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Original Research

Taste Impairment and Compliance Improvement of Branched-Chain Amino Acids in Patients with Liver Cirrhosis

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Abstract

Background: Branched-chain amino acids (BCAAs) are nutrients with a bitter taste, which causes low compliance in patients who need BCAA supplementation. Moreover, chronic liver disease is frequently complicated by taste impairment. The present study was designed to improve patient noncompliance regarding nutrients in liver disease.

Methods: A taste questionnaire was administered to healthy volunteers, chronic hepatitis patients, and cirrhotic patients. 11 different flavored powders that can be added to BCAA nutrients to reduce their unpleasant taste and smell were evaluated and categorized into three groups: delicious, fair, and not good to drink. Patient serum zinc levels were measured and analyzed regarding their relationship to taste dysfunction.

Results: 22 healthy volunteers, 11 chronic hepatitis patients, and 36 liver cirrhosis patients were enrolled. Of the study subjects, 81.8% of healthy volunteers, 72.7% of chronic hepatitis patients, and 50% of liver cirrhosis patients reported that a usual meal was delicious. The fruit-derived flavor and the yogurt flavor powders were well liked among each group. The mean serum zinc value of liver cirrhosis patients (53.7 μg/dl) was significantly lower than that of chronic hepatitis patients (69.6 μg/dl, $P < 0.01$).

Conclusions: Half of the cirrhotic patients were dissatisfied with the taste of the usual meal. Zinc deficiency could be one cause of taste dysfunction and poor appetite in chronic liver disease patients. Flavors derived from fruits, which provide acidity and sweetness to counteract the taste of BCAA nutrients, could improve the palatability of BCAA supplementation for patients with liver disease.

Keywords

Liver cirrhosis; taste impairment; branched-chain amino acids

1. Introduction

Supplementation with branched-chain amino acids (BCAAs) has demonstrated to provide many benefits to patients with liver disease [1]. As essential nutrients, BCAAs have been confirmed to increase albumin, the most abundant blood protein produced by the liver [1]. Furthermore, long-term oral supplementation with BCAA nutrients is more effective than ordinary food as a late evening snack to improve the serum albumin level and energy metabolism of patients with cirrhosis [2]. BCAA supplementation also enhances the non-protein respiratory quotient as well as the branched-chain amino acid/tyrosine ratio in patients with liver cirrhosis [3] and may reduce the risk of liver cancer in cirrhotic patients [4-6]. It has

been reported that BCAAs reduce the production of oxidative stress in hepatitis C virus-positive patients with liver cirrhosis, possibly leading to a decrease in the development of hepatocellular carcinoma [7]. Another study reported that supplementation with BCAA-enriched nutrients for 1 year in cirrhotic patients with hepatocellular carcinoma after radiofrequency ablation therapy can improve patients' nutritional state and quality of life [8].

Although BCAA nutrients for patients with chronic liver disease seem to be useful according to the above reports, the distastefulness of BCAA preparations frequently leads to poor compliance in patients who need such supplementation [9]. Liver cirrhosis is associated with energy malnutrition, numerous metabolic disorders like hypoalbuminemia, an imbalance between branched-chain amino acids and aromatic amino acids, and reduced zinc serum concentrations [10]. Zinc deficiency can result in a spectrum of clinical manifestations, such as poor appetite and altered taste and smell; thus, many patients with liver disease suffer taste dysfunction [11]. Nevertheless, in view of these difficulties, few studies to date have investigated the changes in taste that develop in patients with chronic liver disease. The purpose of this study is to clarify taste impairment caused by liver disease and to seek strategies for improving the noncompliance of patients who require nutritional supplementation with BCAAs.

