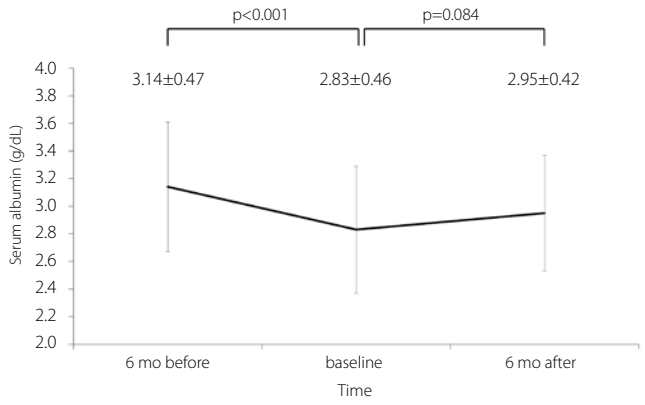

Figure 2. Serum albumin levels 6 months before, at, and 6 months after baseline (n=40).

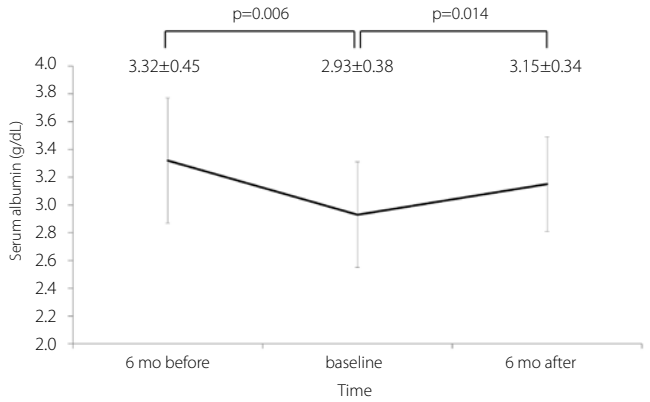

Figure 3. Serum albumin levels 6 months before, at, and 6 months after baseline in the patients without HCC treatment, upper gastrointestinal tract bleeding or albumin infusion in the study period (n=23).

(3.32±0.45 g/dL) to baseline (2.93±0.38 g/dL) despite the treatment with BCAA granules (p=0.006) and significantly increased from baseline to 6 months after baseline (3.15±0.34 g/dL) with the administration of BCAA-enriched nutrients (p=0.014) (Figure 3).

In the subset of 17 patients with HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion, serum albumin levels significantly decreased from 6 months before baseline (2.90±0.41 g/dL) to baseline (2.69±0.52 g/dL) despite the treatment with BCAA granules (p=0.033) and did not increase at 6 months after baseline (2.67±0.36 g/dL) despite the treatment with BCAA-enriched nutrient mixtures (Figure 4). Additional analyses were performed in 17 patients according to the presence of HCC treatment or upper gastrointestinal tract bleeding from 6 months before baseline to baseline. Serum albumin levels did not significantly decrease from 6 months before baseline to baseline in neither the eight patients with HCC treatment and upper gastrointestinal tract bleeding nor the nine patients without these criteria (Figure 5).

Subset analyses according to Child-Pugh grades

In the subset analyses of 40 patients, serum albumin levels significantly decreased from 6 months before baseline (3.20±0.50

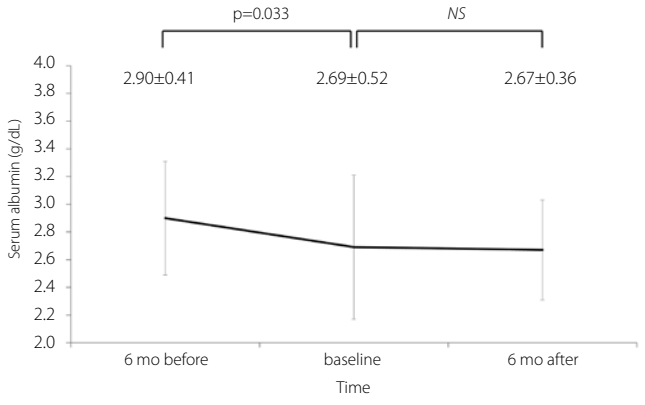

Figure 4. Serum albumin levels 6 months before, at, and 6 months after baseline in the patients with HCC treatment, upper gastrointestinal tract bleeding or albumin infusion in the study period (n=17).

