Table 1 Baseline characteristics of patients

	All patients ($n = 50$)	Patients who started entecavir ($n = 20$)
Age (years)†	50 ± 13	50 ± 14
Sex (male/female)‡	28/22	14/6
Body mass index (kg/m^2)†	22.4 ± 2.7	22.1 ± 2.8
ALT (IU/L)§	75 (40–125)	111 (67–186)
Platelet count (×10^9/L)†	158 ± 63	152 ± 57
HBeAg (+/−)‡	27/23	8/12
HBV DNA ($\log_{10}$ copies/mL)†	5.9 ± 2.1	7.0 ± 1.1
HBV genotype (A/B/C/D)‡	1/4/39/0	1/2/17/0
Grade of necroinflammation‡ (A1/A2/A3)	19/17/2	10/6/1
Stage of fibrosis‡ (F1/F2/F3/F4¶)	20/10/5/15	6/8/4/2

†Mean ± SD; ‡Numbers of patients; §Median (interquartile range). ¶F4 includes cirrhosis clinically diagnosed on the basis of specific signs.
ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

$P = 0.0014$). At the F1 to F4 stages of fibrosis, there was no significant correlation of liver stiffness with serum ALT levels ($r = 0.40$, 0.097, 0.60, and 0.11; $P = 0.083$, 0.77, 0.23, and 0.69, respectively) or with histological necroinflammatory activity ($r = 0.10$, 0.12, 0.71, and 0.50; $P = 0.67$, 0.73, 0.16, and 0.48, respectively).

Liver stiffness during entecavir treatment

Among the 20 patients who started entecavir, 6 (30%) were histologically classified as F1, 8 (40%) as F2, 4 (20%) as F3, and 1 (5%) as F4; cirrhosis was clinically diagnosed in 1 (5%) patient. Serum HBV DNA levels decreased to below the lower detection limit of the PCR assay in 8 (40%) patients at 3 months, 16 (80%) patients at 6 months, and 19 (95%) patients at 12 months. Serum ALT levels decreased to within the reference range in 5 (25%) patients at 3 months, 12 (60%) patients at 6 months, and 14 (70%) patients at 12 months. The changes in liver stiffness during the first 12 months of entecavir treatment are shown in Figure 3. Median liver stiffness (interquartile range) significantly decreased from 11.2 (7.0–15.2) kPa to 7.8 (5.1–11.9) kPa ($P = 0.0090$) during the 12 months. The rate of decrease in liver stiffness did not correlate with the rate of decrease in serum ALT levels ($r = 0.38$; $P = 0.88$).

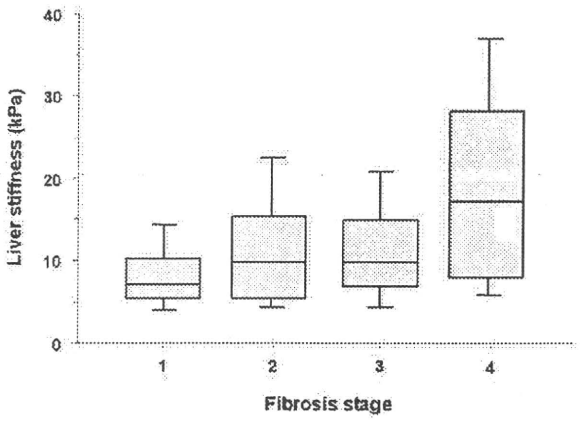

Figure 2 Box plots of liver stiffness measurements according to the stage of fibrosis in all patients with chronic hepatitis B virus. The length of the box represents the interquartile range, within which 50% of the values are located. The lines in the boxes represent the median values. The error bars represent the minimum and maximum values (range). The stage of fibrosis significantly correlated with liver stiffness ($r = 0.46$; $P = 0.0014$).

Serum fibrosis markers during entecavir treatment

The changes in serum fibrosis marker levels during the first 12 months of therapy in the 20 patients treated with entecavir are shown in Figure 4. Median PIIINP levels significantly decreased from 0.9 (0.6–1.3) U/mL to 0.6 (0.5–0.7) U/mL ($P = 0.0010$). Median levels of type IV collagen 7S domain significantly decreased from 5.0 ng/mL (4.4–6.7) to 3.9 ng/mL (3.2–4.4; $P = 0.015$). The rate of decrease in liver stiffness significantly correlated with the rate of decrease in serum PIIINP levels ($r = 0.46$; $P = 0.040$), but not with the rate of decrease in type IV collagen 7S domain levels ($r = 0.27$; $P = 0.26$).

Case presentations

Figures 5 and 6 show the results of paired liver biopsies in two patients, performed at baseline and after

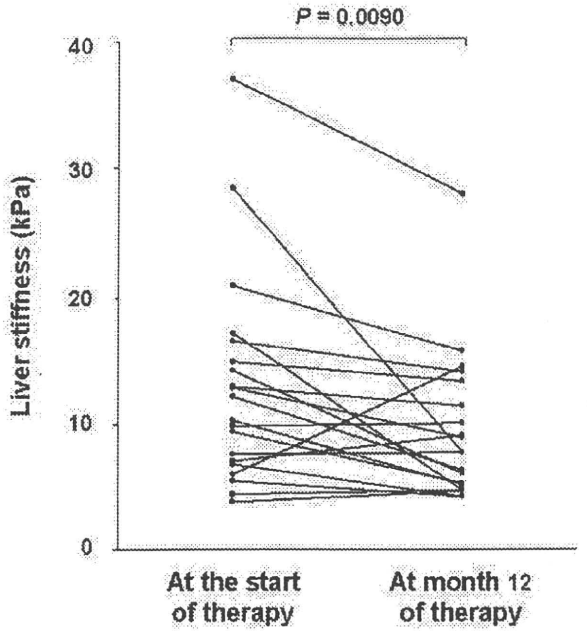

Figure 3 Changes in liver stiffness during the first 12 months of therapy in the 20 patients treated with entecavir. Median liver stiffness (interquartile range) significantly decreased from 11.2 kPa (7.0–15.2) to 7.8 kPa (5.1–11.9; $P = 0.0090$) during the 12 months.

12 months of entecavir treatment. One patient (case 1) was a 41-year-old man in whom the percentage decrease in liver stiffness was highest during the 12 months of treatment (28.4 kPa at baseline, 7.8 kPa at 12 months). The pretreatment HBV DNA level was 7.4 $\log_{10}$ copies/mL and became undetectable on PCR by month 6. The ALT activity was 215 IU/L and fell to the normal range by month 6. The histological grade and stage improved from A2/F4 to A1/F3. The proportion of fibrosis area on morphometric analysis decreased from 12.3% to 8.3% in specimens stained with Sirius red (Fig. 5a) and from 7.0% to 3.7% in specimens stained with α-smooth muscle actin (Fig. 5b). Serum markers of liver fibrosis also decreased (PIIINP, 1.4 U/mL to 0.5 U/mL; type IV collagen 7S domain, 7.1 ng/mL to 3.8 ng/mL).

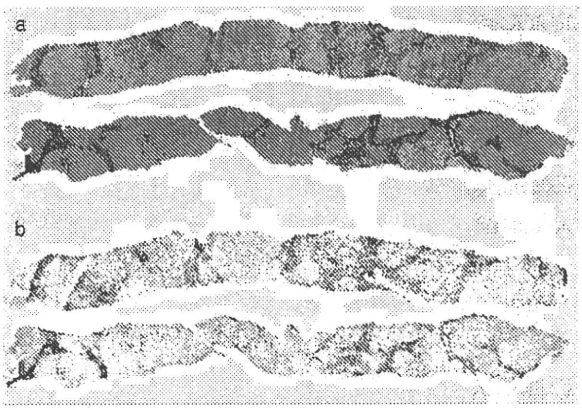

Figure 5 Paired liver biopsies performed in case 1 at baseline and after 12 months of entecavir treatment. The proportion of fibrosis area on morphometry decreased from (a) 12.3% at baseline to 8.3% after 12 months of therapy in specimens stained with Sirius red, and (b) from 7.0% to 3.7% in specimens stained with α-smooth muscle actin.

