## Patients and methods

This meta-analysis was initiated by Dr Suzuki H (Yamanashi Medical College, Japan) with a cooperation of Dutch and Japanese project teams: SW Schalm, B Hansen, BJ Veldt and E Verheij from Holland; and S Iino, H Kumada and K Ikeda from Japan. An advisory committee was also organized by experts from France (T Poynard), Holland (T Stijnen), and Japan (C Hirayama and N Hayashi). In order to gather reliable patient data, a total of 12 institutions were selected among large-scale, specialized hepatology centres throughout Japan: Sapporo Kousei Hospital (Sapporo), Hokkaido University (Sapporo), National Tokyo Hospital (Tokyo), Musashino Red Cross Hospital (Tokyo), Kiyokawa Hospital (Tokyo), East Hospital of Kitasato University (Kanagawa), Aikawa Hospital (Ibaraki), Yamanashi Prefecture Central Hospital (Yamanashi), Shinshu University (Nagano), Kawasaki Hospital of Kawasaki University(Okayama), Oono Gastroenterology Hospital (Ehime), and Kumamoto University (Kumamoto).

Patient data were collected from the 12 hospitals by eligibility criteria consisting of: chronic hepatitis or cirrhosis diagnosed by peritoneoscopy and/or liver biopsy, a history of interferon therapy from 1990 to 1995, non-sustained virological response under the therapy.

Individual patient data consisted of histological findings before IFN therapy, virological data, haematological and biochemical data before IFN therapy, details of IFN therapy, method of SNMC therapy, biochemical findings before and during SNMC therapy, development to cirrhosis, date of HCC development, and survival.

Data from 1093 patients were subjected to the same analysis as those of a retrospective cohort. A follow-up observation was made for a median period of 6.1 years with a range of 2.5–9.0 years.

Standard statistical methods, including chi-square test and Mann–Whitney *U*, were used for the analysis of differences of background factors between patients with and without SNMC treatment. A Kaplan–Meier method[17] was adopted to estimate cumulative carcinogenesis rate after cessation of interferon. Cox proportional hazards analysis[18] was performed to evaluate the independent predictors for future carcinogenesis rate in patients with chronic hepatitis.

## Results

### *Background of patients*

A total of 1093 patient data were collected from the 12 Japanese institutions. There were 634 men and 459 women, with a median age of 54 years, ranging from 17 to 81. Among the 1093 patients, 733 patients had HCV genotype 1, 210 had genotype 2, and 13 had genotype 3 or 4. At the beginning of the observation period, 451 patients had chronic hepatitis in a fibrosis stage 1 (F1) according to the classification of Desmet V, 372 in F2 stage, 202 in F3 stage, and the remaining 54 were in F4 stage or had cirrhosis.

### *Development to cirrhosis, carcinogenesis and death*

During an observation period of 6.1 years, 138 (13.3%) of 1093 patients progressed to cirrhosis: 192 patients were finally diagnosed as having cirrhosis at the end of the observation period.

A total of 107 patients (9.8%) developed HCC and 33 patients (3.0%) died during the observation period. Of the 192 who eventually progressed to cirrhosis, 79 patients (41.1%) showed HCC by the end of the observation period, and 23 (12.0%) died with or without HCC. Cumulative hepatocellular carcinogenesis rates were 6% at the end of the 5th year, and 25% at the end of the 10th year.

The crude hepatocellular carcinogenesis rate of all 1093 patients was 6% at the end of the 5th year and 25% at the end of the 10th year (Figure 4). When carcinogenesis rates were calculated according to the fibrosis stages at the initiation of observation (Figure 5), HCC appeared in 10 (2.2%) of the 451 patients in F1 stage, 31 (8.3%) of the 372 patients in F2 stage, 42 (20.8%) of the 202 patients in F3 stage, and 20 (37.7%) of the 53 patients with cirrhosis, during a median observation period of 6.1 years. The more severe the hepatic fibrosis, the higher was the future risk of carcinogenesis.

Carcinogenesis curves were also generated according to initial ALT values. Initial ALT values were found to be clearly correlated with future carcinogenesis rates (Figure 6).

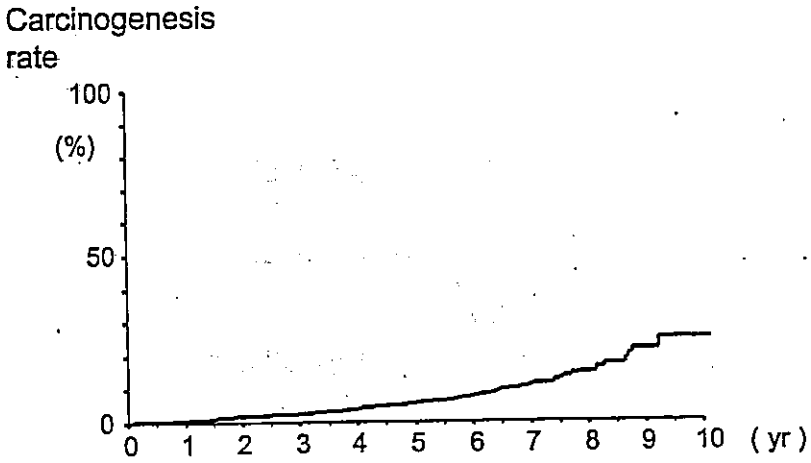


**Figure 4** Study II: Carcinogenesis rate of entire patients with chronic liver disease caused by hepatitis C virus

### *SNMC therapy for patients with chronic hepatitis C*

A total of 465 patients (42.5%) received SNMC therapy after ineffective IFN therapy: SNMC therapy was performed with or without other therapies (ursodeoxycholic acid and so on). A multivariate analysis revealed that SNMC therapy had been performed in older patients, in patients with advanced liver disease and in patients with high ALT values.