2. Materials and Methods

2.1 Patients

The study subjects were enrolled from June 2011 to January 2013 and consisted of 22 healthy volunteers, 11 patients with chronic hepatitis, and 36 patients with liver cirrhosis. These chronic liver disease patients were diagnosed in Takasaki General Medical Center. The eligible patients were men and women aged 20 years old or older and diagnosed with chronic hepatitis or cirrhosis. The diagnosis of chronic hepatitis was made by positive hepatitis C virus antibody or hepatitis B surface antigen for more than 6 months with elevated serum alanine aminotransferase (ALT). The diagnosis of non-alcoholic steatohepatitis (NASH) was made by liver biopsy. The diagnosis of cirrhosis was confirmed by liver histology, clinical signs (encephalopathy or ascites), evidence of esophagogastric varices by endoscopy, or imaging modalities, such as ultrasonography, computed tomography, or magnetic resonance imaging. Patients with active intraoral disease, grade C of Child-Pugh classification, or advanced hepatocellular carcinoma were excluded. All patients were informed of the aim and methodology of the study, received a written synopsis, and gave their written consent to participate. This study was approved by the Institutional Review Board of Takasaki General Medical Center (Takasaki, Japan).

2.2 The taste questionnaire

The taste questionnaire was administered to the healthy volunteers, chronic hepatitis patients, and cirrhotic patients. The questionnaire consisted of a self-evaluation in four areas:

taste of daily meals, appetite status, status of the sense of taste, and status of the sense of smell (**Figure 1**). Participants completed a series of 100-mm visual analog scale (VAS) rating questionnaires (VAS paper) in question 3 [12, 13].

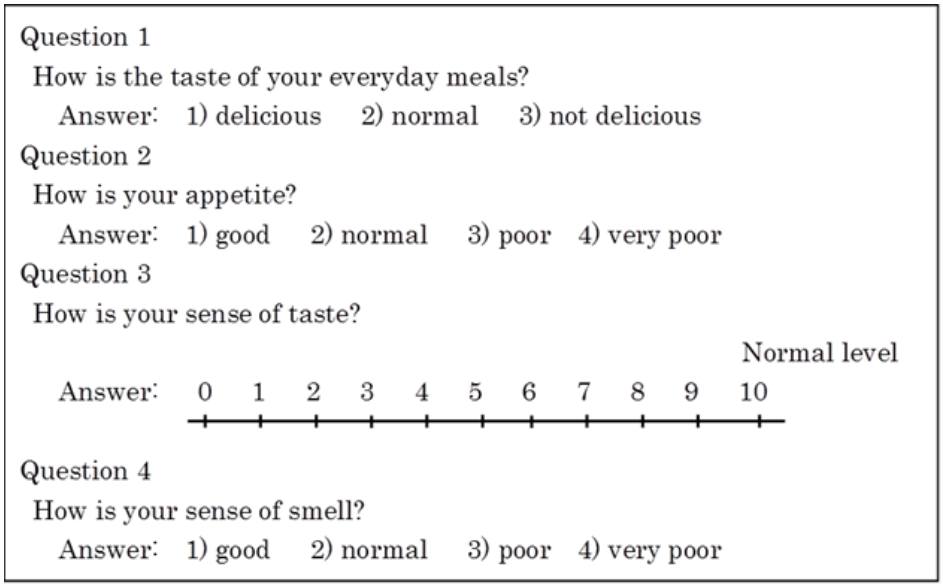

Figure 1 The taste questionnaire.

2.3 Sampling of the flavors added to BCAA nutrients

Various flavored powders were added to BCAA nutrients to reduce their unpleasant taste and smell. The 11 different flavored powders included orange, coffee, yogurt, green apple, grapefruit, pineapple, plum, tomato, milk, tea with lemon, and mango (Ajinomoto Pharmaceuticals Co. Ltd., Tokyo, Japan). We used Hepan-ED (Ajinomoto Pharmaceuticals Co. Ltd., Tokyo, Japan) as the BCAA nutrients [14], which contains 61.7 g carbohydrates, 2.8 g lipids, 11.2 g protein (5.46 g of BCAA), and 3.6 mg zinc per bag. We added one bag (80 g) of Hepan-ED and a flavored powder (6 g each) to approximately 250 mL of water at 4℃ into a suitable container and stirred immediately. This yielded approximately 300 mL (1 kcal/mL) of solution and was stored in a refrigerator at 4℃. Hepan-ED with flavor ready for use was taken within 1 hour after dissolution. Next, we evaluated Hepan-ED with each flavored powder according to three different ratings: delicious (score 3), fair (score 1), or not good to drink (score 0). We purposely did not use a score of 2 in order to emphasize the variances in taste preferences on the graph.