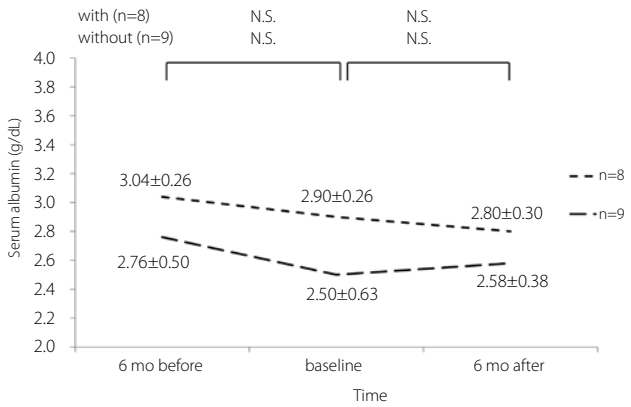

Figure 5. Serum albumin levels 6 months before, at, and 6 months after baseline in the patients with/without HCC treatment or upper gastrointestinal tract bleeding from 6 months before baseline to baseline in the 17 patients (n=8/n=9).

g/dL) to baseline (2.81±0.37 g/dL) (p=0.008) in Child–Pugh B (n=22) and from 6 months before baseline (2.83±0.41 g/dL) to baseline (2.49±0.46 g/dL) (p=0.020) in Child–Pugh C (n=10), despite the treatment with BCAA granules. However, serum albumin levels did not increase at 6 months after baseline, despite the treatment with BCAA-enriched nutrient mixtures in all Child–Pugh grades (Figure 6).

In the subset of 23 patients without HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion, serum albumin levels significantly decreased from 6 months before baseline (3.41±0.48 g/dL) to baseline (2.81±0.34 g/dL), despite the treatment with BCAA granules (p=0.008), and significantly increased from baseline to 6 months after baseline (3.07±0.38 g/dL) with the administration of BCAA-enriched nutrient mixtures (p=0.045) in Child–Pugh B (n=14). However, serum albumin levels did not increase in Child–Pugh A and C (Figure 7).

In the subset of 17 patients with HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion, serum albumin

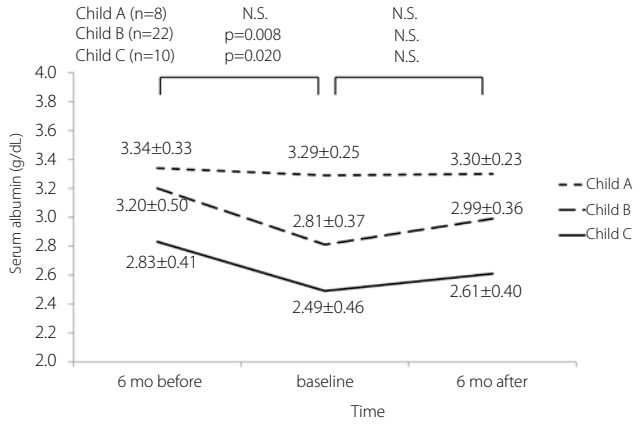

Figure 6. Serum albumin levels 6 months before, at, and 6 months after baseline classified according to Child–Pugh grades (n=40).

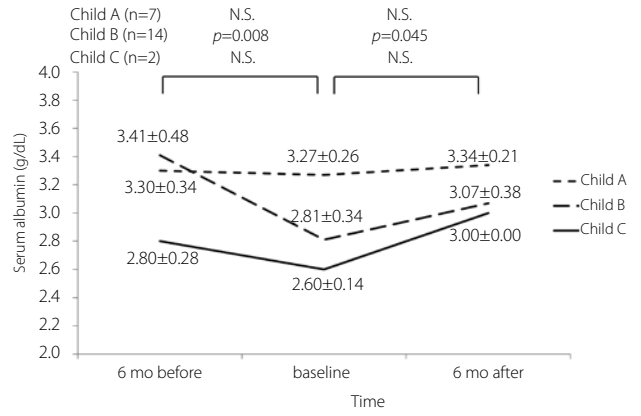

Figure 7. Serum albumin levels 6 months before, at, and 6 months after baseline in the patients without HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion in the study period classified according to Child–Pugh grades (n=23).