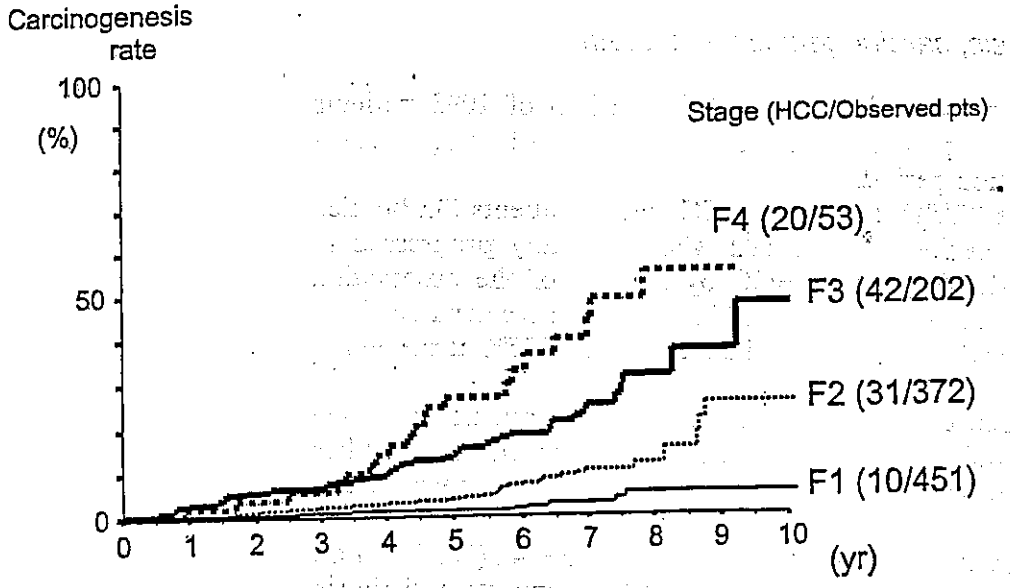


**Figure 5** Study II: Carcinogenesis rates according to fibrotic stages at the initiation of observation

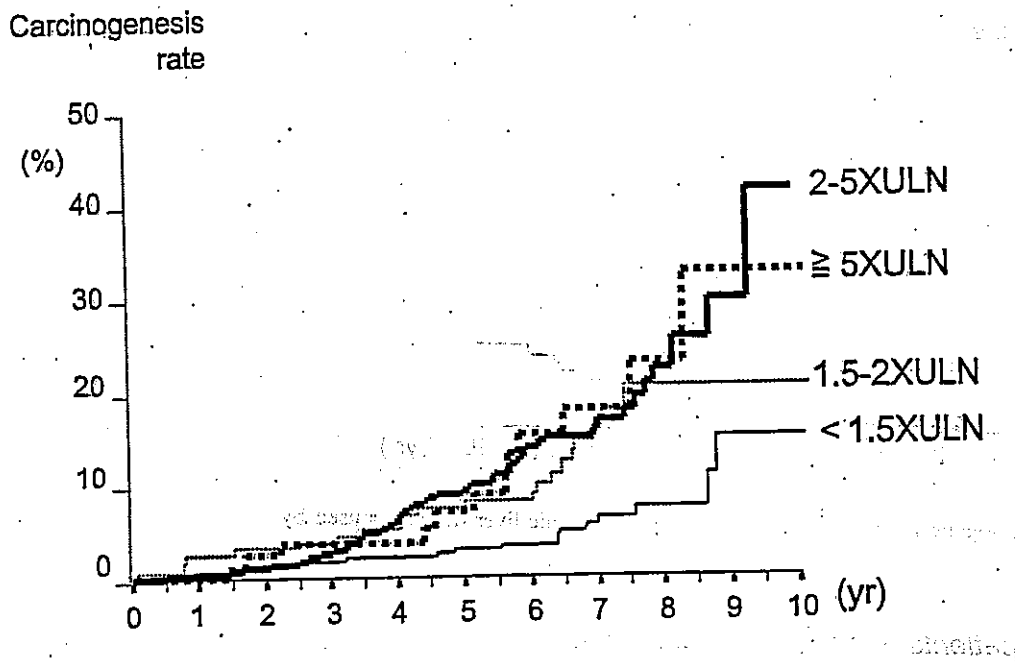


**Figure 6** Study II: Carcinogenesis rates according to initial ALT value

Table 1 Study II: Independent predicting factors for future carcinogenesis rate in patients with F3 and F4 stage hepatitis (time-dependent Cox proportional hazards analysis)

| *Factor* | *Category* | *Hazard ratio (95% confidence interval)* | *p-Value* |
|---|---|---|---|
| Age | +1 year | 1.1 (1.0–1.1) | <0.001 |
| Gender | Men | 1 | |
| | Women | 0.3 (0.2–0.5) | <0.001 |
| SNMC | No | 1 | |
| | Yes | 0.4 (0.2–1.0) | 0.04 |

The median dose of SNMC injection was 191 ml per week and the median duration of the therapy was 196 weeks.

Among the 395 patients who continued SNMC injection therapy for 16 weeks or longer, 169 (42.8%) showed a decrease of ALT values down to the level of less than 1.5 times ULN.

### *Influence of SNMC on carcinogenesis*

A multivariate Cox proportional hazards analysis was performed only in patients in hepatitis stage F3 or F4, using the length of waiting time until the SNMC injection as a time-dependent variable. Older age ($p<0.001$), female sex ($p<0.001$) and use of SNMC ($p = 0.04$) were independently associated with carcinogenesis rate. In this analysis, after adjusting the background differences of the treated and untreated group with significant covariates (Table 1), SNMC was found to have significantly decreased the risk of cancer development.

## DISCUSSION

Yamamoto et al.[10] first treated patients with chronic hepatitis with SNMC and found a remarkable improvement in their ALT levels. Suzuki et al.[12] confirmed the effect of SNMC to suppress serum aminotransferase in patients with chronic hepatitis in a randomized controlled trial. Hino et al.[13] and Yasuda et al.[14] also confirmed that SNMC was useful in the improvement of transaminase levels and liver histology. We previously reported that SNMC was beneficial for improvement of carcinogenesis rate in patients with chronic hepatitis C when it was administered for 10 years or longer[19]. In these retrospective studies, we assessed the role of SNMC therapy in the prevention of hepatocellular carcinogenesis in patients with chronic hepatitis C.

This retrospective study was undertaken to evaluate whether SNMC injection therapy could decrease the HCC rate in patients with HCV-related chronic hepatitis with or without cirrhosis not responding to IFN therapy. Since it requires at least 5 years to obtain a statistically valid finding in carcinogenesis

rate from hepatitis with or without cirrhosis between the glycyrrhizin-treated and the 'untreated' groups, a prospective randomized trial using untreated control patients is difficult from both ethical and medical viewpoints in Japan where SNMC injection therapy is covered by medical insurance, and it is already regarded as a usual choice of therapy as a salvaging procedure for IFN-ineffective patients. We therefore attempted to carry out a retrospective cohort study (study I) and meta-analysis of a large number of data from multiple hepatology centres (study II), with a statistical adjustment using possible covariates explored in multivariate analysis.