The other patient (case 2) was a 45-year-old man who had the greatest increase in liver stiffness (6.0 kPa at

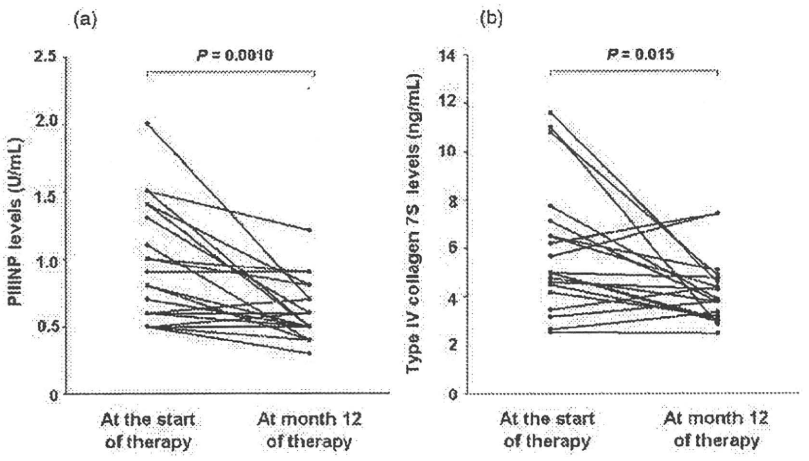

Figure 4 Changes in serum fibrosis marker levels during the first 12 months of therapy in the 20 patients treated with entecavir. There were significant decreases in the levels of (a) peptide of type III procollagen (PIIINP; $P = 0.0010$) and (b) type IV collagen 7S domain in serum ($P = 0.015$).

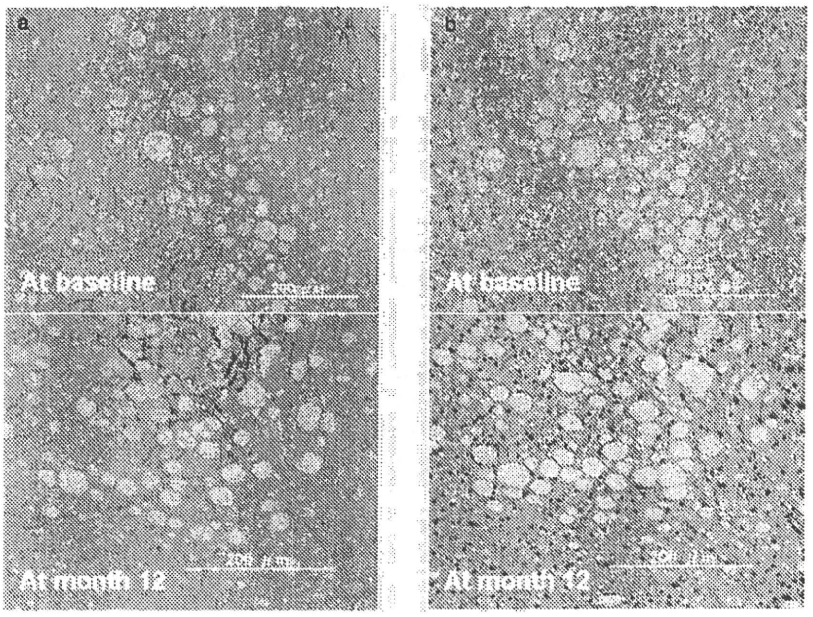

Figure 6 Paired liver biopsies performed in case 2 at baseline and after 12 months of entecavir treatment. The proportion of fibrosis area on morphometry increased from (a) 3.4% to 4.4% on Sirius red staining, and (b) from 0.9% to 1.5% on α-smooth muscle actin staining. At baseline, hepatic steatosis involved less than 5% of the biopsy specimen; the presence of steatosis was noted at the second biopsy involving about 20% of the specimen. The perisinusoidal/pericellular fibrosis was seen around hepatocytes distended by steatosis.

baseline to 14.5 kPa at 12 months). He did not drink alcohol, but body weight increased by 3.0 kg during the 12 months of treatment. Although the HBV DNA level rapidly decreased from 7.6 $\log_{10}$ copies/mL to below the detection limit by month 7, ALT activity did not fall significantly from baseline value (41 IU/L). The results of histological evaluations were unchanged on the paired biopsies performed 12 months apart (A1/F2). The proportion of fibrosis area on morphometric analysis increased from 3.4% to 4.4% on Sirius red staining (Fig. 6a) and from 0.9% to 1.5% on α-smooth muscle actin staining (Fig. 6b). On the second biopsy, the presence of hepatic steatosis was noted, involving about 20% of the biopsy specimen; perisinusoidal/pericellular fibrosis was seen around hepatocytes distended by steatosis. Serum fibrosis markers also did not decrease (PIIINP, 0.9 U/mL to 0.9 U/mL; type IV collagen 7S domain, 4.8 ng/mL to 5.0 ng/mL).

DISCUSSION

OF THE 50 patients studied, 45 were Japanese, two were Chinese, two Korean, and one Philippine. In Japan and other countries in east Asia, genotype C is the most prevalent type of HBV,[18,19] and most patients with chronic HBV acquire the virus perinatally or in early childhood.[20] The rates of virological and biochemical responses to interferon are thus lower than those reported in Europe and the United States. Guidelines proposed by the Japanese Study Group of the Standardization of Treatment of Viral Hepatitis Including Cirrhosis recommend that nucleos(t)ide-naïve patients with chronic HBV who are 35 years or older should receive entecavir as the treatment of choice.[21] In our patients, characterized by a predominance of genotype C, the rate of response to entecavir was similar to the rates obtained in randomized controlled trials conducted worldwide.[4,5]

Liver stiffness as measured by transient elastography significantly correlated with the stage of fibrosis in our patients with chronic HBV (Fig. 2), consistent with the results of previous studies.[12,13] Factors other than fibrosis, including necroinflammatory activity,[22–24] obesity,[25] and extrahepatic cholestasis,[26] can affect the results of liver stiffness measurement. In particular, chronic HBV is associated with more frequent acute exacerbations than chronic hepatitis C. In this study, we did not include patients with acute exacerbation. There was no significant correlation between liver stiffness and serum ALT levels or histological necroinflammatory activity. No patient was obese as defined by a body mass index of >30 kg/m^2.

Liver stiffness measurement is generally less accurate for the diagnosis of liver fibrosis in chronic HBV than in chronic hepatitis C.[27] In previous studies that included both chronic HBV and C,[28,29] median liver stiffness at each stage of fibrosis was lower in chronic HBV than in

chronic hepatitis C. The reported cutoff value for predicting cirrhosis in chronic HBV ranged from 9.0 to 11.0 kPa,[30,31] which is lower than 13.0 kPa, the optimal cutoff value based on a meta-analysis of 17 studies of various chronic liver diseases (mostly chronic hepatitis C).[13] In the present study, liver stiffness was lower than 13.0 kPa in 5 (33%) of the 15 patients with cirrhosis (data not shown). In addition, it was difficult to predict advanced fibrosis (≥F3), since median liver stiffness was similar in F2 and F3 (9.8 kPa). One possible explanation for difference in diagnostic accuracy is that the amount of fibrosis in the cirrhotic liver is lower in chronic HBV than in chronic hepatitis C because macronodular cirrhosis, characterized by large nodules delimited by thin septa, is more common in patients chronically infected with HBV.

Median liver stiffness as measured by transient elastography significantly decreased during the 12 months of entecavir treatment (Fig. 3). Our results may reflect an improvement in liver fibrosis by treatment with entecavir, similar to that demonstrated in a *post hoc* descriptive analysis of randomized controlled trials.[6] To exclude the possibility that the decrease in liver stiffness was caused by regression of necroinflammatory activity, we also measured the levels of serum markers of liver fibrosis. In general, liver fibrosis markers can be divided into two groups, either direct or indirect. Direct markers of fibrosis reflect serum extracellular matrix turnover. For example, PIIINP, a product formed by cleavage of procollagen III, is released into the serum during matrix deposition.[32] Type IV collagen 7S domain is located in basement membranes and released during interstitial filament degradation, thereby reflecting matrix degradation.[33] In this study, both markers significantly decreased during the 12 months of entecavir treatment (Fig. 4).