levels significantly decreased from 6 months before baseline (2.84±0.46 g/dL) to baseline (2.46±0.51 g/dL), despite the treatment with BCAA granules (p=0.034) in Child–Pugh C (n=8). However, serum albumin levels did not increase at 6 months after baseline, despite the treatment with BCAA-enriched nutrient mixtures in all Child–Pugh grades (Figure 8).

Other treatments that may affect serum albumin levels

There were no patients who started treatments that may affect serum albumin levels, such as nucleoside analog for hepatitis B, steroid therapy for autoimmune hepatitis, or abstention from alcohol in the study period. There was only one patient who started low-dose interferon monotherapy for hepatitis C on baseline. However, his serum albumin levels did not change from baseline (3.2 g/dL) to 6 months after baseline (3.2 g/dL).

Other laboratory data

No significant change in total lymphocyte counts, platelets, total bilirubin, cholinesterase, serum ammonia, or hemoglobin A1c was noted during the administration of BCAA-enriched nutrient mixtures (data not shown). No adverse side effects of

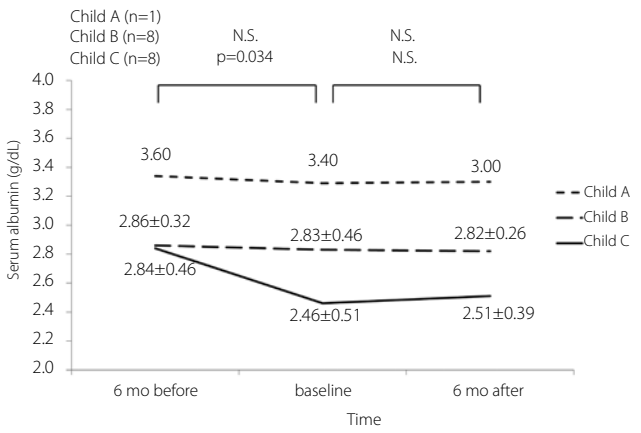

Figure 8. Serum albumin levels 6 months before, at, and 6 months after baseline in the patients with HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion in the study period classified according to Child–Pugh grades (n=17).

BCAA granules and BCAA-enriched nutrient mixtures were observed during the study period.

DISCUSSION

The present study showed that additional therapy with BCAA-enriched nutrient mixtures significantly increased the serum albumin levels of cirrhotic patients with hypoalbuminemia, despite the treatment with BCAA granules in the subset of patients without HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion in the study period, particularly in patients with Child–Pugh B. Serum albumin level is an important predictive factor for patients with liver cirrhosis, and compensated cirrhosis with a serum albumin level above 3.5 g/dL has a better prognosis (16-18). Therefore, this additional therapy with BCAA-enriched nutrient mixtures may be one of the useful options for decompensated cirrhotic patients who do not respond to treatment with BCAA granules.

Muto et al. (11) performed a multicenter, randomized controlled trial, in which 622 cirrhotic patients were administered BCAA granules for 2 years. They reported that serum albumin concentrations were significantly increased in the BCAA granule group compared with those in the control group. However, in another randomized controlled trial by Marchesini et al. (13), treatment with BCAA granules did not significantly increase serum albumin concentration. Although the reason for this contradiction is unclear, a probable explanation is the difference in the stages of cirrhosis among the subjects in the two trials. Approximately 36% of enrolled patients were at Child–Pugh grade A in the former trial, whereas all patients were at Child–Pugh grade B or C in the latter trial. In the present study, the patients whose serum albumin levels continued to be less than 3.5 g/dL, despite the treatment with BCAA granules, were studied and 80% of them were at Child–Pugh grade B or C.