In both studies, when crude carcinogenesis rates were compared between the treated and untreated patient group, the hepatocellular carcinogenesis rate in the SNMC therapy group was found to be significantly higher than that in the untreated group. Since anti-inflammatory therapy using SNMC was usually performed for those patients with a high ALT value and high hepatitis activity, it seemed to be a plausible result that the carcinogenesis rate in the treated group was higher than that in the untreated group. Actually the treated group consisted of significantly more patients with a high ALT value, of twice ULN or more.

In study I, when carcinogenesis rates were assessed only in patients with a high ALT value of twice ULN or more, the rate in the SNMC-treated group came out slightly higher than that in the untreated group (data not shown). Some of the patients in the treated group received SNMC therapy several months or a few years after judgement of no response to IFN therapy. In order to elucidate the potential effect of SNMC to prevent carcinogenesis in patients with an active HCV-related liver disease, we further stratified the treated patients into two subgroups: early treatment subgroup of patients who received SNMC therapy within 2 years after judgement of no response to IFN therapy and late treatment subgroup of patients receiving treatment over 2 years after the event. Since the patients in the latter subgroup were observed without therapy for a considerable period, they were regarded as only partly and insufficiently treated with SNMC from the viewpoint of the entire observation period. We therefore compared carcinogenesis rates between treated and untreated patients, excluding those patients in the late treatment subgroup. The hepatocellular carcinogenesis rate of the patients who received SNMC therapy for a sufficient period of time was significantly lower than that in those who did not receive the therapy ($p = 0.038$). In the treated group the median ALT values decreased significantly after initiation of SNMC injection, suggesting that suppression of the necroinflammatory process of liver disease by SNMC therapy was working as a primary factor in reducing carcinogenesis in the high-risk patients. The current study dealing with a large cohort ($n = 1249$) showed that the carcinogenesis rate was reduced when SNMC therapy was started at an early time after judgement of no response to INF therapy.

In study II, background biases between the SNMC-treated group and the untreated group were adjusted by significant covariates using multivariate analysis. The final Cox proportional model showed that SNMC therapy reduced the hepatocellular carcinogenesis rate in F2–3 stage hepatitis patients, after statistical adjustment of differences of age and gender ratio. The reason why SNMC did not show an effect to reduce the carcinogenesis rate in F1 stage

hepatitis patients was presumed to be that the carcinogenesis rate in the untreated patients in F1 stage was too low to prove the effect of SNMC.

As carcinogenesis is not a single-step event, but a complex, multi-step process, the way in which SNMC works to suppress liver carcinogenesis still remains unclear. One of the principal roles played by SNMC in long-term administration seemed to be its anti-inflammatory actions, which would block the active carcinogenic process through a continuous hepatic necroinflammation and cell damage. SNMC may, however, only postpone the time of HCC appearance in the clinical course of cirrhosis. Since the entire process of hepatocellular carcinogenesis from the initial transformation of a hepatocyte to a detectable growth of cancer is considered to take several years, the influence of SNMC on the carcinogenesis rate will not be evaluated in a short period of a few years. Future studies should therefore be aimed at defining the basic oncogenic mechanisms underlying in liver disease, and the roles of long-term administration of SNMC in prevention of carcinogenesis in patients with cirrhosis caused by HCV.

In conclusion a long-term intermittent SNMC therapy over a few years or more successfully reduced hepatocellular carcinogenesis in patients with HCV-related chronic liver disease. A randomized control study with a larger number of cases, with or without SNMC therapy, is expected to confirm the effectiveness of this therapy in cancer prevention.

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# Effect of Oral Supplementation with Branched-Chain Amino Acids on Albumin Concentration in the Early Stage of Cirrhosis

Shuhei Nishiguchi[1], Daiki Habu[1], and Susumu Shiomi[2]

*Summary.* The present study was undertaken to examine changes in the levels of amino acids, particularly branched-chain amino acids (BCAAs), following exacerbation of liver cirrhosis and to determine the optimal timing of starting nutritional therapy using BCAA. In patients with well-compensated cirrhosis, both the amino-acid composition and the albumin level were normal. However, as the disease advanced, BCAA first began to decrease, causing amino-acid imbalance, and this change was later followed by a decrease in albumin. We reviewed the criteria for determining indications for treatment with a BCAA formula (Livact), which is currently used after a decrease in albumin level. In patients in whom the BCAA-to-tyrosine ratio (BTR) was less than 4.0 despite normal albumin levels, the use of the BCAA preparation prevented a decrease in albumin. In view of this result, it is advisable to administer the BCAA formula following a reduction in BTR rather than to begin its use following a decrease in albumin.

*Key words.* Albumin, Branched-chain amino acid, Liver cirrhosis, Nutritional therapy

## Introduction

Viral liver cirrhosis is sometimes treated, with agents such as interferon (IFN) and lamivudine which are related to the cause of the cirrhosis. However, many patients with this condition receive liver-protective therapy with ursodeoxycholic acid (UDCA) or other drugs that is aimed at reducing the alanine aminotransferase (ALT) level; drugs used are ursodeoxy-cholic acid (UDCA) or other drugs. The survival rate of patients with liver cirrhosis has been improved by such liver-protective therapy, by the treatment of esophageal varices, and by various other treatments. As the survival time of such patients becomes longer, the importance of diet therapy increases.

Serum albumin concentrations, which are considered to be a good and stable indicator of visceral protein nutritional status, are often low in patients with liver cirrho-

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sis. This is caused not only by insufficient protein intake but also by various other factors, including reduced liver protein synthesis, increased extravascular leakage. In patients with low albumin concentration, half-life of albumin was extended to keep its level. Therefore, it is very difficult to assess serum albumin concentrations in patients with liver cirrhosis. However, it has been demonstrated that this concentration plays an important role in the prognosis of these patients [1–3]. It has been reported that prognosis generally differs between patients with a serum albumin concentration of more than 3.5 g/dl and patients with a serum albumin concentration of 3.5 g/dl or less [1]. This value (3.5 g/dl) is also used in the criteria for Child-Pugh classifications. A decrease in Fischer's ratio, i.e., the branched-chain amino acid/ aromatic amino acid (BCAA/ AAA) ratio, is an indicator of disorders of amino-acid metabolism which are characteristic of liver cirrhosis [4]. It has been reported that a decreased Fischer's ratio is not only a direct risk factor for hepatic encephalopathy (which is a significant complication of liver cirrhosis) but is also an independent prognostic factor [5].

