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Effect of a Late Evening Snack of *Amazake* in Patients with Liver Cirrhosis: A Pilot Study

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Abstract

Background: Liver Cirrhosis (LC) is a state of accelerated starvation. A late evening snack improves protein-energy malnutrition, caused by overnight starvation and the catabolic state of patients with LC. This study was designed to evaluate the effects of *amazake*, a traditional sweet Japanese beverage, as a late evening snack for cirrhotic patients.

Methods: Serum biochemical parameters and the visual analogue scale (VAS) were examined at 0, 4, 8, and 12 weeks. Each patient drank 200 kcal of *amazake* at bedtime every night for 12 weeks. Trial registration: UMIN-CTR UMIN000010550

Results: Four patients (mean age 67.3 ± 5.7 years) with viral LC were recruited and their VAS score determined, along with a biochemical examination of the blood. White blood cell counts (WBC), especially neutrophil counts, were elevated following a period of *amazake* intake. Each VAS score was reduced following *amazake* intake. *Amazake* intake improved the Quality of Life (QOL) in all terms of sense of abdomen distension, edema, fatigue, muscle cramps, loss of appetite, taste disorder, constipation, diarrhea, vomiting, and sleep disorder. Any sense of abdominal distension, constipation and vomiting had disappeared after 8 weeks of *amazake* intake and taste disorder and sleep disorder had disappeared after 12 weeks of *amazake* intake. No major clinical events or virological rebounds occurred in the subjects.

Conclusions: *Amazake*, which is rich in vitamins and amino acids, could be effective in reducing the subjective symptoms and improving the QOL of patients with LC.

Keywords: *Amazake*; Liver cirrhosis; Late evening snack; Quality of life

Abbreviations: HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; LC: Liver Cirrhosis; HCC: Hepatocellular Carcinoma; PEM: Protein-Energy Malnutrition; QOL: Quality of Life; BCAA: Branched-Chain Amino Acids; WBC: White Blood Cell Counts; RBC: Red Blood Cell Counts; Hb: hemoglobin; PLT: Platelets; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; γ-GTP: Gamma-Glutamyl Transpeptidase; ALP: Alkaline Phosphatase; LDH: Lactate Dehydrogenase; Alb: Albumin; T.Bil: Total Bilirubin; Crea: Creatinine; HbA1c: Hemoglobin A1c; FBS: Fasting Blood Glucose; IRI: Immunoreactive Insulin; BTR: BCAA Tyrosine Ratio

Introduction

The liver is a central organ of metabolism in the body with many functions-carbohydrate metabolism, detoxification and protein synthesis. Because the liver performs many complex metabolic functions, there are many possible complications that can develop on a background of liver cirrhosis (LC) [1,2]. In addition, malnutrition in patients with LC is known to increase the risk of postoperative complications and mortality [3]. Protein-energy malnutrition (PEM) is frequently a complication in patients with chronic liver disease [4-6]. Malnutrition in cirrhotic patients is readily understood as a consequence of metabolic disturbances in combination with low spontaneous dietary intake [4]. Several studies have reported that the protein nutritional state determines the survival of cirrhotic patients [7,8].

The European Society for Clinical Nutrition and Metabolism (ESPEN) guideline recommends non-protein energy of 25-35 kcal/kg for cirrhotic patients without malnutrition [9] and that cirrhotic patients who need to be managed nil by mouth should be given glucose i.v. at a rate equal to the endogenous hepatic glucose production [10]. In 2002, the American Society for Parenteral and Enteral Nutrition (ASPEN) suggested that patients with liver cirrhosis should divide their dietary intake into 4 to 6 meals per day, including a late evening snack [11].

A late evening snack is reported not only to improve protein metabolism [12,13] and glucose intolerance [14-17] but also to suppress hepatocarcinogenesis in cirrhotic patients [18]. The long-term consumption of late evening snacks has been reported to be helpful in maintain a greater health-related quality of life (QOL) of patients with cirrhosis [19,20]. It is necessary for food to be of low cost to continue late evening snacking and to provide sufficient nutrition [21].