2.4 Objective data assessment

The serum albumin level was measured by the modified bromocresol purple method [15]. The serum zinc level was spectrophotometrically measured by the Shino-Test Kit (Shino-Test Corporation, Tokyo, Japan), and the relation of serum zinc level to taste dysfunction was

analyzed. Fasting blood samples were collected to measure the serum zinc level and other laboratory data.

2.5 Statistical analysis

The results are presented as mean ± standard deviation. Mann-Whitney U test was used for the comparison of unpaired continuous variables between groups. Categorical data were compared using Pearson's chi-squared test and Fisher's exact test, where a p-value less than 0.05 was considered significant. All statistical analyses were performed using the IBM Statistical Package for the Social Sciences software version 21 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1 Patient characteristics

The study subjects included 22 healthy volunteers, 11 chronic hepatitis patients, and 36 liver cirrhosis patients. Baseline characteristics of the participants are listed in **Table 1**. Liver cirrhosis patients were significantly older than chronic hepatitis patients (*P*=0.004). The serum albumin level, prothrombin time, and platelet number were significantly lower in patients with cirrhosis than in patients with chronic hepatitis (*P*=0.001, *P*<0.001, *P*=0.004, respectively). Patients with chronic hepatitis and cirrhosis had no significant difference in etiology.

Table 1 Baseline characteristics of the subjects.

Factors	**Healthy volunteers**	**Chronic hepatitis**	**Liver cirrhosis**	***P*-values**		
	(HV)	**(CH)**	**(LC)**	**HV *vs.* CH**	**HV *vs.* LC**	**CH *vs.* LC**
Number of people	22	11	36	-	-	-
Gender (male/female)	8 / 14	8 / 3	23 / 13	0.071	0.059	0.725
Age (years)	59 ± 17	64 ± 13	71 ± 9	0.510	0.004	0.158
T.Bil (mg/dl)	ND	0.9 ± 0.4	1.7 ± 1.7	-	-	0.165
Alb (g/dl)	ND	4.4 ± 0.3	3.8 ± 0.6	-	-	0.001
ALT (U/l)	ND	50 ± 18	49 ± 28	-	-	0.629
PT (%)	ND	104 ± 13	82 ± 19	-	-	< 0.001
Plt ($\times 10^4/\mu l$)	ND	15 ± 4	10 ± 5	-	-	0.004

Etiology						
HCV	0	8	27	-	-	> 0.99
HBV	0	1	1	-	-	0.417
NASH	0	2	0	-	-	0.051
Alcohol	0	0	4	-	-	0.560
Others	0	0	4	-	-	0.560
Child-Pugh grade (A/B/C)	-	-	28 / 5 / 3	-	-	-

Data are expressed as means ± standard deviation or the number of subjects.
T.Bil; total bilirubin, Alb; albumin, PT; prothrombin time, Plt; platelet, HCV; hepatitis C virus, HBV; hepatitis B virus, NASH; non-alcoholic steatohepatitis, ND; not determined.