The correction of hypoalbuminemia and the decreased Fischer's ratio, factors which closely interact and are representative indicators of malnutrition in patients with liver cirrhosis, leads to amelioration of the pathophysiological condition and prevention of deterioration in quality of life, and finally improvement of mortality rates. For these purposes, in Japan, supplementation with BCAAs is mainly used as nutritional therapy and nutritional intervention. Evidence about the usefulness of this therapy is being accumulated. In this article, among various issues relating to supplementation with BCAAs, we focus on its usefulness for patients with early-stage liver cirrhosis, which we have previously advocated.

## The Purpose of BCAA Administration

A gradual decrease in the BCAA/AAA ratio is associated with the progression of chronic liver disorders [6]. Since AAAs undergo metabolism exclusively in the liver, AAA levels increase in patients with liver cirrhosis, who have decreased metabolic function [7]. It has been reported that, after liver transplantation, AAA levels rapidly return to normal as liver function recovers [8]. We have previously mentioned that portosystemic shunt causes AAAs to 'pass through' the liver, and that this may play a role in the mechanism of the increase in AAA levels in cirrhosis with Child-Pugh A [9].

On the other hand, there are various opinions about the mechanism of decreasing BCAA levels. It has been reported that hyperinsulinemia increases BCAA uptake [10], that BCAAs are increasingly consumed as energy substrates which are directly used [11], and that the consumption of BCAAs increases in accordance with increased ammonia metabolism in skeletal muscles [12]. As a result, the Fischer's ratio (BCAA/AAA) decreases, which directly and indirectly decreases serum proteins such as albumin, and destroys muscle proteins.

Originally, the purpose of using BCAA administration for the correction of Fischer's ratio focused on the awakening from hepatic encephalopathy [13]. Decreased BCAA concentrations reflect metabolic kinetics, mainly involving protein hypercatabolism. 15 years ago, Yoshida et al. [14] more than 10 years ago, started using BCAAs

and showed that this therapy gave patients with liver cirrhosis an improved quality of life and an extended prognosis. Subsequently, BCAA preparations were placed on the market, and their usefulness is becoming commonly recognized. An extensive multicenter post-marketing survey of BCAA granules has recently been conducted in more than 600 patients with liver cirrhosis, and the usefulness of these granules has been confirmed. When the results of this survey are reported, they will show conclusive evidence that the administration of BCAAs to patients with liver cirrhosis not only ameliorates hepatic encephalopathy and the pathophysiological condition but also extends the prognosis of these patients by enhancing the function and reserve capacity of the liver.

## Target Patients for BCAA Administration

Currently, the main target patients for nutritional therapy for liver cirrhosis are patients in the decompensated stage, who clearly exhibit clinical symptoms. The effects of treatments for peritoneal effusion and hepatic encephalopathy are easy to recognize due to the evident deterioration and resolution of these symptoms. Additionally, it only takes a short time to assess the prognosis of patients in the decompensated stage. However, there is an opinion that, for patients with liver cirrhosis, it may be better to start nutritional therapy in the compensatory stage or even earlier, rather than starting it in the decompensated stage.

We performed supplementation with BCAAs in patients in the compensatory stage of liver cirrhosis [15]. During this treatment, as an indicator of disorders of amino-acid metabolism, we used the BCAA/tyrosine ratio (BTR) instead of Fischer's ratio. The measurement method for BTR is simple and inexpensive, and BTR can generally be a substitute for Fischer's ratio, and is being commonly used in Japan [16]. The BTR of healthy people is considered to be 5.82–8.64 (mean ± 1 SD) or 4.41–10.05 (mean ± 2 SD). It has been demonstrated that BTR regularly and gradually decreases as liver diseases progress. We used platelet counts to classify 448 patients with hepatitis C virus (HCV)-related chronic liver diseases, who were outpatients at our hospital, and analyzed the mean BTR in each class ification group (Fig. 1). To obtain better correction of disorders of amino-acid metabolism and protein metabolism—which are associated with chronic liver diseases—the optimal timing of nutritional interventions with appropriate amounts of BCAA supplementation is an interesting issue.

After conducting the study with the 448 patients noted above, we studied 84 patients with Child-Pugh A liver cirrhosis in the compensatory stage, who were enrolled from March 1996 to July 1997. These patients were divided into two groups (the BTR ≥ 4 group $n = 57$ and the BTR < 4 group; $n = 27$), and were followed for up to 4 years. The percentage of these patients in whom the cirrhosis severity changed to Child-Pugh B, even transiently, was 21% in the BTR ≥ 4 group, which was significantly lower than that in the BTR < 4 group (70%). Additionally, multivariate analysis revealed that BTR was an independent risk factor for a change in the severity from Child-Pugh A to Child-Pugh B. Therefore, we considered a patient with a BTR value less than 4 as a patient with amino-acid imbalance even in the compensatory stage of liver cirrhosis, and we conducted the randomized study, outlined below, in order to make a comparison

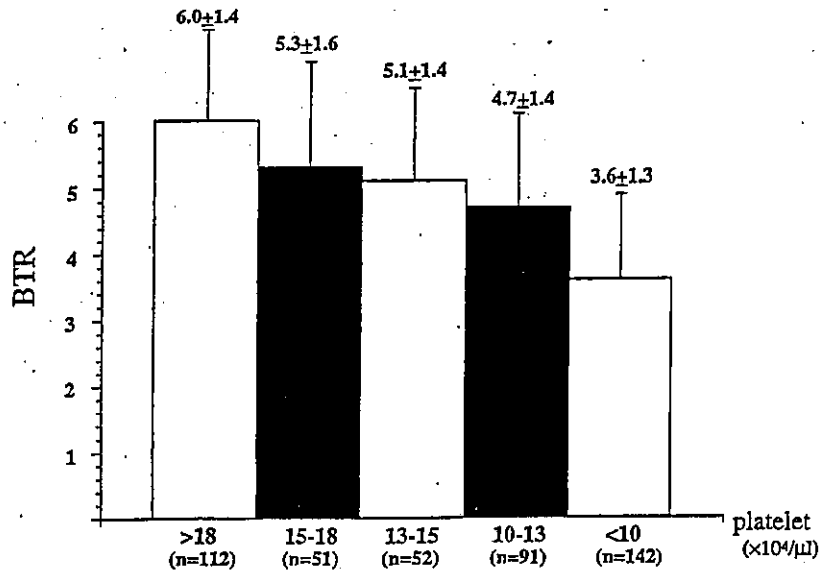


Fig. 1. The mean branched-chain amino acid (BCAA)/tyrosine ratio (*BTR*) of patients with hepatitis C virus (HCV)-related chronic liver diseases ($n = 448$), who were classified using platelet counts (mean ± SD). We used platelet counts to classify 448 patients with HCV-related chronic liver diseases, who were outpatients at our hospital, and analyzed the mean BTR in each class ification group. The BTR of healthy people is considered to be 5.82–8.64 (mean ± 1 SD) or 4.41–10.05 (mean ± 2 SD). It has been demonstrated that BTR regularly and gradually decreases as liver diseases progress.