Amazake is a traditional sweet and non-alcoholic Japanese beverage made from fermented rice. The *Amazake*-drinking culture dates from late in the third century to early in the seventh century and is mentioned in the "Nihon Shoki", the second oldest book of classical Japanese history. *Amazake* is made from rice, *rice-koji* and water. *Rice-koji* is produced by adding a fungus, *Aspergillus oryzae*, to steamed rice.

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Amazake, which is rich in vitamins and amino acids, is a nutritious drink called Japanese yogurt.

Recent progressive studies showed that sake cake and *rice-koji* had various physiological effects, such as anti-hypertension, anti-obesity and anti-amnesia properties [22-24]. In this study, the effect and QOL of *amazake* as a late evening snack on energy metabolism was investigated in patients with LC. Visual analogue scales (VAS) are often used in clinical research to measure the intensity or frequency of various symptoms, particularly pain [25].

Materials and Methods

Subjects

Eligibility criteria were LC with sufficient food intake and a serum albumin concentration below 4.0 g/dL.

The exclusion criteria were as follows: (a) hepatic encephalopathy, ascites, hepatocellular carcinoma (HCC) or renal failure, (b) diabetes mellitus on medication for anti-diabetic drugs, (c) ongoing, self motivated consumption of late evening snacks, (d) ongoing interferon therapy, (e) refusal or inability to give informed consent and (f) follow-up not possible.

This study included four Japanese patients (2 males and 2 females) with LC who visited our clinic at the Kurume University Hospital in Japan from December 22, 2009 to August 24, 2010. The patients ranged in age from 59 to 72 years, with an average age of 67.3 ± 5.7 years. LC was diagnosed by documented laboratory data, imaging, and/or histology. The Child-Pugh score corresponds to the total of points for each item and, according to the total of these points, patients were categorized into Child-Pugh grades A (5 to 6 points), B (7 to 9 points) or C (10 to 15 points). This study included three patients with Child-Pugh's grade A and one with grade B. The diagnosis of liver disease was hepatitis C Virus (HCV)-related LC (n=3) and hepatitis B Virus (HBV)-related LC (n=1). A 68-year-old Japanese male with LC-B had taken a branched-chain amino acid (BCAA) agent (Livact®, Ajinomoto Pharmaceuticals Co., Ltd. Tokyo, Japan) two times (three packs) per day, one pack after breakfast and two packs after dinner. A 70-year-old Japanese female with LC-C had taken a BCAA-enriched zinc component nutritional supplement (Aminofeel®, Seikatsu Bunkasya Co. Inc, Tokyo, Japan), one pack (4.0 g) per day in morning. The two remaining cirrhotic patients did not take BCAA granules.

Study protocol

The intervention schedule is presented in Figure 1. Each patient used a measuring cup and drank 150 mL of *amazake* (equivalent to 200 kcal) (KITAYA Co., Ltd, Fukuoka, Japan) at bedtime, every night for 12 weeks. The constituents of *amazake* are summarized in Table 1. *Amazake* yielding 200 kcal contains 46.1 g carbohydrates, 3.0 g protein, 0.5 g fat and vitamins. Essential amino acids also are present in *amazake*, as shown in Table 1. The study period comprised 12 weeks with evaluations at baseline (visit 1), 4 weeks (visit 2), 8 weeks (visit 3) and 12 weeks (visit 4). The schedule for each visit is shown in Table 2.