Indirect markers of liver fibrosis reflect alterations in hepatic function, but do not directly reflect hepatic extracellular matrix metabolism. Indirect markers include platelet count, the results of coagulation studies, hepatic aminotransferases, and combined indices/scores derived from these variables. Combined indices/scores such as aspartate aminotransferase/ALT ratio,[34] aspartate aminotransferase-to-platelet ratio index,[35] cirrhosis discriminant score,[36] and Lok index,[37] are not suitable for on-treatment assessment of liver fibrosis in chronic HBV, because these indices/scores include hepatic aminotransferases, which rapidly decrease after the start of antiviral treatment.

Many studies have shown significant correlations between the results of morphometric image analysis and those of semiquantitative histological staging,[38,39] although potential limitations of morphometry include the sampling error. On liver biopsy, only 1/50 000 of the organ (and 1/100 of the region of interest for liver stiffness measurement) is analyzed. In addition, to accurately measure liver fibrosis, it is necessary to carefully exclude necroinflammation in fibrous areas, requiring significant time and labor, even for a trained hepatopathologist. We did a morphometric analysis in two patients with paired liver biopsy specimens stained with Sirius red for collagen or with α-smooth muscle actin for activated hepatic stellate cells. One patient (case 1) showed regression of both histological stage and extent of fibrosis on morphometry. The results of liver stiffness measurement and serum fibrosis markers also improved. More interestingly, in the other patient (case 2), both the extent of fibrosis as estimated by morphometry and liver stiffness increased, despite a virological response to entecavir. We speculate that pericellular fibrosis caused by steatohepatitis was the main cause of increase in liver stiffness in this patient. In the previous study,[40] liver stiffness correlated more strongly with pericellular fibrosis than with periportal or perivenular fibrosis. The histological stage of fibrosis was unchanged, probably because it reflects liver architectural abnormalities, not directly the amount of fibrosis. If liver stiffness increases during antivairal treatment for chronic HBV, liver biopsy should be considered to exclude other potential causes of chronic liver disease.

The major limitation of this study is the short duration of observation during entecavir treatment. In the 5 patients treated with entecavir for more than 24 months, median liver stiffness decreased slightly, but not significantly from 7.8 kPa to 7.0 kPa during the second 12 months of entecavir treatment (data not shown). The decrease in liver stiffness during the second 12 months of treatment might be attributed solely to an improvement in liver fibrosis, not an improvement in necroinflammation. Another limitation of this study is the small number of patients. The rate of decrease in liver stiffness significantly correlated with rate of decrease in the serum level of PIIINP, but not with that of type IV collagen 7S domain, possibly because of an insufficient number of patients. Larger studies are required to confirm the usefulness of transient elastography as a tool for on-treatment monitoring of the regression of liver fibrosis.

In conclusion, transient elastography is a rapid, noninvasive, objective, and promising technique for the assessment of fibrosis by measuring liver stiffness in

patients with chronic HBV, as well as those with chronic hepatitis C virus. Liver stiffness measurement might be useful for monitoring regression of liver fibrosis during entecavir treatment for chronic HBV.

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Original Paper

Comparison of the Effect of BCAA Granules on Between Decompensated and Compensated Cirrhosis

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ABSTRACT

Background/Aims: We designed a randomized trial to examine whether increase or preservation of serum albumin levels was attained with administration of branched-chain amino acid (BCAA) granules for compensated cirrhosis, compared with decompensated cirrhosis.

Methodology: Sixty-five patients with HCV-related cirrhosis with serum albumin level less than 4.0 g/dl were enrolled in this study. Half of the patients were randomly assigned to receive 14.22 g/day of BCAA granules orally, and half were assigned to a control group. Patients were evaluated at entry and at 1-year intervals for at least 2 years. The parameters were divided into 3 categories. Class 1 was decompensated cirrhosis with serum albumin level less than 3.5 mg/dl. Class 2 was compensated cirrhosis with serum albumin level over 3.6 mg/dl and molar ratio of BCAA to tyrosine (BTR) less than 4. Class 3 was compensated cirrhosis with serum albumin level over 3.6 mg/dl and BTR over 4.

Results: In class 1 and class 2, the BCAA group exhibited significantly higher rates of maintaining serum albumin level than the control group for 2 years. In contrast, there was no significant difference between the BCAA group and control group in rate of maintaining serum albumin levels in class 3.

Conclusions: Those results suggested that if cirrhotic patients were in the compensated stage at the entry but with lower BTR, as for decompensated cirrhosis, oral BCAA supplementation might be effective in maintaining serum albumin level for 2 years.

KEY WORDS: LHCV–related cirrhosis; Branched–chain amino acid; Serum albumin level; Branched–chain amino acid tyrosine ratio (BTR)

ABBREVIATIONS: Branched–Chain Amino Acid (BCAA)

INTRODUCTION

Oral administration of BCAA for the purpose of improving hepatic encephalopathy or hypo- albuminemia with decompensated cirrhosis is generally accepted in Japan (1, 2). We have suspected that, for at least some patients oral supplementation of BCAA for compensated cirrhosis can maintain serum albumin level and hinder dropping into the decompensated stage. We therefore planed the randomized control trial with HCV-related cirrhosis to compare the effect of oral supplementation of BCAA between decompensated cirrhosis and compensated cirrhosis in changes in serum albumin level over 2 years.

METHODOLOGY

Patients and Methods

Sixty-five patients with HCV-related cirrhosis with serum albumin level under 4.0 g/dl who visited our hospital between December 1998 and November 1999 were enrolled in this study. None of the patients had previously been given BCAA supplementation. No patients had hepatocelluar carcinoma, hepatitis B virus infection or other liver diseases such as autoimmune hepatitis, primary biliary cirrhosis and alcoholic liver disease at entry. Diagnosis of cirrhosis was made based on the council system by not less than three hepatologists based on abdominal ultrasonography (3). Entry characteristics of the patients are shown in **Table 1**.

Half of the patients were randomly assigned to receive 14.22 g/day of BCAA granules (Livact; Ajinomto Co. Tokyo, Japan) orally (BCAA group), and half were assigned to a controls (control group). All patients were underwent diet education to maintain total calorie: 30 kcal/kg and protein 1.3g/kg (including BCAA granules 14.22 g/day for BCAA group) a day for standard body weight (height(m)2x22) and in principal kept this diet through the study period. All patients gave written informed consent. The procedures used accorded with the Helsinki Declaration (1996) and were approved by the Ethics Committee of Osaka City University Medical School.

Hepato-Gastroenterology 2009; 56:1719-1723

TABLE 1 Baseline Characteristics of the Patients

	Patients
Sex (male/female)	22/38
BCAA/Control	28/32
Average age	65.1 + 6.9
Average BTR	3.6 + 1.0
BTR<4 / BTR>4	38/22
Albumin (g/dl)	3.6 + 0.3
Alb<3.5 / Alb>3.5	25/35
Platelets (10^4/mm^3)	11.0 + 5.5
Pl<10 / Pl>10	29/31
ALT (IU/l)	100.8 + 63.4
ALT>80 / ALT<80	36/24
Average T-bilirubin (mg/dl)	1.1 + 0.5
T-Bil>1.0 / T-Bil<1.0	26/34

Patients were evaluated at entry and at 1-year intervals for at least 2 years. We evaluated results as follows: Increase in serum albumin level over 0.2mg/dl compared with serum albumin level at entry was evaluated as "increased". Decrease in serum albumin level over 0.2mg/dl compared with serum albumin level at entry was evaluated as "decreased". Other patients were in the "unchanged group".

At entry, we measured serum molar concentrations of branched-chain amino acids divided by those of tyrosine (branched-chain tyrosine ratio; BTR). BTR were measured by an enzymatic method (Ono Pharmaceutical Co., Ltd., Osaka, Japan). Normal range of BTR is from 5.82 to 8.64. The clinical significance of the results obtained resemble those for Fisher's ratio (4-7).

We divided the parameters into 3 categories. Class 1 was de-compensated cirrhosis with serum albumin level less than 3.5 mg/dl. Class 2 was compensated cirrhosis with serum albumin level over 3.6 mg/dl and BTR less than 4. Class 3 was compensated cirrhosis with serum albumin level over 3.6 mg/dl and BTR over 4. For division of patients into class 2 and class 3, we chose a BTR of 4.0 (which corresponds roughly to Fischer's ratio of 2.0), for two reasons. First, 4.0 is the lower limit of the reference range (4). Second, another cross-sectional study showed that a significantly larger population of patients with cirrhosis (mostly viral) and with a BTR of less than 4 had esophageal varices or portal hypertension (or both) than similar patients with higher BTR (unpublished). A scatter graph representing the relationship between serum albumin level and BTR of the parameters is shown in **Figure 1**.