between the effects of BCAA granules in patients who met the criterion of having a BTR value of 4 or less and patients who met the conventional criterion of having a serum albumin concentration of 3.5 g/dl or less [17]. All the subjects of this study were patients with HCV-related liver cirrhosis, and they were classified into three classes. Class 1 had a serum albumin concentration of 3.5 g/dl or less (25 patients, conventional targets of BCAA supplementation), class 2 had a serum albumin concentration between 3.6 g/dl and 3.9 g/dl and a BTR of less than 4 (18 patients), and class 3 (17 patients) had a serum albumin concentration between 3.6 g/dl and 3.9 g/dl, and a BTR of 4 or more. These patients ($n = 60$) were randomly allocated to two groups: the group that was given a BCAA preparation (Livact; Ajinomoto, Tokyo, Japan; BCAA group) and the group that was not (control group). The effect of BCAA administration was evaluated according to changes in the serum albumin concentration after 2 years as an indicator. The BCAA administration was considered to have been effective when the albumin concentration increased by 0.2 g/dl or more. The characteristics of the patients in each class are shown in Table 1. The patients continued to consume a diet that had a total daily calorie intake of 30 kcal/kg and a protein intake of 1.3 g/kg (including amino-acid preparations). The results of this study were: (1) in class 1, the effective rate (increase in serum albumin concentration of 0.2 g/dl or more) in the BCAA group was 46%, which was significantly higher than the 8% rate in the control group, (2) in class 2, the effective rate in the BCAA group was 44%, which was significantly higher than the 0% rate in the control group, and (3) in class 3, the effective rate in the BCAA group was 67%, which was not significantly different from the 36% rate in the control group (Fig. 2).

Table 1. Baseline characteristics of three classes of patients

| | 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 (years) | 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 ($\times 10^4/mm^3$) | 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 (branched-chain amino-acid (BCAA)/tyrosine ratio), serum albumin, platelets, alanine aminotransferase (ALT), and total bilirubin; $\chi^2$ test for sex ratio and BCAA/control ratio (adapted from reference [23])

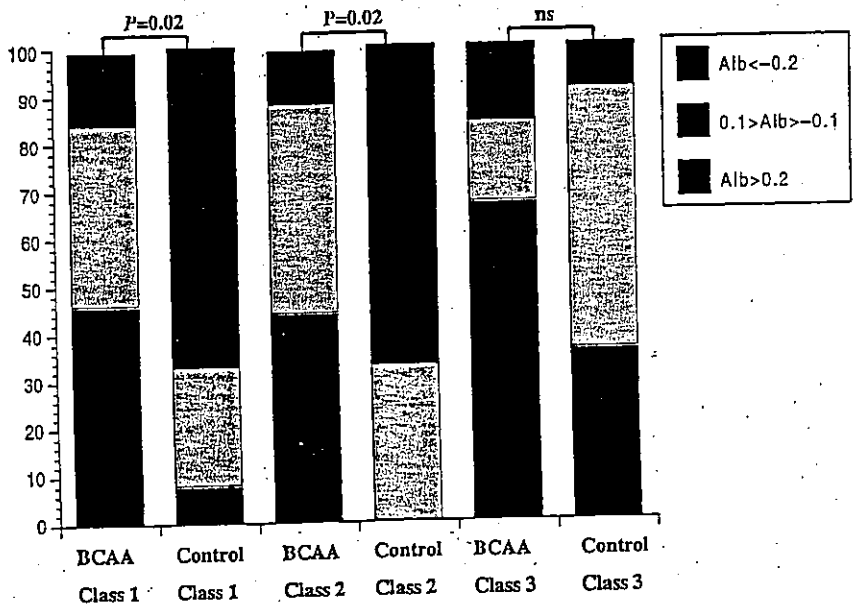


Fig. 2. Comparison of serum albumin (*alb*) levels at 2 years after study enrollment between the BCAA and control groups in class 1, class 2, and class 3. Patients in class 1 had decompensated cirrhosis, with a serum albumin concentration of 3.5 g/dl or less. Class 2 patients had compensated cirrhosis, with a serum albumin concentration between 3.6 g/dl and 3.9 g/dl, and a BTR of less than 4. Class 3 patients had compensated cirrhosis, with a serum albumin concentration between 3.6 g/dl and 3.9 g/dl, and a BTR of 4 or more. The BCAA groups in classes 1 and 2 exhibited a significantly higher rate of maintaining serum albumin levels compared with that at enrollment in the respective control groups ($\chi^2$ test for independence, $P = 0.02$), but the difference between the BCAA group and the control group in class 3 was not significant (*ns*). (adapted from reference [17])

Table 2. Odds ratios for decrease in serum albumin level 2 years after study enrollment in the control group

| | Odds 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 for risk factors are expressed as per 1 year for age. The values for all parameters in Table 4 were each categorized into two groups: albumin, >3.5 and ≤3.5 g/dl; BTR, ≥4.0 and <4; total bilirubin, ≤1.0 and >1.0; ALT level, <80 and ≥80 IU/ml; platelet count, ≥100 000 and <100 000/mm³, and odds ratios are indicated for each set of two groups (adapted from reference [17])
CI, confidence interval

Additionally, in the control group, which was followed up without BCAA administration, we performed multivariate analysis to determine the defining factors in the decrease in serum albumin concentrations 2 years after study enrollment, and found that BTR was the only risk factor (Table 2). The results of this study showed that, in patients with liver cirrhosis in the compensatory stage classified in class 2 who had relatively constant serum albumin concentrations (between 3.6 g/dl and 3.9 g/dl), when amino-acid imbalance was manifested (BTR < 4), the administration of BCAA granules increased the serum albumin concentrations to levels similar to those observed in the patients in the decompensated stage.