3.2 Results of the taste questionnaire

The taste questionnaire (**Figure 1**) was administered to the healthy volunteers, chronic hepatitis patients, and liver cirrhosis patients. Among the subjects, 81.8% (18/22) of the healthy volunteers, 72.7% (8/11) of the chronic hepatitis patients, and 50% (18/36) of the liver cirrhosis patients rated the taste of usual meals as delicious. None of the healthy volunteers (0/22) or chronic hepatitis patients (0/11) reported appetite loss, but 8.3% (3/36) of the liver cirrhosis patients reported appetite loss. Thus, the patients with liver cirrhosis tended to be less satisfied with the taste of the usual meal. According to the ten grades of the self-evaluation taste scale, 9.8 was the mean grade for the healthy volunteers, 9.5 for the chronic hepatitis patients, and 9.3 for the liver cirrhosis patients. We did not find any statistically significant differences between the ten grades of the taste self-evaluation. Poor sense of smell was rated by 9.1% (2/22) of the healthy volunteers, 9.1% (1/11) of the chronic hepatitis patients, and 19.4% (7/36) of the liver cirrhosis patients. The patients with liver cirrhosis seemed to have a disturbance in their sense of smell.

3.3 Sampling of flavors for BCAA nutrients (Figure 2A)

The 11 different flavored powders were added to Hepan-ED, as the BCAA nutrient, to improve the unpleasant taste and smell, given to test subjects, and tested based on the mentioned rating scale. The green apple flavored powder was significantly palatable for both the healthy volunteers and patients with chronic hepatitis compared to no flavor ($P<0.01$). Although no statistical difference was obtained, the patients with liver cirrhosis also preferred the green apple flavored powder. The grapefruit flavor was also favorable for the healthy volunteers, while yogurt was the second most favored flavor for the chronic hepatitis and liver cirrhosis patients.

3.4 Evaluation of serum albumin and zinc levels

The serum albumin and zinc levels are shown in **Table 2**. The average serum albumin value of the liver cirrhosis patients was significantly lower than that of the chronic hepatitis patients (*P*<0.01). The average serum zinc values of the chronic hepatitis and liver cirrhosis patients were 69.6 μg/dl and 53.7 μg/dl, respectively. The serum zinc value of the liver cirrhosis patients was significantly lower than that of chronic hepatitis patients (*P*<0.01). The serum zinc values of chronic hepatitis and liver cirrhosis patients were significantly lower than that of the manufacture's normal controls (*P*<0.01).

Table 2 The serum albumin and zinc levels of patients with chronic hepatitis and liver cirrhosis.

Characteristics	Chronic hepatitis	Liver cirrhosis	*P*-value
Serum albumin (g/dl)	4.4 ± 0.3	3.8 ± 0.6	0.001
Serum zinc (μg/dl)	69.6 ± 8	53.7 ± 28	0.005

Data are expressed as means ± standard deviation.

3.5 Serum zinc level and its relationship to taste preference

Serum zinc levels were measured in 42 of the chronic hepatitis and liver cirrhosis patients, which were divided into two groups of approximately equal size: zinc level ≥50 μg/dl and zinc level <50 μg/dl. After measurements, 25 patients were placed in the high serum zinc level group and 17 patients in the low serum zinc level group. Results show that the group with high serum zinc levels favored fruit-flavored powders (**Figure 2B**), particularly the pineapple-flavored powder (*P*<0.05). The questionnaire answers further reveal that, among the participants who rated their daily meals as delicious, 35.3% were in the low serum zinc level group and 64% were in the high serum zinc level group (P=0.07). Among the participants who indicated that their appetite was poor, 11.8% (2/17) were in the low serum zinc level group, and 4% (1/25) were in the high serum zinc level group (*P*=0.34). According to the ten grades of taste evaluation, the low serum zinc level group averaged 9.4, and the high serum zinc level group averaged 9.2. Dysosmia was reported in 23.5% subjects of the low zinc group and 12% of the high zinc group (*P*=0.33).