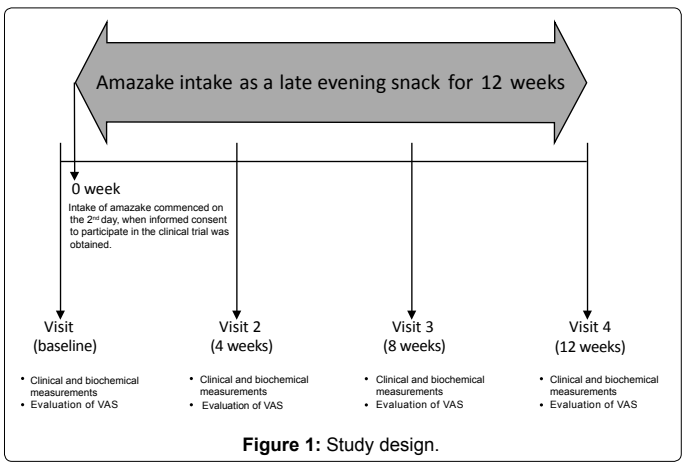

Figure 1: Study design.

Substance	Amount
Energy	122 kcal
Fluid	69.9 g
Carbohydrate	28.0 g
Protein	1.8 g
Fat	0.3 g
Ash	0 g
Sodium	6 mg
Vitamin B1	0.01 mg
Vitamin B2	0.02 mg
Vitamin B6	0.02 mg
Pantothenic acid	0.12 mg
Isoleucine (Ile)	63 mg
Leucine (Leu)	130 mg
Lysine (Lys)	54 mg
Methionine (Met)	45 mg
Phenylalanine (Phe)	82 mg
Threonine (Thr)	61 mg
Tryptophan (Trp)	23 mg
Valine (Val)	99 mg
Histidine (His)	37 mg

Table 1: The constituents of *amazake* per 100 g produced by KITAYA Co., Ltd.

	Visit 1	Visit 2	Visit 3	Visit 4
	Baseline	4 weeks	8 weeks	12 weeks
Informed consent form	•			
Medical history taking	•			
Physical examination	•	•	•	•
Measurement of body weight	•	•	•	•
Serological assays	•	•	•	•
Abdominal echography	•	•	•	•
Evaluation of VAS	•	•	•	•

Table 2: Study schedule at each visit.

Serological assays

Sera were evaluated for white blood cell counts (WBC), red blood cell counts (RBC), hemoglobin (Hb) and platelets (PLT) and the following liver function tests were carried out: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GTP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), albumin (Alb), total bilirubin (T.Bil), and creatinine (Crea). The blood levels of hemoglobin A1c (HbA1c), fasting blood glucose (FBS), BCAA, tyrosine, immunoreactive insulin (IRI), and zinc were measured. The formula for the HOMA-IR is: HOMA-IR=FBS×fasting insulin/405. BCAA tyrosine ratio (BTR) was calculated as BCAA/ tyrosine.

Abdominal imaging

Ultrasonographic examination was performed on all patients in order to investigate the shape of the liver and lesions occupying the