We assume that when BCAA therapy is not given to patients in class 2, the decreased Fischer's ratio will trigger a decrease in albumin synthesis, and their condition is likely to progress to Child-Pugh B (serum albumin, 3.5 g/dl or less). Consequently, we assume that, in many patients with liver cirrhosis, as the compensatory stage progresses, the Fischer's ratio decreases prior to a decrease in serum albumin concentration (Fig. 3).

The mechanism whereby BCAA administration increases serum albumin concentration is shown in detail in the chapter by K. Yonezawa. It has been assumed that the correction of Fischer's ratio promotes protein synthesis [18], improves the metabolic kinetics of albumin [19], and inhibits proteolysis [20]. Therefore, in patients in the conpensatory stage with high serum albumin levels, low BTR level or low Fisher's ratio in the correction of Fischer's ratio by BCAA administration may prevent a decrease in albumin synthesis.

It has been demonstrated that when patients with advanced liver cirrhosis are given BCAA granules, serum albumin concentrations do not increase sufficiently, because these patients have only a small total number of functioning hepatocytes. At present, it is assumed that only such cells (liver parenchymal cells) can synthesize albumin. Therefore, the results of this study suggest that the administration of BCAA granules is more effective in increasing and maintaining serum albumin concentrations when it is started at an early stage, of patients who have a sufficient number of functioning hepatocytes (the total number of cells which can synthesize albumin by BCAA).

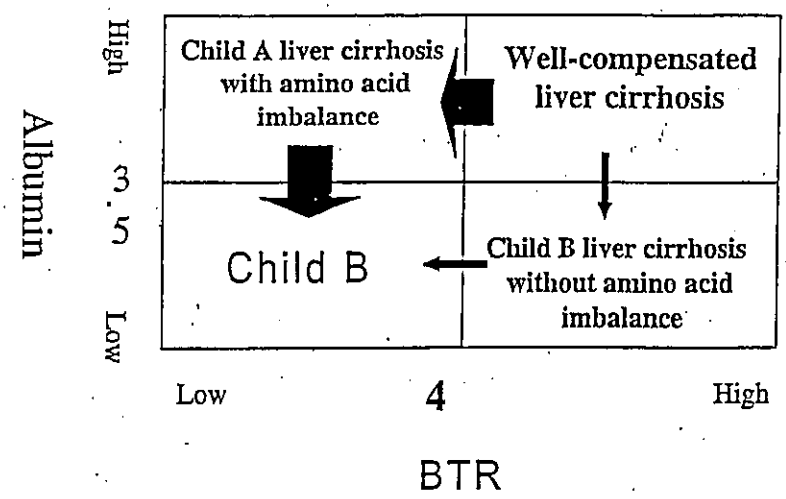


Fig. 3. Progression of compensated liver cirrhosis to decompensated liver cirrhosis. It is assumed that, in the majority of patients during the progression of compensated liver cirrhosis, Fischer's ratio decreases (*large arrows*) prior to a decrease in serum albumin concentration.

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# Effect of oral supplementation with branched-chain amino acid granules in the early stage of cirrhosis

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**Abstract**

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

*Patients and method:* 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. We divided the parameters into three 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. Stating appropriate nutritional interventions, such as supplementation of BCAA, in the early stage of cirrhosis may improve prognosis and maintain QOL.


*Keywords:* Branched-chain amino acid (BCAA); Compensated cirrhosis; Branched-chain amino acid tyrosine ratio (BTR)

## 1. Introduction

Serum albumin concentrations, which are considered to be a good and stable indicator of visceral protein nutritional status, are often low in patients with liver cirrhosis. The reason for this is not only insufficient protein intake, but is a mixture of various factors including reduced liver protein synthesis, increased extravascular leakage, and the extended half-life of albumin which occurs due to low albumin concentrations. Therefore, it is very difficult to assess serum albumin concentrations in patients with liver cirrhosis. However, it has been demonstrated that this concentration plays an important role in the prognosis of these patients [1–5]. It has been reported that prognosis generally differs between patients with a serum albumin concentration of more than 3.5 g/dl and patients with a serum albumin concentration of 3.5 g/dl or less [1,2]. This value (3.5 g/dl) is also used in the criteria for Child-Pugh classification. A decreased Fischer's ratio (branched-chain amino acid/aromatic amino acid) (BCAA/AAA) is an indicator of disorders of amino acid metabolism, which are characteristic for liver cirrhosis [6–8]. It has been reported that a decreased Fischer's ratio is not only a direct risk factor for hepatic encephalopathy [6,7], which is a significant compli-

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cation of liver cirrhosis, but is also an independent prognostic factor [9].

Correction of hypoalbuminemia and a decrease in the Fischer's ratio, which closely interact and are representative indicators of malnutrition in patients with liver cirrhosis, leads to an improved pathophysiological condition, prevention of a deterioration in QOL, and an attempted improvement of mortality as the ultimate achievement. For these purposes, in Japan, supplementation with BCAAs is mainly attempted as a nutritional therapy and a nutritional intervention. Evidence about the usefulness of this therapy is being accumulated. In this article, among various issues relating to supplementation with BCAAs, we focus on its usefulness for patients with early stage liver cirrhosis, which we have previously advocated.

## 2. Present situation of supplementation with BCAAs

A gradual decrease in the BCAA/AAA ratio is associated with the progression of chronic liver disorders [10]. Since aromatic amino acids (AAAs) undergo metabolism exclusively in the liver, AAA levels increase in patients with liver cirrhosis, who have decreased metabolic function [11]. It has been reported that after liver transplantation, AAA levels rapidly return to a normal as liver function recovers [12]. We have previously mentioned that portosystemic shunt causes AAAs to "pass through" the liver, and that this may play a role in the mechanism of the increase in AAA levels [13].

On the other hand, there are various opinions about the mechanism of the decrease in branched-chain amino acid (BCAA) levels. It has been reported that hyperinsulinemia increases BCAA uptake [14], that BCAAs are increasingly consumed as energy substrates, which are directly used [15], and that the consumption of BCAAs increases in accordance with increased ammonia metabolism in skeletal muscles [16]. As a result, the Fischer's ratio (BCAA/AAA) decreases, which directly and indirectly decreases serum proteins such as albumin, and destroys muscle proteins.