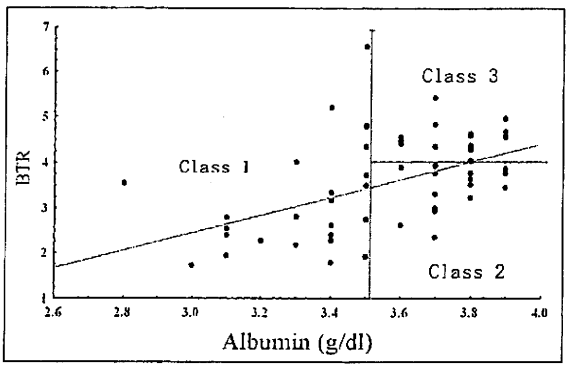

FIGURE 1 Scatter graph representing the relationship between serum albumin level and BTR of the parameters

The number of patients in class 2 was almost equal to that in class 3. Twenty-eight patients in the BCAA group and 32 in the control group completed 2 years of treatment. Four patients in the BCAA group and one in the control group dropped out.

At entry, we measured serum albumin, total bilirubin, ALT and platelets. Baseline characteristics of the 3 groups are shown in **Table 2**.

Statistical analysis

For statistical testing, the chi-square test for independence was used. Differences with $p < 0.05$ were considered statistically significant. Five baseline variables were assessed in the study, including serum albumin, BTR, total bilirubin, ALT level and platelet cell counts. Multivariate analysis was performed to determine the significance of the parameters using a proportional odds model.

RESULTS

Comparison of serum albumin levels at 2 years since enrollment between BCAA group and control group in class 1 (**Table 3**).

The BCAA group exhibited a significantly higher rate of maintenance of serum albumin level compared with enrollment than the control group (chi-square test for independence: p =0.02).

Comparison of serum albumin levels at 2 years since enrollment between BCAA group and control group in the class 2 (**Table 4**).

The BCAA group exhibited a significantly higher rate of maintenance of serum albumin level compared with enrollment than the control group (chi-square test for independence: p=0.02).

Comparison of serum albumin levels at 2 years since enrollment between BCAA group and control group in the class 3 (**Table 5**).

There was no significant difference between the BCAA group and control group in rate of maintenance of serum albumin levels (chi-square test for independence).

Results of multivariate analysis of BCAA supplementation using proportional odds model (**Table 6**).

No factors were selected as significant independent risk factors for maintenance of serum albumin levels by oral supplementation of BCAA granules.

TABLE 2 Baseline Characteristics of 3 Classes

	Class 1 (Alb < 3.5)	Class 2 (Alb>3.5, BTR<4)	Class 3 (Alb>3.5, BTR > 4)	
Sex (male/female)	11/14	6/12	5/12	ns
BCAA / Control	13/12	9/9	6/11	ns
Average age	64.3 + 4.9	63.8 + 7.0	67.5 + 8.8	ns
Average BTR	3.1 + 0.2	3.4 + 0.5**	4.6 + 0.3**	$p<0.001$
Albumin (g/dl)	3.3 + 0.2	3.8 + 0.1**	3.8 + 0.1**	$p<0.001$
Platelets ($10^4/mm^3$)	8.6 + 4.8	10.4 + 3.9*	15.1 + 5.8*	$p<0.01$
ALT (IU/l)	117.0 + 84.0	98.4 + 42.7	79.4 + 38.1	ns
Bilirubin (mg/dl)	1.3 + 0.5	1.0 + 0.3	0.9 + 0.4	ns

Wilcoxon rank-sum test for age, BTR, serum albumin, platelets, alanine aminotransferase (ALT) and total bilirubin; chi-square test for sex ratio and BCAA/Control ratio.

Results of multivariate analysis of maintenance of serum albumin levels in the control group using a proportional odds model (**Table 7**).

BTR only was selected as an independent risk factor for maintenance of serum albumin levels 2 years after enrollment in the control group.

DISCUSSION

As liver function deteriorates, ammonia metabolism in the liver slows downs, and in compensation muscles begin to detoxify ammonia, consuming serum BCAA (8). Another reason for low BTR is that tyrosine (in the denominator of the equation) increases as cirrhosis worsens because of protein breakdown (9). BCAA, especially leucine, help regulate gene expression and protein turnover. In the control group, BTR alone was selected as an independent risk factor for maintenance of serum albumin levels 2 years after the enrollment because lower level of BCAA might not trigger albumin synthesis (10).

It has been reported that correction of the BCAA to aromatic amino acid (AAA) ratio improves protein synthesis and that BCAA supplementation prevents degeneration of body protein in cirrhosis (11-13). The clinical safety and usefulness of supplementation of BCAA granules for decompensated cirrhosis has already been established (1, 14). The short-term usefulness of BCAA administration for liver cirrhosis has also already been reported (15, 16).

In this prospective trial, the results of patients in class 2 (with higher serum albumin and lower BTR) and those of patients in class 1 (decompensated cirrhosis with lower serum albumin level), were almost the same. In both classes, the BCAA group exhibited a significantly higher rate of maintenance of serum albumin levels compared with that at enrollment than the control group.

In contrast, there was no significant difference between the BCAA group and control group in rate of maintenance of serum albumin level in class 3. These results suggested that if cirrhotic patients are in compensated stage at entry but with lower BTR, as for decompensated cirrhosis, oral BCAA supplementation might be effective in maintaining serum albumin level for 2 years.

HCV-related cirrhosis with BTR less than 4 might be a stage in which insufficiency of BCAA has clearly occurred, and therefore oral supplementation of BCAA granules might be effective in maintaining serum albumin levels. In contrast, BTR over than 4 might be a stage in which insufficiency

TABLE 3 Effect of Oral BCAA Supplementation on Serum Albumin Level at 2 Years since Enrollment in Class 1

	Alb>0.2	0.1>Alb>-0.1	Alb<-0.2
BCAA	46% (6/13)	38% (5/13)	15% (2/13)
Control	8% (1/12)	25% (3/12)	67% (8/12)

The BCAA group exhibited a significantly higher rate of maintaining serum albumin levels compared with that at enrollment than the control group (chi-square test for independence: $p = 0.02$).

TABLE 4 Effect of Oral BCAA Supplementation on Serum Albumin Level at 2 Years since Enrollment in Class 2

	Alb>0.2	0.1>Alb>-0.1	Alb<-0.2
BCAA	44% (4/9)	44% (4/9)	11% (1/9)
Control	0% (0/9)	33% (3/9)	67% (6/9)

The BCAA group exhibited a significantly higher rate of maintaining serum albumin levels compared with that at enrollment than the control group (chi-square test for independence: $p = 0.02$).

TABLE 5 Effect of Oral BCAA Supplementation on Serum Albumin Level at 2 Years since the Enrollment in Class 3

	Alb>0.2	0.1>Alb>-0.1	Alb<-0.2
BCAA	67% (4/6)	17% (1/6)	17% (1/6)
Control	36% (4/11)	55% (6/11)	9% (1/11)

There was no significant difference between the BCAA group and control group in rate of maintaining serum albumin levels (chi-square test for independence).

TABLE 6 Risk Ratio of Increase or Decrease in Serum Albumin Level after 2 Years of Supplementation of Oral BCAA Granules

	Risk ratio	95% CI	*p* - value
Serum albumin	0.813	0.161 – 4.099	0.8016
BTR	0.788	0.117 – 5.299	0.8063
Total bilirubin	3.131	0.659 – 14.872	0.1510
ALT	1.400	0.291 – 6.736	0.6749
Platelet count	2.002	0.324 – 12..72	0.4553

Odds ratios are expressed as per 1 year for age. Since albumin value was categorized into two groups, >3.5 and <3.5g/dl, as were BTR > 4.0 and < 4, Total bilirubin < 1.0 and >1.0, ALT level < 80 and > 80 IU/ml, platelet count >100 and < 100 thousand / mm^3, odds ratios are indicated between each set of two groups.