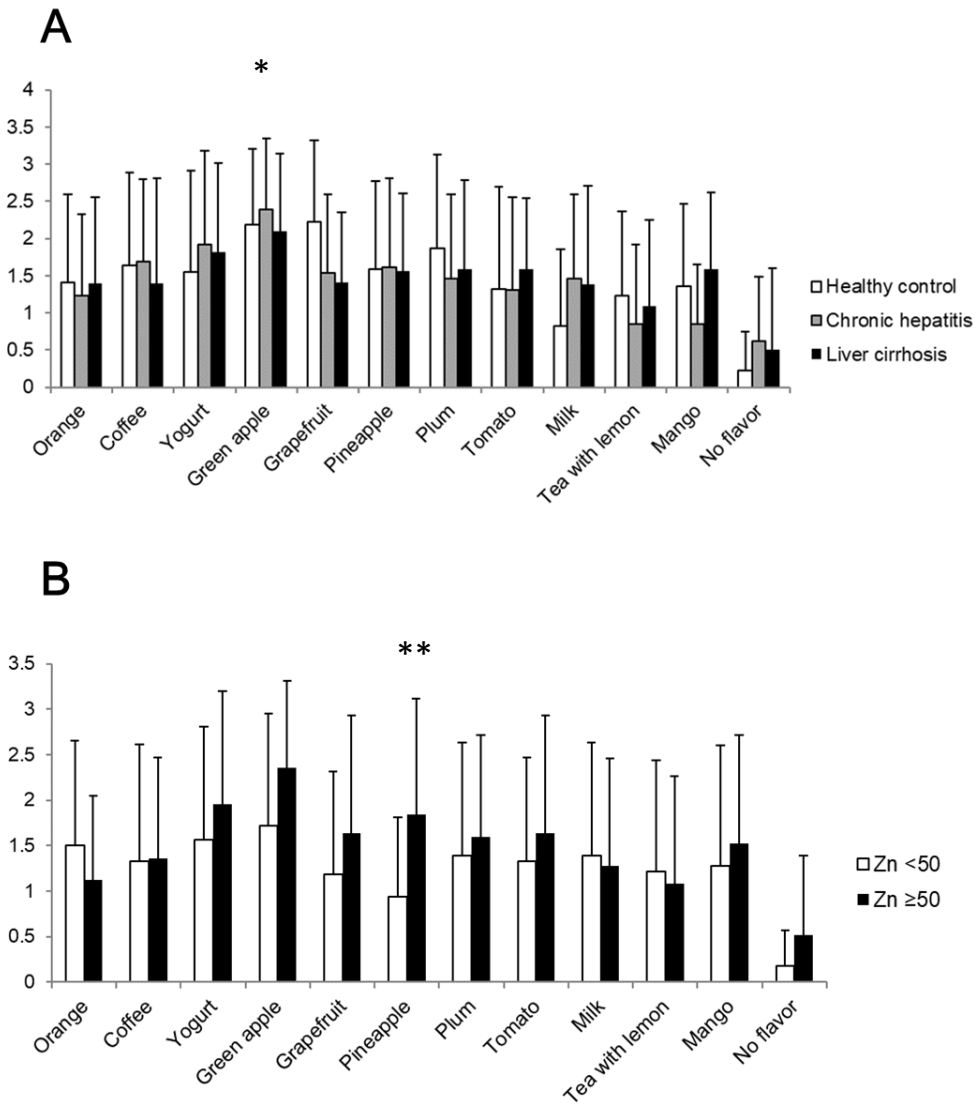

Figure 2 The differences in preference among the 11 flavored powders added to BCAA nutrients to reduce their unpleasant taste and smell. (A) The flavored powders added to the BCAA nutrients (Hepan-ED) were evaluated for their ability to improve the taste: delicious (score 3), fair (score 1) and not good to drink (score 0) in healthy volunteers, chronic hepatitis patients, and cirrhotic patients. The vertical axis shows the mean scores. (B) The patients with chronic hepatitis and cirrhosis were divided according to having serum zinc levels above or below 50 g/dl, and the means of the scores were compared. *; $P<0.01$, **; $P<0.05$.