Originally, the purpose of using BCAA administration for the correction of the Fischer's ratio was focused on awakening from hepatic encephalopathy [17]. Decreased BCAA concentrations reflect metabolic kinetics mainly involving protein hypercatabolism. Therefore, a nutritional therapy, which increases albumin concentrations by supplying BCAAs that are relatively lacking, is performed in Japan. Muto et al. futuristically started the administration of BCAAs and showed that this therapy gives patients with liver cirrhosis an improved QOL and an extended prognosis [18]. Thereafter, BCAA preparations were placed on the market, and their usefulness is becoming commonly recognized. An extensive multi-centered post-marketing survey on BCAA granules has recently been conducted on more than 600 patients with liver cirrhosis, and the usefulness of these granules has been freshly confirmed. When an article is written to report the results of this survey, it will be a conclusive evidence to show that the administration of BCAAs to patients with liver cirrhosis not only improves hepatic encephalopathy, but also improves the pathophysiological condition and extends the prognosis of these patients by enhancing the function and reserve capacity of the liver.

## 3. Timing of the start of BCAA administration: attempts to administer BCAA in the early stages

Currently, the main targets of nutritional therapy for liver cirrhosis are patients in the decompensatory stage, who clearly exhibit clinical symptoms. The effects of treatments for peritoneal effusion and hepatic encephalopathy are easy to recognize due to the evident deterioration and resolution of these symptoms. Additionally, it only takes a short time to assess the prognosis of patients in the decompensatory stage. However, there is an opinion that for patients with liver cirrhosis, it might be better to start nutritional therapy in the compensatory stage or even earlier, rather than starting it in the decompensatory stage.

Therefore, we performed supplementation with BCAAs in the compensatory stage of liver cirrhosis, and obtained certain evidence [19]. During this treatment, as an indicator of disorders of amino acid metabolism, we used the BCAA/tyrosine ratio (BTR, Ono Pharmaceutical Co., Ltd., Osaka, Japan) instead of the Fischer's ratio. The measurement method of BTR is simple and inexpensive, and BTR can generally be a substitute for the Fischer's ratio and is being commonly used in Japan [20–22]. Prior to this study, we divided the patients with Child A liver cirrhosis in the compensatory stage, who were enrolled from March 1996 to July 1997, into two groups: the BTR $\geq 4$ group (57 patients) and the BTR $< 4$ group (27 patients), and followed them up for 4 years. The percentage of the patients in whom the severity changed to Child B, even transiently, was 21% in the BTR $\geq 4$ group, which was significantly lower than in the BTR $\geq 4$ group (70%). Additionally, multivariate analysis revealed that BTR was an independent risk factor of a change in the severity from Child A to B (unpublished data). Therefore, we considered BTR 4 as a turning point for amino acid imbalance in the compensatory stage of liver cirrhosis and conducted the below mentioned randomized study in order to make a comparison between the effects of BCAA granules in patients who met the criterion of having a BTR of 4 or less and patients who met the conventional criterion of having a serum albumin concentration of 3.5 g/dl or less [23]. All the subjects of this study were patients with HCV-related liver cirrhosis and were classified into three classes. Class 1 had a serum albumin concentration of 3.5 g/dl or less (25 patients, conventional targets of BCAA supplementation), class 2 had a serum albumin concentration between 3.6 and 3.9 g/dl and a BTR of less than 4 (18 patients) and class 3 had a serum albumin concentration between 3.6 and 3.9 g/dl, and a BTR of 4 or more. These patients were randomly allocated to two groups: the group that was given a BCAA preparation (Li-

Table 1
Baseline characteristics of three 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 | $P < 0.05$ |
| Bilirubin (mg/dl) | 1.3 ± 0.5 | 1.0 ± 0.3 | 0.9 ± 0.4 | $P < 0.01$ |

Scheffe's *F*-test for age, BTR, serum albumin, platelets, alanine aminotransferase (ALT) and total bilirubin; chi-square test for sex ratio and BCAA/control ratio.

vact, Ajinomoto Co., Ltd., Tokyo, Japan) (BCAA group) and the group that was not (control group). The effect of BCAA administration was evaluated using the changes in the serum albumin concentration after 2 years as an indicator. The administration was considered to have been effective when the albumin concentration increased by 0.2 g/dl or more. The characteristics of the patients in each class are shown in Table 1. The patients continued to consume a diet containing a total daily caloric intake of 30 kcal/kg and a protein intake of 1.3 g/kg (including amino acid preparations). The results of this study were: (1) In class 1, the effective rate (increase in serum albumin concentration: 0.2 g/dl or more) in the BCAA group was 46%, which was significantly higher than in the control group (8%), (2) In class 2, the effective rate in the BCAA group was 44%, which was significantly higher than in the control group (0%), and (3) In class 3, the effective rate in the BCAA group was 67%, which was not significantly different from the control group (36%) (Fig. 1). Additionally, in the control group, which was followed up without BCAA administration, we performed multivariate analysis on the defining factors in the decrease in serum albumin concentrations 2 years after the enrollment, and found that BTR was the only risk factor (Table 2). The results of this study showed that in patients with liver cirrhosis in the compensatory stage who had relatively constant serum albumin concentrations (between 3.6 and 3.9 g/dl), when amino acid imbalance surfaced (BTR < 4), the administration of BCAA granules increased the serum albumin concentrations to similar levels as observed in the patients in the decompensatory stage.

We assume that when BCAA therapy is not given to patients in this condition, the decreased Fischer's ratio will