TABLE 7 Risk Ratio of Increase or Decrease in Serum Albumin Level after 2 Years since Enrollment in Control Group

	Risk ratio	95% CI	*p* - value
Serum albumin	1.586	0.281 – 8.960	0.6015
BTR	9.444	1.524 – 58.521	0.0158
Total bilirubin	0.463	0.071 – 3.028	0.4214
ALT	1.549	0.322 – 7.452	0.5849
Platelet count	5.619	0.954 – 33.101	0.0564

Odds ratios are expressed as per 1 year for age. Since albumin value was categorized into two groups, >3.5 and <3.5 g/dl, as were BTR > 4.0 and < 4, Total bilirubin < 1.0 and >1.0, ALT level < 80 and > 80 IU/ml, platelet count >100 and < 100 thousand / mm^3, odds ratios are indicated between each set of two groups.

of BCAA has not clearly occurred yet, and therefore oral supplementation of BCAA granules might not significantly affect the synthesis of albumin.

Serum albumin level is an important regulatory factor for liver cirrhosis, and compensated cirrhosis with serum albumin level above 3.5g/dl appears to have a better prognosis (17-21). This trial suggested that oral supplementation of BCAA for compensated cirrhosis with BTR less than 4, which may have accounted for about half of patients with compensated cirrhosis in our study, was effective in maintaining serum albumin level and thus might improve prognosis, as well as it dose that of decompensated cirrhosis.

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LIVER TRANSPLANTATION 15:790-797, 2009

ORIGINAL ARTICLE

A Randomized Pilot Trial of Oral Branched-Chain Amino Acids in Early Cirrhosis: Validation Using Prognostic Markers for Pre-Liver Transplant Status

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Because of the chronic shortage of liver donors, hepatologists are required to prolong the liver transplant waiting period by preserving the hepatic reserve of scheduled recipients. This study examined the effectiveness of oral branched-chain amino acids (BCAAs), using outcome markers indicating pretransplant hepatic reserve. Fifty-six consecutive eligible patients with Child class A cirrhosis without major complications were randomly assigned to receive oral BCAA granules (12.45 g/day) for least 1 year or no BCAAs. Differences between groups in the Model for End-Stage Liver Disease (MELD) score, Child-Turcotte-Pugh (CTP) score, asialoscintigraphic clearance index (CI), and complications were examined. Of 50 remaining patients, 27 received BCAAs, and 23 received no BCAAs (mean duration, 3.2 years). The mean annual changes in the MELD score, CTP score, and asialoscintigraphic CI were smaller in the BCAA group than in the control group (-0.06 ± 0.23 versus 0.10 ± 0.40, $P = 0.024$, 0.06 ± 0.30 versus 0.30 ± 0.48, $P = 0.037$, and 0.00 ± 0.02 versus 0.02 ± 0.04, $P = 0.040$, respectively). The mean annual changes in the serum total bilirubin and the serum albumin in the BCAA group were better preserved than those in the control group (-0.07 ± 0.20 versus 0.12 ± 0.18 mg/dL, $P < 0.001$, and 0.07 ± 0.13 versus -0.02 ± 0.19 g/dL, $P = 0.005$, respectively); other laboratory variables were not significant. The incidence of overall major cirrhotic complications was lower in the BCAA group than in the control group [14.8% (4 of 27 patients) versus 30.4% (7 of 23 patients) at 3 years, $P = 0.043$]; only ascites was significant individually. In conclusion, early interventional oral BCAAs might prolong the liver transplant waiting period by preserving hepatic reserve in cirrhosis. ***Liver Transpl 15:790-797, 2009.***

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The 5-year survival rate after liver transplantation has recently been improved to 70% to 75%.[1] Liver transplantation is the only means available for the radical treatment of severe liver cirrhosis. All patients with liver cirrhosis have the potential to become liver recipients in the near future. Furthermore, the 5-year survival rate

Abbreviations: 99mTc-GSA, technetium-99m diethylenetriaminepentaacetic acid galactosyl human serum albumin; BCAA, branched-chain amino acid; CI, clearance index; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HGF, hepatocyte growth factor; MELD, Model for End-Stage Liver Disease; mTOR, mammalian target of rapamycin.

The registration number is UMIN000001360 (http://www.umin.ac.jp/ctr/index.htm).

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following liver transplantation has been improved to 65% to 80% even in patients whose condition is complicated by hepatocellular carcinoma (HCC).[2] Liver transplantation thus appears to be the best means of dealing with HCC satisfying the Milan criteria.[3] However, because of the shortage of liver donors with respect to the growing demand for liver transplantation, the mortality rate of patients during the liver transplant waiting period has been rising markedly (currently about 20%-30%) across the world.[4] The posttransplant survival rate decreases as the pretransplant waiting period lengthens, with a reduction of hepatic reserve.[5] Hepatologists thus need to suppress the reduction of hepatic reserve as long as possible in patients with liver cirrhosis awaiting liver transplantation.

Pre–liver transplant nutritional status is one of the major factors associated with outcome after transplantation. Protein-energy malnutrition associated with liver cirrhosis is already observed in the compensated phase.[6] Controversy continues because of the limited clinical evidence available to clarify the optimal time for initiation of oral branched-chain amino acid (BCAA) supplementation for cirrhosis,[7,8] although anecdotal findings suggest that nutritional intervention should begin in an early stage of disease.[9] It is clear that liver transplantation has been carried out with inadequate nutritional control. We believe that improving nutritional status helps to delay a fatal reduction of hepatic reserve in patients with early liver cirrhosis registered in waiting lists for liver transplantation. We planned a pilot study to examine whether oral BCAA treatment, begun in the early stages of liver cirrhosis, can preserve hepatic reserve until a liver donor becomes available.

In the present study, we used the Model for End-Stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) scores, the asialoscintigraphic clearance index (CI), and major cirrhotic complications as markers for pretransplant status.[10-12] The natural course of hepatic reserve is transient in cirrhosis, and the disease rapidly becomes worse with Child class B cirrhosis.[13] The present study was designed to use these markers to evaluate the efficacy of oral BCAAs for patients with uncomplicated Child class A cirrhosis who may be registered in transplantation waiting lists.

PATIENTS AND METHODS

The study was performed at the Department of Hepatology of Osaka City University Hospital in an open-label, randomized, controlled parallel group design. The inclusion criteria were as follows: (1) an age of 20 to 75 years; (2) Child class A cirrhosis; and (3) hepatitis C virus, hepatitis B virus, or alcohol-related cirrhosis. Patients with other types of cirrhosis were excluded because of their extremely low prevalence in Japan. Patients were also excluded if they (1) had received an albumin infusion at least once per week for 1 month or longer, (2) had a history of oral BCAA supplementation/dietary protein restriction for 6 months or longer, (3) had major complications of cirrhosis such as HCC, ascites, esophagogastric varices, or hepatic encephalopathy, or (4) had other nonhepatic major diseases. The study protocol agreed with the Helsinki Declaration and was approved by the Ethics Committee of Osaka City University Medical School. Each patient provided written informed consent.

Study Design

Eligible patients were randomly assigned to receive oral BCAAs or no BCAAs by the study investigators according to a computer-generated list. The date of study entry was defined as the date of initial asialoscintigraphy. Investigators were informed of treatment assignments on the same day, and BCAA therapy was started within 1 week.

The primary endpoint of the study was the incidence of cirrhosis-related complications after enrollment. Such complications included the first confirmation of HCC, ascites, esophagogastric varices, and hepatic encephalopathy. Eligible patients had to undergo the assigned treatment for at least 1 year. Secondary endpoints were defined as the receipt of any of the following treatments, which can influence outcome markers, including the MELD score, CTP score, and asialoscintigraphic CI: (1) an albumin infusion for ascites; (2) endoscopic sclerotherapy/ligation for varices; (3) open surgery, interventional radiological procedures, or percutaneous local ablation for HCC; and (4) parenteral BCAAs for hepatic encephalopathy.