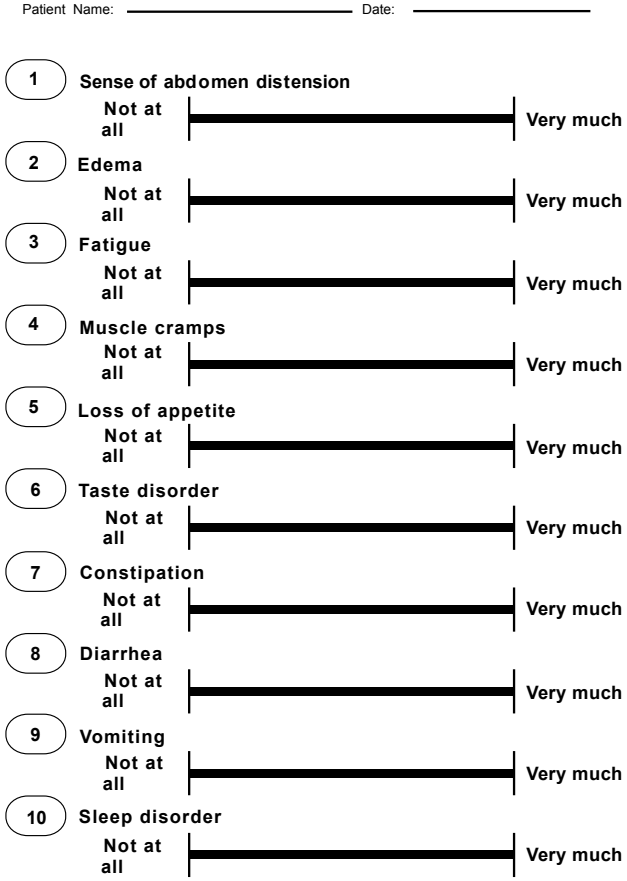

Figure 2: VAS of 10 items.
A VAS is a horizontal line, 100 millimeters in length, anchored by word descriptors at each end.

liver. Computed tomography and liver biopsy were performed in some patients.

Evaluation of VAS

A VAS is a horizontal line, 100 millimeters in length, anchored by word descriptors at each end, as illustrated in Figure 2. The patients is asked to mark the line the point that they feel represents their perception of their current state, such as sense of abdomen distension, edema, fatigue, muscle cramps, loss of appetite, taste disorder, constipation, diarrhea, vomiting, and sleep disorder. The VAS score was determined by measuring in millimeters from the left hand end of the line to the point that the patient had marked.

Ethical considerations

This study was approved by the Ethics Committee of Kurume University on December 1, 2009 (reference number: 09149) in accordance with the Declaration of Helsinki and was registered in the national UMIN Clinical Trials Registry (ID: UMIN 000010550). Written informed consent was obtained from all participants.

Results

Effects of amazake on protein, lipid and glucose metabolism

The characteristics of the four patients are shown in Table 3. We analyzed any differences in laboratory data before and after intake of *amazake*. WBC, especially neutrophil counts, was elevated following the period of *amazake* intake. No changes in lipids (total cholesterol, LDL cholesterol, or triglycerides), glucose, insulin, or the homeostasis model assessment of insulin resistance (HOMA-IR) were observed overall.

The distributions of VAS score

The distributions of VAS scores before and after intake of *amazake* are as shown in Table 4. Each VAS score was lower after intake of *amazake* than before. Therefore, *amazake* improved the QOL according to all criteria. Any sense of abdominal distension, constipation and vomiting had disappeared after 8 weeks of *amazake* intake and taste disorder and sleep disorder had disappeared after 12 weeks of *amazake* intake.

Safety

No major clinical events or virological failures were recorded.

Discussion

Amazake is fermented food related to several other traditional Japanese products, soy sauce, miso and mirin. *Amazake* is produced by combining cooked *rice-koji*, which is made by mixing rice with *Aspergillus oryzae* and incubating it at a warm temperature to ferment for several hours. *Amazake* contains vitamin B1, vitamin B2, vitamin B6, pantothenic acid, all of the essential amino acids, and a large amount of glucose; these nutrients are the same as those contained in intravenous fluids provided at hospitals.

Aspergillus flavus, known to be a producer of aflatoxin, and *Aspergillus oryzae*, both belong to the *Flavi* section of the *Circumdati* subgenus of *Aspergillus*. Aflatoxin B1 is the most potent naturally occurring chemical liver carcinogen known. Nevertheless, *Aspergillus oryzae* does not produce aflatoxin or any other carcinogenic metabolites [26] and an important microorganism with a long history in the Japanese food fermentation industry [27]. *Aspergillus oryzae* is affirmed as Generally Recognized as Safe (GRAS) by the Food and Drug Administration (FDA) in the USA. Sequencing the genome of *Aspergillus oryzae* RIB40 (ATCC-42149) was completed in 2005 [28]. The *Aspergillus* oryzae genome consists of eight chromosomes with an entire genome size of 37.6 Mb. The *Aspergillus oryzae* genome is extremely rich in genes involved in biomass degradation, primary and secondary metabolism, transcriptional regulation, and cell signaling [29]. The *Aspergillus oryzae* genome contains more genes than the genomes of other species in the genus *Aspergillus* [28]. It is predicted to code for 12,074 proteins of >100 amino acids, which is 1,412 more proteins than *Aspergillus nidulans* and 2,444 more than *Aspergillus fumigatus* [30].