4. Discussion

Despite the existing published studies on supplements containing BCAA for liver disease, further research is needed to develop new BCAA formulas or more palatable nutritional support to avoid noncompliance [1, 16, 17]. Therefore, this presented study aimed to clarify taste impairment and determine strategies to improve the noncompliance in liver disease

patients who need nutritional supplementation with BCAA. The taste questionnaire showed that the liver cirrhosis patients were less satisfied with the taste of everyday meals and experienced poorer appetite compared with the other groups. In the taste self-evaluation, the cirrhosis patients had the lowest scores and a duller sense of smell than the other groups. These results are compatible with a past report [18]. Doty reported disturbances in both the ability to smell and taste are common in older persons [19], it may also be relevant that patients with cirrhosis were older than those in other groups.

In patients with liver cirrhosis, about two-thirds of the serum zinc was reported to be combined with albumin [20]. The reasons for the low serum zinc level in patients with liver cirrhosis can be attributed to increased urinary excretion of zinc through portal-systemic shunting and hypoalbuminemia-induced low affinity of zinc coupling to albumin [21]. Taste disturbance in patients with liver disease is suggested to be caused by low serum zinc levels [20].

From the questionnaire results, it was found that the high serum zinc group rated more daily meals as delicious and reported higher appetite than the low serum zinc group. In addition, disorder of the sense of smell was reported less frequently in the high serum zinc group than in the low serum zinc group. Because of varying serum zinc levels in liver disease patients, the high serum zinc level group rated the BCAA nutrients with each flavored powder as more delicious than the patients with low serum zinc levels. According to these results, low serum zinc levels seem to disturb the sense of taste in patients with liver disease.

Among the patients with liver disease, the most favored powders added to the BCAA nutrients were fruit- and yogurt-flavored. For instance, the cirrhotic patients preferred the mango flavor more than the chronic hepatitis patients. One of the reasons for this preference is that the refreshing acidity and sweetness relieves the bitterness of the BCAA nutrients, making the preparation easier and enjoyable to drink [9]. Furthermore, the mango-flavored powder includes only the products of real mango fruit, as well as the fragrance, compared with the other artificial fruit flavors.

As previously reported, patients with chronic liver disease exhibited disordered gustatory acuity based on subjective responses, objective measurements of detection and recognition thresholds, and scaling for sodium chloride, sucrose, hydrochloric acid, and urea [22]. This disorder of gustatory acuity may be one cause of anorexia commonly found in patients with liver disease. It has been reported that a supplement enriched with BCAA improved the sensitivity to different tastes and increased zinc levels in patients with hepatitis C virus liver disease [23]. Nagao et al. reported that sensitivity to sour and sweet tastes increased after the administration of a supplement enriched with BCAA and zinc in chronic liver disease patients [23].

In the sampling results of the present study, all patients preferred the fruit-derived and yogurt flavors, for which the acidity and sweetness were easier to detect. It is supposed that the various tastes added to the BCAA nutrients make it easy to perceive the nutrients as delicious.

The limitation of this study included the small sample size. Also, there is no guarantee that improvement via addition of flavored powder can improve long-term nutritional compliance even if participants rated the BCAA nutrients as palatable. Therefore, long-term research with a larger sample size is needed to produce more reliable results.

Although further studies are needed to resolve the molecular mechanisms of taste disturbance, we conclude that zinc deficiency could be one cause of taste dysfunction and poor appetite in chronic liver disease patients. Flavors derived from fruits, which provide acidity and sweetness to counteract the bitterness of BCAA nutrients, could improve the palatability of BCAA supplements for patients with liver cirrhosis.

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Author Contributions

Conception and study design: Naganuma A.; Data collection: Adachi S., Sawada S., Hoshino T., Takagi H.; Analysis and interpretation: Naganuma A., Kakizaki S., Ogawa Y., Araki T.; Writing of manuscript: Naganuma A., Kakizaki S.; Critical review of manuscript: Tanaka T., Ogawa T., Sasaki T., Sato K., Takagi H., Uraoka T. All authors have read and approved the final version of the manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

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