Baseline Assessments

All patients underwent a pretrial evaluation that included an evaluation of hepatic reserve as follows: laboratory studies and assessment of physical findings required to calculate the MELD score and CTP score, abdominal ultrasonography or dynamic computed tomography to assess the extent of ascites or the existence of HCC, endoscopy to evaluate esophagogastric varices, and scintigraphy with technetium-99m diethylenetriaminepentaacetic acid galactosyl human serum albumin (99mTc-GSA; Asialoscinti Injectable, Nihon Medi-Physics., Inc., Tokyo, Japan). For scintigraphy, computer acquisition of data with a gamma camera (Vertex-Plus, ADAC Laboratories Inc., Silicon Valley, CA) was started just before the injection of 185 MBq of 99mTc-GSA. After the acquisition of 20-minute summed digital images (128 × 128 pixels), the asialoscintigraphic CI was calculated by the division of the radioactivity in the region of interest in the heart 15 minutes after injection by that in the heart region of interest 3 minutes after injection.[14]

Contents of the Daily Nutritional Treatment

Patients in the BCAA group received a cirrhotic diet supplemented with a Japanese nutritional preparation (LIVACT, Ajinomoto Co., Inc., Tokyo, Japan; 4.15 g of BCAA granules per sachet containing 952 mg of L-isoleucine, 1904 mg of L-leucine, and 1144 mg of L-valine) 3 times daily. The daily cirrhotic diet consisted of a total caloric intake of 25 to 35 kcal/kg and a protein intake of

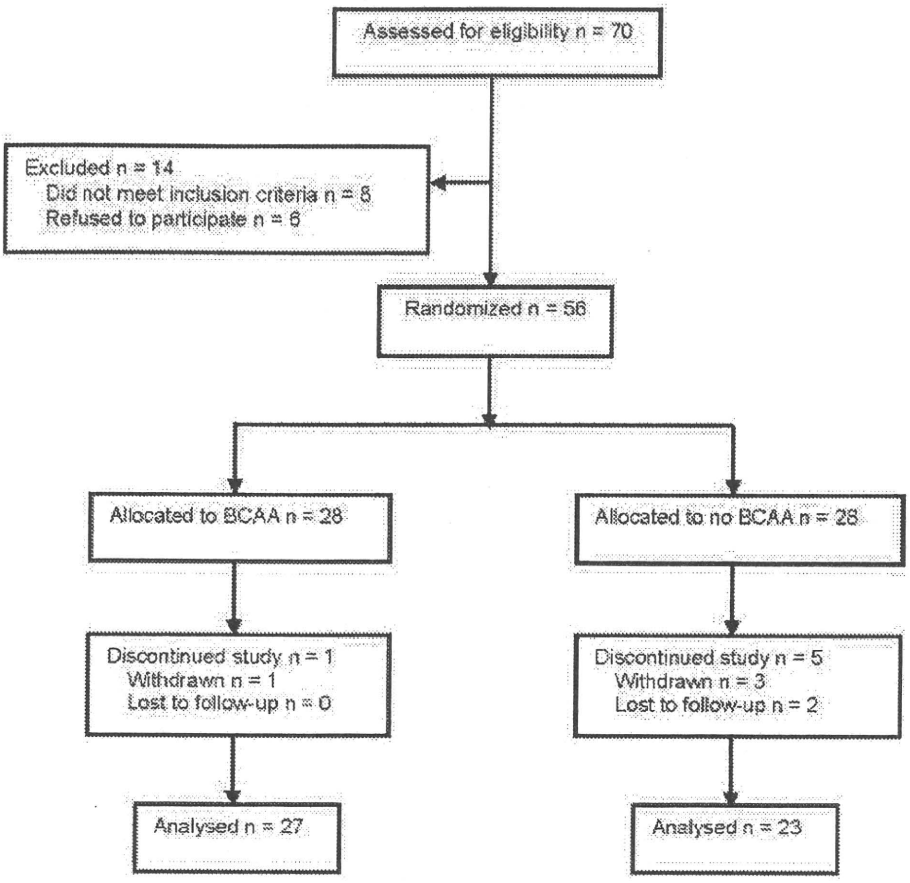


Figure 1. Flow chart of the participants in the study. Abbreviation: BCAA, branched-chain amino acid.

1.0 to 1.2 g/kg (including 12.45 g/day BCAAs in the BCAA group), and it was adjusted to the standard body weight [height $(m)^2 \times 22$] according to the guidelines of the European Society of Parenteral and Enteral Nutrition.[15] All patients received the same dietary instructions throughout the study. Patients in the control group received the same dietary instructions without BCAAs. All patients completed questionnaires on their diet at 6-month intervals after enrollment. Patients with excessive or deficient dietary intakes of energy or protein were given written dietary instructions prepared by the dietitians at our hospital.

Follow-Up

Patients underwent the following follow-up examinations: laboratory studies, including serum total bilirubin, albumin, and creatinine levels, prothrombin activity, and other clinical findings at a mean interval of 0.3 years; abdominal ultrasonography or dynamic computed tomography at a mean interval of 0.4 years; endoscopy at a mean interval of 0.5 years; and asialoscintigraphy at a mean interval of 1.0 year. Needle biopsy specimens of the liver were obtained and examined histologically as needed in patients with suspected liver tumors.

Statistical Analysis

Results were analyzed with SAS 9.1 statistical software (SAS Institute, Inc., Cary, NC). Continuous variables were expressed as mean ± standard deviation and were compared with the Mann-Whitney *U* test. Categorical variables were compared with Fisher's exact test or the chi-square test. Annual changes in the MELD score, CTP score, asialoscintigraphic CI, and laboratory results related to hepatic function were calculated by the division of the difference between the results of the first examination and those of the last examination by the interval (ie, duration of follow-up in years) between these 2 examinations. The cumulative rates of complications were calculated and plotted with the Kaplan-Meier method and compared with the log-rank test. A 2-tailed *P* value of <0.05 was considered to indicate statistical significance.

Given the magnitude of this sample size and the lack of definitive evidence establishing that early interventional oral BCAAs reduce risk,[16] we decided to perform a pilot study in 70 patients.

RESULTS

Of 70 outpatients with liver cirrhosis, 14 were ineligible, and 56 (27 men and 29 women; mean age, 62.52 years)

TABLE 1. Pretrial Characteristics of the Patients

	BCAA Group (n = 27)	Control Group (n = 23)	*P*
Age (year)*	62.70 ± 10.08	62.30 ± 7.30	0.537
Sex ratio (male:female)	13:14	12:11	>0.999†
Etiology (HCV:HBV:alcohol)	22:3:2	19:2:2	0.951‡
Total bilirubin (mg/dL)*	0.97 ± 0.51	0.96 ± 0.34	0.550
Albumin (g/dL)*	3.70 ± 0.38	3.81 ± 0.32	0.230
Platelets ($\times 10^4/\mu L$)*	11.52 ± 4.85	11.10 ± 5.01	0.616
Alanine aminotransferase (IU/L)*	70.92 ± 17.96	64.17 ± 13.51	0.095
Prothrombin activity (%)*	81.52 ± 10.55	84.39 ± 13.39	0.802
Creatinine (mg/dL)*	0.68 ± 0.16	0.63 ± 0.13	0.230
Cholinesterase (IU/L)*	349.07 ± 151.57	322.83 ± 116.92	0.616
Cholesterol (mg/dL)*	153.19 ± 25.64	156.05 ± 42.12	0.913
BCAA/tyrosine ratio*	4.11 ± 0.20	3.98 ± 0.91	0.712
α-Fetoprotein (ng/mL)*	10.93 ± 5.12	14.1 ± 2.43	0.805
Body mass index (kg/m^2)*	22.55 ± 2.10	24.01 ± 0.29	0.707
MELD score*	6.88 ± 0.98	7.01 ± 0.72	0.187
CTP score*	5.41 ± 0.50	5.22 ± 0.42	0.253
Asialoscintigraphic clearance index*	0.61 ± 0.09	0.60 ± 0.11	0.685
Hepatocellular carcinoma (absence:presence)	27:0	23:0	>0.999†
Ascites (absence:presence)	27:0	23:0	>0.999†
Esophagogastric varices (absence:presence)	27:0	23:0	>0.999†
Hepatic encephalopathy (absence:presence)	27:0	23:0	>0.999†

NOTE: Unless otherwise indicated, comparisons were made by the Mann-Whitney U test.
Abbreviations: BCAA, branched-chain amino acid; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease.
*Data are shown as mean ± standard deviation.
†Fisher's exact test.
‡Chi-square test.

were randomly assigned to receive oral BCAAs (n = 28, BCAA group) or no BCAAs (n = 28, control group; Fig. 1). The diagnosis of liver cirrhosis was made clinically by a team of 3 or more hepatologists. Because liver biopsy is invasive, it is difficult to perform this test in all patients. Of the 56 patients, 41 (22 from the BCAA group and 19 from the control group) underwent liver biopsy. In the remaining 15 patients, the diagnosis was made with the findings of diagnostic imaging (eg, abdominal ultrasonography) and hematological and biochemical tests taken into account.[17] Six patients were lost to follow-up. The remaining 50 patients were included in the final analysis. The mean duration of therapy was 3.2 years (range, 1.0-6.3 years). The BCAA group and control group were similar with respect to the virus type, total bilirubin, albumin, prothrombin activity, MELD score, CTP score, asialoscintigraphic CI, and other variables (Table 1).