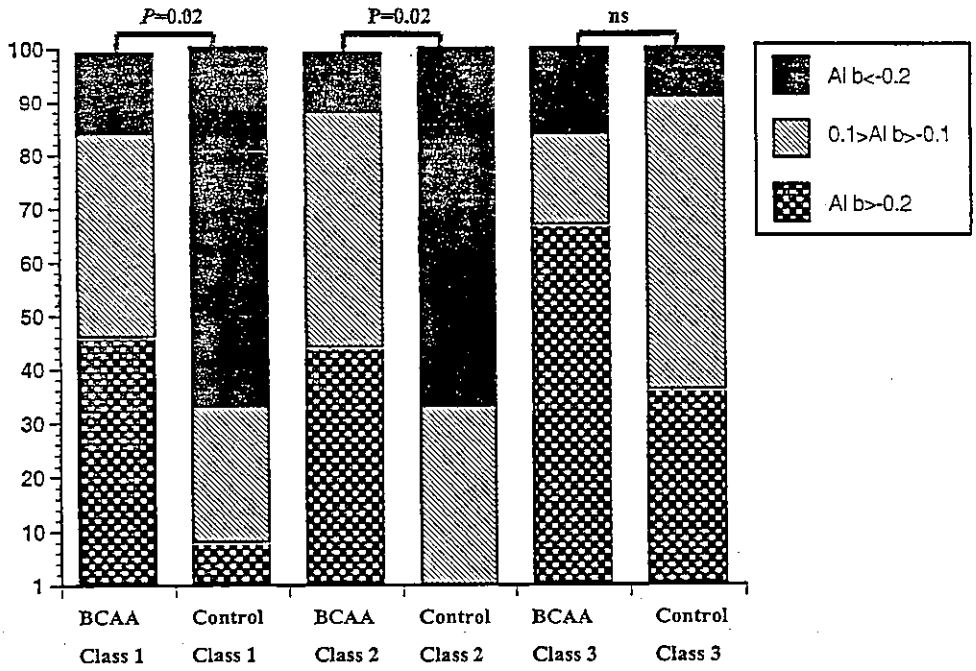


Fig. 1. Comparison of serum albumin levels at 2 years since enrollment between BCAA group and control group in the classes 1, 2 and 3. Class 1 was decompensated cirrhosis with serum albumin concentration of 3.5 g/dl or less. Class 2 was compensated cirrhosis with serum albumin concentration between 3.6 and 3.9 g/dl and a BTR of less than 4. Class 3 was compensated cirrhosis with serum albumin concentration between 3.6 and 3.9 g/dl, and a BTR of 4 or more. 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: $P = 0.02$) in classes 1 and 2, but no significant difference between the BCAA group and control group in class 3.

Table 2
Risk ratio of 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 <100,000/mm$^3$, odds ratios are indicated between each set of two groups. (Revised from Ref. [23]).

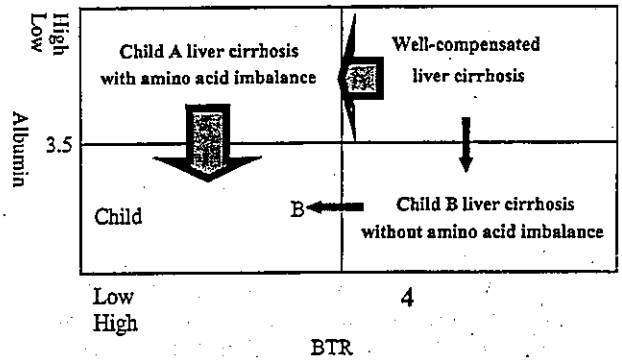


Fig. 2. Progression of compensated liver cirrhosis to decompensated liver cirrhosis. It is assumed that during the progression of compensated liver cirrhosis, the Fisher's ratio decreases prior to a decrease in serum albumin concentration in the majority of patients.

trigger a decrease in albumin synthesis, and their condition is likely to progress to Child B (serum albumin: 3.5 g/dl or less). Consequently, we assume that in many patients with liver cirrhosis, as the compensatory stage progresses, the Fischer's ratio decreases prior to a decrease in serum albumin concentration (Fig. 2).

The mechanism of BCAA administration in increasing serum albumin concentration is shown in detail in another section. It has been assumed that correction of the Fischer's ratio promotes protein synthesis [24], improves metabolic kinetics of albumin [25], and inhibits proteolysis [26]. Therefore, in patients in the previously mentioned condition, the correction of the Fischer's ratio by BCAA administration may prevent a decrease in albumin synthesis.

It has been demonstrated that when patients with advanced liver cirrhosis are given BCAA granules, serum albumin concentrations do not sufficiently increase, because these patients only have a small total number of functioning hepatocytes. Currently, liver parenchymal cells are considered to exclusively synthesize albumin. Therefore, the results of this study suggest that the administration of BCAA granules is more effective in increasing and maintaining serum albumin concentrations when it is started in an early stage, in which the total number of functioning hepatocytes (the total number of cells which can synthesize albumin) can be sufficiently maintained.

## 4. Issues in the future: the possibility that the administration of BCAA is effective in the earlier stages

Many reports have shown the natural course of chronic hepatitis C, which is the largest cause of liver cirrhosis in Japan [27–32]. In summary, it has been shown that chronic hepatitis C, including liver cancer, progresses regularly and gradually. When we regard liver cirrhosis in the same way

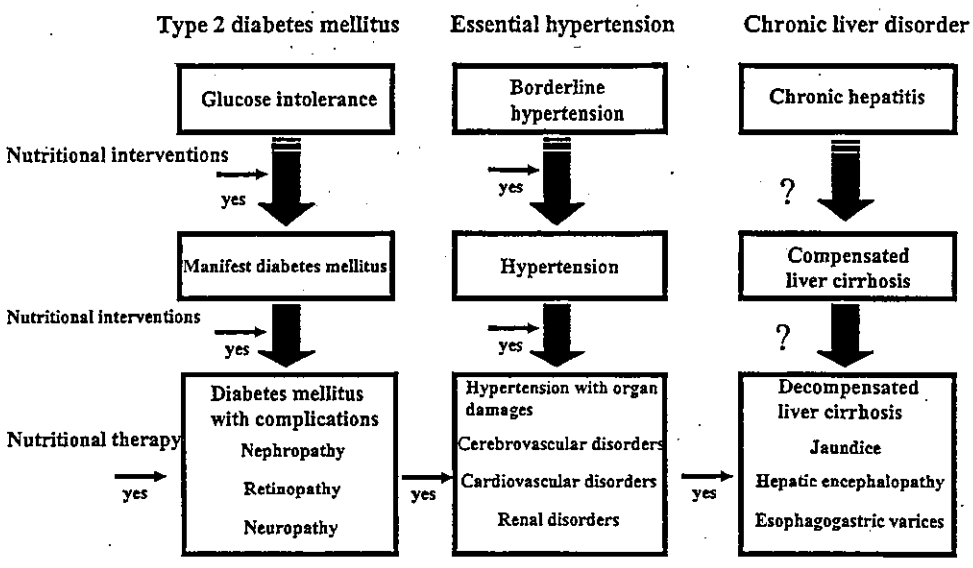


Fig. 3. Advancement of progressive chronic diseases and the timing of nutritional interventions and nutritional therapy. When we regard liver cirrhosis in the same way as other chronic diseases that progress gradually, such as type 2 diabetes mellitus and essential hypertension, starting appropriate nutritional interventions in the early stages of chronic liver diseases is expected to improve prognosis and to maintain QOL. The reason for this is that these interventions are very effective when they are started in patients with glucose intolerance and in patients with borderline hypertension, who exhibit no organ-related symptoms.