In recent years, the beneficial effects of *amazake* have been widely studied and blood pressure-lowering effects, anti-obesity effects, liver-protecting effects and anti-amnesic effects have been reported. Oura et al. [24] demonstrated some benefits of *amazake*–anti-obesity, anti-hypertension and anti-amnesia–in mice. However, there are few studies that have shown the effects of *amazake* on patients with liver disease. In this study, *amazake* intake contributed to improvement of the QOL of cirrhotic patients, and was a useful beverage as a late evening snack.

Decreases in serum levels of branched-chain amino acids (BCAA) are often seen in patients with chronic liver diseases and lead to a decline in the production of albumin and detoxification of ammonia. Therefore, BCAAs are used for the treatment of hypoalbuminemia and

	Normal range	Baseline	4 weeks after *amazake* intake	8 weeks after *amazake* intake	12 weeks after *amazake* intake
BMI (kg/m^2)		21.0 ± 2.0	21.1 ± 2.1	21.1 ± 2.1	21.1 ± 1.9
WBC (/μL)	4000-9000	3775.0 ± 1302.2	4425.0 ± 1621.5	4625.0 ± 2376.8	6250.0 ± 4197.2
Neutrophil count (%)	40.0-70.0	47.5 ± 12.1	57.3 ± 11.7	56.1 ± 17.7	56.3 ± 20.0
Eosinophil count (%)	2.0-4.0	4.0 ± 2.5	3.4 ± 2.7	4.5 ± 4.3	4.8 ± 5.3
Basophil count (%)	0.0-1.0	0.8 ± 0.3	0.8 ± 0.4	0.6 ± 0.7	0.7 ± 0.5
Lymphocyte counts (%)	30.0-43.0	39.5 ± 10.3	31.3 ± 9.2	31.6 ± 11.4	30.1 ± 13.6
Monocyte count (%)	3.0-6.0	8.3 ± 2.9	7.3 ± 1.9	7.2 ± 3.0	8.1 ± 2.5
RBC (x10^4/μL)	Male: 430-570, Female: 380-500	410.8 ± 21.9	404.5 ± 29.3	404.0 ± 14.0	409.8 ± 21.1
Hb (g/dL)	Male: 14.0-18.0, Female: 11.0-15.0	13.0 ± 0.9	12.8 ± 1.2	12.6 ± 0.7	12.6 ± 1.1
Plt (x10^4/μL)	13.0-36.0	10.4 ± 3.4	9.8 ± 2.8	10.1 ± 3.3	11.3 ± 4.2
PT (%)	70-130	83.0 ± 14.1	80.0 ± 14.5	80.5 ± 13.6	81.0 ± 15.5
AST (U/L)	13-33	62.3 ± 29.4	65.8 ± 31.4	58.3 ± 24.8	58.5 ± 24.0
ALT (U/L)	6-30	43.5 ± 23.5	44.5 ± 22.5	38.3 ± 19.7	41.3 ± 21.6
γGTP (U/L)	10-47	24.5 ± 13.5	24.8 ± 14.0	24.8 ± 16.0	26.3 ± 15.7