Compliance and Adverse Effects of BCAA Treatment

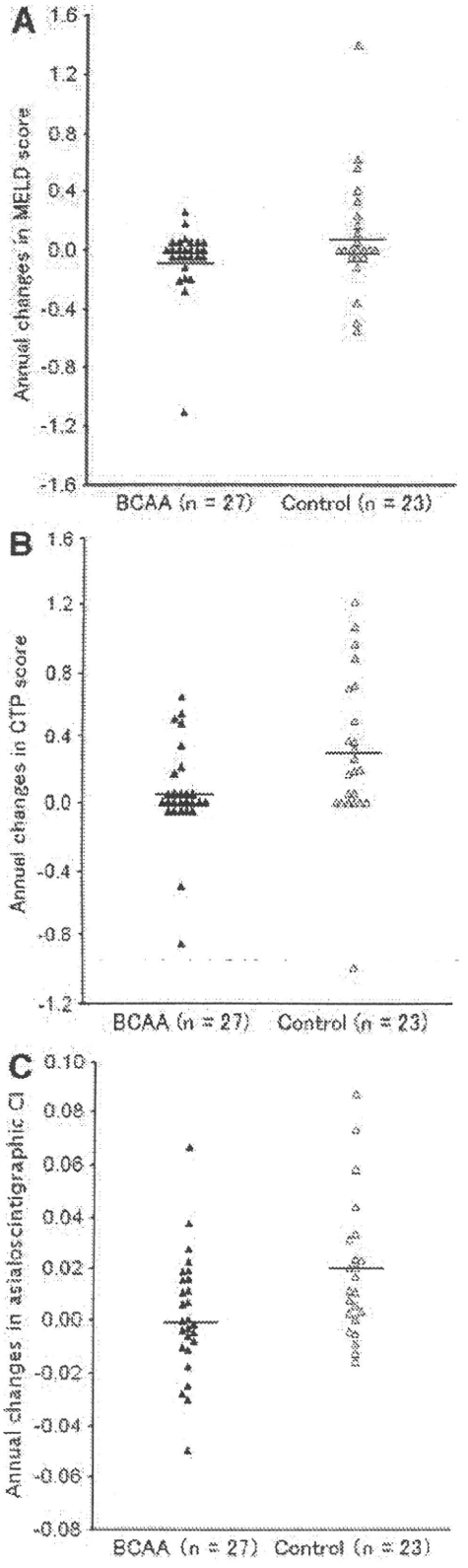
Of 28 patients in the BCAA group, 27 continued to take BCAA granules (12.45 g/day) for at least 1 year [mean duration, 3.3 years (range, 1.3-6.2 years)]. No adverse reactions to the BCAA treatment were found in any patient.

Outcome Measures Related to Hepatic Function

The mean annual change in the MELD score was significantly smaller in the BCAA group than in the control group (−0.06 ± 0.23 versus 0.10 ± 0.40, $P = 0.024$; Fig. 2A). The mean annual change in the CTP score was significantly smaller in the BCAA group than in the control group (0.06 ± 0.30 versus 0.30 ± 0.48, $P = 0.037$; Fig. 2B). The mean annual change in the asialoscintigraphic CI was also significantly smaller in the BCAA group than in the control group (0.00 ± 0.02 versus 0.02 ± 0.04, $P = 0.040$; Fig. 2C). The mean annual change in the total bilirubin level in the BCAA group was significantly smaller than that in the control group (−0.07 ± 0.20 versus 0.12 ± 0.18 mg/dL, $P < 0.001$). The mean annual change in the serum albumin level was significantly greater in the BCAA group than in the control group (0.07 ± 0.13 versus −0.02 ± 0.19 g/dL, $P = 0.005$; Table 2).

Major Cirrhotic Complications

The cumulative incidence of overall major cirrhotic complications (HCC, ascites, esophagogastric varices, and hepatic encephalopathy) is shown in Fig. 3. The incidence was 14.8% (4 of 27 patients) in the BCAA group and 30.4% (7 of 23 patients) in the control group



at 3 years and 18.5% (5 of 27 patients) in the BCAA group and 47.8% (11 of 23 patients) in the control group at 5 years. The cumulative incidence of complications was significantly lower in the BCAA group than in the control group ($P = 0.043$). Among specific complications, the incidence of ascites was significantly lower in the BCAA group ($P = 0.037$), whereas the incidence of varices was slightly but not significantly lower in the BCAA group ($P = 0.092$). The incidence of HCC did not significantly differ between the groups ($P = 0.364$). No hepatic encephalopathy developed in either group.

DISCUSSION

For patients awaiting liver transplantation, it is desirable that the hepatic reserve be preserved even when the waiting period is prolonged. As one measure to achieve this, the present study evaluated the usefulness of pretransplant nutritional therapy. Long-term BCAA therapy, begun in the early stages of liver cirrhosis, as in the present study, involves 2 possible issues. One pertains to facilitation of abnormal glucose tolerance by BCAA therapy, whereas the other pertains to stimulation of HCC growth, also by BCAA therapy. It has been reported that perioperative patients exhibiting malnutrition or abnormal glucose tolerance are at elevated risk for problems such as posttransplant wound infection and anastomotic failure of the operative wound.[18,19] However, BCAA therapy has been reported to be useful not only in correcting malnutrition but also in alleviating abnormal glucose tolerance.[20,21] Furthermore, BCAAs have been shown to exhibit pharmacological activity suppressing the growth of HCC[22] and have been clinically reported to suppress complications of transarterial embolization and the onset of HCC in obese males with liver cirrhosis as well as hepatitis C virus–positive patients with liver cirrhosis.[23-25] These previous reports suggest that long-term BCAA treatment of liver cirrhosis patients does not involve a high risk of significant adverse reactions such as exacerbation of abnormal glucose tolerance and stimulation of liver carcinogenesis.

In previous studies, both pretransplant MELD and CTP scores strongly correlated with pretransplant waiting-list mortality.[26] These scores also positively correlated with posttransplant hepatic decompensation and mortality.[27,28] In the present study, oral BCAA supplementation was useful in maintaining MELD and CTP scores for more than 3 years on average. Our findings suggest that initiation of oral BCAAs in patients with a MELD score of 6 to 9 or a CTP score of 5 to 6 may contribute to solving current problems related to trans-

Figure 2. Annual changes in hepatic reserve markers in the 2 groups. Horizontal bars show means. (A) $P = 0.024$, (B) $P = 0.037$, and (C) $P = 0.040$ (Mann-Whitney U test). Abbreviations: BCAA, branched-chain amino acid; CTP, Child-Turcotte-Pugh; CI, clearance index; MELD, Model for End-Stage Liver Diseases.

TABLE 2. Annual Changes in Laboratory Data Related to Hepatic Function

	BCAA Group (n = 27)	Control Group (n = 23)	P*
Total bilirubin (mg/dL)	−0.07 ± 0.20	0.12 ± 0.18	<0.001
Albumin (g/dL)	0.07 ± 0.13	−0.02 ± 0.19	0.005
Platelets ($\times 10^4$/mL)	−0.09 ± 0.85	−0.32 ± 0.59	0.140
Alanine aminotransferase (IU/L)	1.38 ± 3.32	1.81 ± 2.25	0.817
Prothrombin activity (%)	−2.20 ± 1.89	−3.76 ± 7.36	0.705
Cholinesterase (IU/L)	−10.69 ± 27.65	−13.10 ± 42.55	0.378
Cholesterol (mg/dL)	0.74 ± 8.89	−0.87 ± 11.98	0.273
BCAA/tyrosine ratio	0.10 ± 0.34	0.01 ± 0.25	0.399

NOTE: Data are shown as mean ± standard deviation.
Abbreviation: BCAA, branched-chain amino acid.
*Mann-Whitney U test.