Cirrhotic patients progress with respect to a catabolic condition more rapidly than healthy individuals. This catabolic con-

dition causes a poor prognosis for them (1,3). Carbohydrate-rich LES improves nitrogen balance and reverses hyperactive protein metabolism and high ketone body levels in cirrhotic patients (19,20). Therefore, energy supplementation at bedtime may protect cirrhotic patients against the progression of malnutrition. A variety of nutrients have been attempted as LES to improve the catabolic condition in liver cirrhotic patients, such as a carbohydrate-rich snack (18) and available prescribed liquid nutrients (21).

Nakaya et al. (22) reported that long-term oral supplementation with a BCAA mixture that contains glucose, lipids, and other nutrients is appropriate for LES compared with ordinary food to improve the serum albumin level and the energy metabolism in cirrhotic patients. Aoyama et al. (23) reported that oral supplementation of BCAA-enriched nutrient mixtures not only improved energy metabolism and liver activity but also enabled the recovery of impaired glucose tolerance. Moreover, Takeshita et al. (24) reported that BCAA-enriched LES for 14 days tempered the reduction of total protein and serum albumin levels and decreased the suppression of liver activity due to TACE in patients with HCC associated with cirrhosis. Thus, BCAA-enriched LES is a preferable nutritional treatment for liver cirrhotic patients to correct hypercatabolism and improve nutritional conditions such as nitrogen balance and serum albumin.

In the subset of 23 patients without HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion, BCAA-enriched nutrient mixtures significantly increased serum albumin levels, whereas they did not increase serum albumin levels in a subset of 17 patients with these criteria. Interventional treatment such as RFA/TACE/hepatectomy may further worsen their nutritional condition. Upper gastrointestinal tract bleeding also often worsens their nutritional condition. Albumin infusion therapy was applied only in patients with a serum albumin level of less than 2.5 g/dL. Thus, in the subset of patients with HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion may not be suitable for assessing the pure effects of BCAA-enriched nutrient mixtures. They have a significantly higher Child–Pugh score, a higher frequency of HCC, and a higher level of total bilirubin at baseline. Additional therapy with BCAA-enriched nutrient mixtures for LES is not likely to be effective in these patients with more severely progressed cirrhosis. In the subset of 23 patients without HCC treatment, upper gastrointestinal tract bleeding, or albumin infusion, serum albumin levels increased with the addition of BCAA-enriched nutrient mixtures only in the patients at Child–Pugh B. This suggests that the additional therapy with BCAA-enriched nutrient mixtures was effective in the patients at Child–Pugh B.

The present study revealed significant increases in total protein at 6 months after baseline, but no significant improvements in platelets, total bilirubin, cholinesterase, serum ammonia, total lymphocyte count, and hemoglobin A1c occurred during additional therapy with BCAA-enriched nutrient mixtures. An elevation of hemoglobin A1c induced by the load of energy was not observed (data not shown).

There were several limitations in the present study: 1) it was a retrospective study; 2) there was no control group; 3) the sample size was insufficient to provide significant differences in some indicators; 4) short-term observation to confirm the improvement of prognosis; and 5) a lack of nutritional parameters such as transthyretin and BCAA to tyrosine ratio. The preliminary findings of the present study requires further verification via a well-controlled, prospective, and long-term observation study to determine whether additional BCAA-enriched nutrient mixtures are better than the single use of BCAA granules.

In conclusion, additional therapy with BCAA-enriched nutrient mixtures increased the serum albumin level of cirrhotic patients with hypoalbuminemia despite the treatment with BCAA granules, and this additional therapy is one of the useful options for patients with decompensated cirrhosis.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - A.F., N.K., K.Y.; Design - A.F., N.K., K.Y.; Supervision - H.K., K.Y.; Resource - A.F., N.K., S.H., M.M., T.N., H.S., T.K., K.N., M.O., Y.T.; Materials - A.F., N.K., S.H., M.M., T.N., H.S., T.K., K.N., M.O., Y.T.; Data Collection &/or Processing - A.F.; Analysis &/or Interpretation - A.F., N.K., K.Y.; Literature Search - A.F.; Writing - A.F.; Critical Reviews - K.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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