ALP (U/L)	115-359	403.5 ± 184.2	456.8 ± 246.4	415.3 ± 213.4	417.3 ± 156.9
LDH (U/L)	119-229	228.3 ± 21.8	228.0 ± 25.5	238.5 ± 28.8	233.5 ± 19.4
ChE (U/L)	214-466	203.5 ± 58.6	199.8 ± 63.3	192.0 ± 50.8	194.3 ± 54.7
T. pro (g/dL)	6.70-8.30	7.86 ± 0.39	7.74 ± 0.62	7.71 ± 0.36	7.86 ± 0.42
Alb (g/dL)	4.00-5.00	3.61 ± 0.40	3.53 ± 0.37	3.52 ± 0.38	3.57 ± 0.41
BTR	4.4-10.0	3.9 ± 1.5	3.6 ± 1.2	3.0 ± 0.9	3.1 ± 1.2
BCAA (μmol/L)	344.0-713.0	392.7 ± 70.1	417.5 ± 38.5	352.3 ± 83.5	366.3 ± 69.9
TVR (μmol/L)	51.0-98.0	110.4 ± 37.7	125.6 ± 45.0	124.4 ± 52.8	124.5 ± 37.8
T.Bil (mg/dL)	0.30-1.20	1.21 ± 0.38	1.05 ± 0.32	1.14 ± 0.34	1.14 ± 0.35
D.Bil (mg/dL)	<=0.60	0.14 ± 0.05	0.12 ± 0.05	0.11 ± 0.03	0.13 ± 0.07
BUN (mg/dL)	8.0-22.0	13.1 ± 5.8	14.8 ± 5.7	12.8 ± 4.2	14.2 ± 4.0
Crea (mg/dL)	Male: 0.60-1.10, Female: 0.40-0.70	0.63 ± 0.11	0.61 ± 0.09	0.62 ± 0.10	0.63 ± 0.10
AFP (ng/mL)	<=8.7	3.4 ± 2.0	4.0 ± 1.9	3.6 ± 2.3	4.1 ± 2.9
PIVKAII (mAU/mL)	<=40	10.8 ± 4.7	11.0 ± 4.1	10.5 ± 4.7	12.0 ± 4.5
NH_3 (μg/dL)	12-66	48.3 ± 32.1	48.8 ± 30.6	48.3 ± 30.0	49.8 ± 32.1
CRP (mg/dL)	<=0.20	0.10 ± 0.08	0.10 ± 0.07	0.07 ± 0.04	0.08 ± 0.05
Na (mmol/L)	138-146	141.5 ± 1.3	140.8 ± 1.0	140.8 ± 1.0	140.8 ± 2.1
K (mmol/L)	3.6-4.9	4.2 ± 0.2	4.2 ± 0.3	4.1 ± 0.3	4.0 ± 0.4
Cl (mmol/L)	99-109	105.5 ± 0.6	105.8 ± 1.0	106.3 ± 1.7	105.8 ± 1.3
TC (mg/dL)	128-219	151.3 ± 15.8	158.3 ± 22.4	154.0 ± 17.1	162.8 ± 28.3
TG (mg/dL)	30-149	91.0 ± 18.7	100.5 ± 36.5	91.8 ± 22.4	102.5 ± 52.0
LDL-C (mg/dL)	<=139.0	78.6 ± 29.2	76.9 ± 28.5	75.7 ± 19.3	81.0 ± 26.4
FBS (mg/dL)	80-109	106.5 ± 5.8	105.5 ± 16.6	101.8 ± 9.9	100.5 ± 10.7
HbA1c (%)	4.3-5.8	5.3 ± 0.3	5.3 ± 0.2	5.3 ± 0.2	5.4 ± 0.2
IRI (μU/mL)	5.0-20.0	8.5 ± 5.7	11.9 ± 8.3	10.0 ± 6.4	13.9 ± 8.3
HOMA-IR	< 5.4	2.2 ± 1.5	3.2 ± 2.4	2.5 ± 1.7	3.4 ± 2.2
Zinc (μg/dL)	80-130	66.8 ± 18.3	60.3 ± 17.1	59.0 ± 11.7	57.5 ± 16.2

Table 3: Characteristic of the biochemical examination of blood in 4 patients.