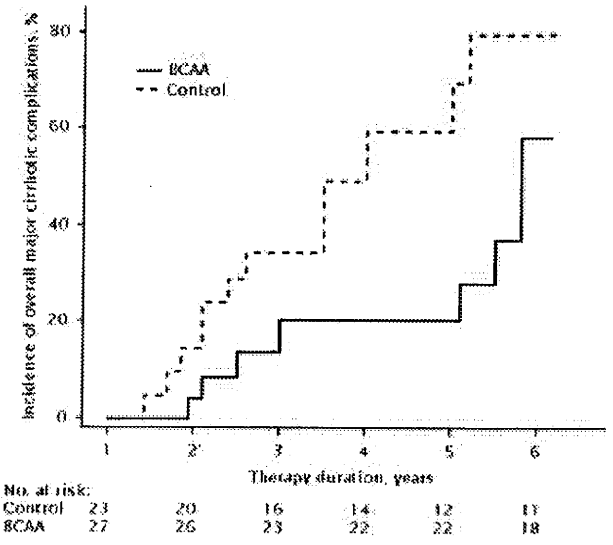


Figure 3. Cumulative incidences of overall major cirrhotic complications diagnosed in patients treated with BCAAs. $P = 0.043$ (log-rank test). Abbreviation: BCAA, branched-chain amino acid.

plantation, such as the donor shortage and availability of only small liver grafts (for patients on waiting lists for living-donor liver transplantation)[29] and also to improving posttransplant mortality by preserving the hepatic reserve of scheduled recipients.

The preservation of hepatocyte function in the BCAA group, as indicated by the inhibition of increases in the asialoscintigraphic CI and serum total bilirubin level, might be attributable to the fact that BCAAs can stimulate the regeneration of an injured liver. Asialoscintigraphy is a useful technique for the quantitative estimation of hepatic reserve and more accurately reflects histological hepatic damage than the 15-minute retention rate of indocyanine green in preoperative cirrhosis.[30]

Our study showed that the incidence of major cirrhotic complications accompanying disease progression was significantly lower in patients who received oral BCAAs. The significant suppression of ascites in the BCAA group may have been related to the inhibition of a decline in the serum level of albumin. Patients with chronic hepatic failure with a low Fischer's ratio due to a decrease in serum BCAAs have been reported to exhibit a concomitant reduction of serum albumin concentrations, which can be improved by oral BCAA administration. The synthesis and secretion of albumin in primary hepatocytes have been reported to be increased when Fischer's ratio is maintained at an appropriate level.[31] BCAAs not only are structural constituents of proteins but also have pharmacological properties. BCAAs have been found to mimic the effects of a complete mixture of amino acids in stimulating protein synthesis both in vivo and in vitro. BCAAs, especially L-leucine, promote albumin synthesis in rat primary hepatocytes through a cell-signaling pathway involving mammalian target of rapamycin (mTOR), a serine/threonine protein kinase and a cellular nutrition sensor for the initiation of protein translation.[32] Although the mTOR signaling pathway is activated by insulin in addition to L-leucine, L-leucine appears to regulate protein synthesis in various tissues by mechanisms independent of insulin. Leucine analogues that are not insulin secretagogues can reproduce the effects of L-leucine.[33] However, it has been reported that inhibition of mTOR by rapamycin is only partially successful in blocking some of the effects of L-leucine, and this suggests that increased albumin synthesis promoted by L-leucine is mediated by at least 2 signaling pathways, one rapamycin-sensitive and the other rapamycin-insensitive.[34] The aforementioned mechanisms may have contributed, at least in part, to the maintenance of serum albumin levels. However, ascites can be due to various other effects on hepatocyte function apart from hypoalbuminemia.[35] Previous studies have reported that L-leucine stimulates hepatocyte growth by promoting the secretion of hepatocyte growth factor (HGF), which regulates cell growth, cell motility, and morphogenesis.[36,37] Administration of HGF has been shown to increase DNA synthesis in the liver and to reduce hepatic injury. L-Leucine has also recently been found to stimulate HGF via hepatic stellate cells through the mTOR pathway.[38]

One of the limitations of the present study is a lack of

placebo. It is ideal to conduct a placebo-controlled, double-blind trial in an assessment of the BCAA granule preparation. In the present study, however, no placebo was given to the control group because the special taste of LIVACT made it impossible to find a placebo with a similar taste that could truly ensure patient blinding. For this reason, the subjects were allocated at random to the BCAA group and diet group, without the inclusion of placebo. Another limitation of this study is that no assessment was performed of protein synthesis, catabolism, balance, and so forth, other than measurements of the serum albumin level. Improvement of nutritional status and recovery of albumin synthesis are pharmacological effects expected with BCAA therapy in patients with liver cirrhosis, as many reports have indicated.[7,16,32] The present study was aimed at demonstrating that BCAAs are useful not only in improving albumin metabolism and nutritional status but also in suppressing the elevation of the serum total bilirubin level and deterioration of the function of residual liver cells, as represented by overall indicators of hepatic failure level such as the MELD score, CTP score, and asialoscintigraphic index.

We believe that our study is the first to provide compelling evidence that early interventional oral BCAAs have favorable effects, when given for a mean period of more than 3 years, on prognostic scores, the results of functional imaging, and complications. A larger multicenter trial is warranted to confirm these findings. We anticipate that oral BCAAs beginning in Child class A cirrhosis will provide additional time and enable surgeons to ensure successful outcomes of liver transplantation.

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＜原　著＞

慢性肝疾患患者を対象とした肝臓病教室での情報提供に対する医療者および患者の意識調査に関する検討

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要旨：関西22病院にて肝臓病教室に関するアンケート調査を行なった．対象は，医療者55名，慢性肝疾患患者176名．肝臓病教室を定期開催しているのは7施設，経験はあるが現在未施行2施設，未施行13施設であった．継続できない理由は，マンネリ化や慣れたスタッフの配置換えによるパワーダウン，教室の効果を把握しにくいなどで，開始できない理由は，準備などの時間がないが最も多かった．医療者と患者とも，各々95%，94%が教室は必要と回答した．提供すべき情報は，医療者は1位：肝臓病とは，2位：治療方法，3位：合併症とその対策/肝臓の働き，患者側は1位：治療方法，2位：治療効果，3位：食事療法を上位に挙げた．教室のメリットは，両者とも1位：自己管理の向上，2位：治療に対して前向きな姿勢になれる，3位：不安の軽減，と一致した．有効な患者教育の普及のためには，方法論の普及，有用な情報の種類や提供方法の検討，情報提供による効果の評価方法を確立し医療者のやる気の維持につなげるなどが必要と考えられた．

索引用語：　患者教育　　チーム医療　　コメディカル　　メンタルサポート

はじめに

慢性肝疾患患者の診療においては，ウイルス性慢性肝炎に対するインターフェロン治療や肝臓癌に対するラジオ波治療など患者にとっては侵襲性の高いものが多いが，患者はその治療選択を外来にて迫られることも多い．外来での短い診療時間で伝えられる情報は一般に十分とは言えず，患者には情報不足という負担があり，また実際治療選択に迷うことも少なくない．その欠点を補う目的で，肝臓病教室などが各施設で行われてはいるが，未だ一般的に施行されているとはいい難い．加藤らは全国医療機関に行なったアンケート結果より，2003年から2004年時点で肝臓病教室を開催しているのは約70施設弱であることを報告している[1)]．高血圧患者や糖尿病患者などでは，薬物療法以外の患者教育によって慢性疾患のコントロール状態を改善させることが指摘されているものの[2)3)]，慢性肝疾患での検討は極めて少ない．

我々は肝臓病患者への情報提供の有り方について検討を加える目的で，2005年より関西肝臓病教室アドバイザリーカンファレンスを立ち上げ，多施設で年1回研究会を行っている．今回，本研究会に参加した22医療機関において医療関係者と通院患者に選択肢を主としたアンケートを行い，肝臓病教室施行の現状を把握するとともに，患者と医療関係者の意識の比較を検討し，今後の方向性を考察したので報告する．

対象と方法

2006年1月から2月にかけて，関西肝臓病教室アド

1）大阪厚生年金病院内科
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