VAS score (mm)	Baseline	4 weeks after *amazake* intake	8 weeks after *amazake* intake	12 weeks after *amazake* intake
Sense of abdominal distension	14.0 ± 18.1	2.3 ± 4.5	0.0 ± 0.0	0.0 ± 0.0
Edema	30.3 ± 28.5	28.0 ± 28.1	30.0 ± 34.6	19.0 ± 28.9
Fatigue	25.5 ± 21.2	17.8 ± 18.1	12.5 ± 20.0	9.8 ± 11.3
Muscle cramps	58.0 ± 26.8	15.5 ± 20.4	15.8 ± 20.5	20.5 ± 29.7
Loss of appetite	37.3 ± 26.0	7.3 ± 8.8	17.5 ± 29.9	9.3 ± 10.7
Taste disorder	4.8 ± 9.5	2.5 ± 5.0	7.0 ± 9.1	0.0 ± 0.0
Constipation	5.0 ± 10.0	2.5 ± 5.0	0.0 ± 0.0	0.0 ± 0.0
Diarrhea	15.0 ± 20.3	14.0 ± 20.3	23.5 ± 22.2	6.8 ± 8.6
Vomiting	4.3 ± 8.5	2.8 ± 5.5	0.0 ± 0.0	0.0 ± 0.0
Sleep disorder	24.0 ± 29.7	18.3 ± 29.6	18.3 ± 22.2	0.0 ± 0.0

Table 4: Effects of VAS score.

hepatic encephalopathy [31,32]. There is additional evidence of the beneficial effects of BCAAs that supports their use in the treatment of malnutrition in patients with advanced cirrhosis. Kawaguchi et al. [33] suggested the following three reasons for improvement of subjective symptoms with BCAA intake: amelioration of hepatic encephalopathy, improvement of malnourishment by elevated tryptophan levels and improvement of impaired cerebral blood flow.

The palatability of a medicine is an important factor in determining compliance. Marchesini et al. [34]. performed a multicenter, randomized trial examining the role of oral BCAA supplementation in 174 patients with advanced liver disease. The most significant limitation that the investigators reported was poor compliance with the BCAA-enriched diet; in the BCAA group, 15% of patients did not complete the treatment course. Poor compliance was attributed to the poor palatability of the BCAA supplement. Noncompliance and withdrawal of consent were mainly attributable to the poor palatability of supplements, which specifically occurred with BCAA supplements. However, because *amazake*, which contains amino acids and vitamins, is a traditional sweet beverage which everyone in Japan knows from childhood, cirrhotic Japanese patients can continue to enjoy it for a long time as a late evening snack.

In this study, it is not clear how the *amazake* intake causes an increase in neutrophil counts. However, BCAA in *amazake* may influence the local immune system of the liver and may improve the phagocytic function of neutrophils and NK activity of lymphocytes in cirrhotic patients [35-37].

Study limitations

The study has provided new insights into nutritional management of cirrhotic patients. However, there are several limitations. Firstly, limitations to our study include the very small sample size. Therefore it is necessary to examine large samples. A second limitation of our study is that we did not investigate cirrhotic patients using a controlled trial. *Amazake* is a Japanese traditional beverage, but the study on the relationship between *amazake* and liver disease had hardly been reported. Therefore, this study is the first report. We reported this as pilot study. Further research with a large-scale, case controlled study is required to document the long-term impact of *amazake*.

Conclusions

In conclusion, we showed in this pilot study that intake of 200 kcal *amazake* as a late evening snack improved the subjective symptoms of four patients with LC. The results of this study indicate that the use of *amazake* could be effective in reducing the subjective symptoms and improving the QOL of patients with LC.

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Authors' contributions

Yumiko Nagao carried out most of the data collection and drafted the manuscript. Michio Sata contributed to data analysis. All authors read and approved the final manuscript.

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