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## Aminofeel® improves the sensitivity to taste in patients with HCV-infected liver disease

### Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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### Summary

#### Background:

Patients with chronic liver diseases have a taste disorder and altered zinc metabolism. We investigated the effects of a supplement enriched with branched-chain amino acids (BCAA) (Aminofeel®) on sensitivity to different tastes in patients with hepatitis C virus (HCV) infected liver disease.

#### Material/Methods:

Nine patients (mean age 63.3±9.1 years) with HCV-related liver diseases were identified and examined for sensitivity to different tastes. Eight patients had no awareness of taste disorders, and 3 patients had oral lichen planus. We examined 4 tastes (sweet, salty, sour, and bitter) using a Taste Disk® and sensitivity to different tastes was rated on a 6-point scale (I, II, III, IV, V, and VI). Each patient was given one sachet of Aminofeel® after breakfast and another at bedtime for 90 days.

#### Results:

Only one patient was aware of a taste disorder before administration of Aminofeel®, but 4 patients had decreased gustatory sensitivity in the sour taste test, and 2 had it in the bitter taste test. Sensitivity to sour tastes significantly increased after the administration of Aminofeel® (P=0.03). Sensitivity to sweet tastes increased after the administration of Aminofeel® (P=0.06). Zinc value significantly increased after the administration of Aminofeel® (P=0.02).

#### Conclusions:

Patients with HCV-infected liver disease have decreased sensitivity to different tastes and decreased zinc levels. Some patients were unaware that they had a taste disorder. Aminofeel® improved sensitivity to different tastes and increased zinc values. Thus, Aminofeel® is a useful therapeutic agent for taste disorders.

#### key words:

taste disorder • zinc • hepatitis C virus (HCV) • lichen planus • branched-chain amino acids (BCAA) • Aminofeel®

#### Abbreviations:

**BCAA** – branched-chain amino acids; **Anti-HCV** – anti-bodies to HCV; **CLEIA** – chemiluminescent enzyme immunoassay; **HBsAg** – hepatitis B surface antigen; **HCC** – hepatocellular carcinoma; **HCV** – hepatitis C virus; **IFN** – interferon

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## BACKGROUND

In Japan, the number of patients seeking treatment from otolaryngologists for taste disorders is approximately 240,000/year; the number has almost doubled in the last 13 years [1]. The main treatment for taste disorders is zinc administration. And many studies have found zinc deficiency in patients with liver diseases [2–4]. Therefore, patients with chronic liver disease may have taste disorders and altered zinc metabolism [5,6]. Several factors, such as poor dietary intake, impaired intestinal absorption, or excessive urinary losses may be responsible for the reduced whole-body zinc content [7].

Decreases in levels of serum branched-chain amino acids (BCAA) are often seen in patients with chronic liver diseases and these decreases lead to a decline in production of detoxified ammonia and albumin. Therefore, BCAAs are used for the treatment of hepatic encephalopathy and hypoalbuminemia [8,9]. The Department of Digestive Disease Information & Research, Kurume University School of Medicine and Seikatsu Bunkasya Co. Inc. (Tokyo, Japan) developed the BCAA-enriched supplement (Aminofeel®) and facilitated the commercialization of the product. On March 1, 2007, Seikatsu Bunkasya Co. Inc. released Aminofeel®. A dose of Aminofeel® contains 5.0 mg zinc as well as 3200.0 mg BCAA [10]. We previously reported that Aminofeel® is a useful therapeutic agent for decreasing insulin resistance in male patients with chronic viral diseases of the liver [10,11]. The administration of Aminofeel® in men for 90 days increases serum albumin levels significantly and also increases serum zinc levels [10].

There are few reports that have used objective outcomes to show that the sense of taste is disordered in patients with liver disease. Accordingly, in this study, we conducted objective, gustatory tests and objectively studied sensitivity to different tastes before and after administration of Aminofeel® in patients with hepatitis C virus (HCV)-infected liver disease.

## MATERIAL AND METHODS

### Subjects

A prospective, consecutive-patient entry study was conducted. Eligibility criteria were chronic viral liver disease, sufficient food intake, and serum albumin concentrations >3.5 g/dl and <4.0 g/dl. Patients with hepatic encephalopathy, ascites, hepatocellular carcinoma (HCC) or renal failure were excluded.

This study included 9 Japanese patients (3 males and 6 females) with HCV-infected liver disease. Eight patients, who had visited our clinic at the Kurume University Hospital in Japan between September 2006 and December 2006, had no awareness of taste disorders associated with their HCV-infected liver disease. The other patient visited our clinic with the main complaint of a taste disorder on December 2008. Patients ranged in age from 51 to 78 years, with an average age of 63.3±9.1 years.

Informed consent for participation in the study was obtained from each patient. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in prior approval by the Ethics Committee of the

Kurume University School of Medicine. None of the subjects were institutionalized.

### Methods

#### Taste test

Taste functions were analyzed using a Taste Disk® (Sanwa Kagaku Kenkyusho Co. Inc, Nagoya, Japan).

The region of taste buds are located is on the front two-thirds of the tongue, which is innervated by chorda tympani; the area located on the rear one-third of the tongue is innervated by the glossopharyngeal nerve, and the region located on the soft palate is innervated by the greater petrosal nerve. We used a taste kit to check the different dominant nerves involved in taste in each area. The type and concentration of test fluid and the area as shown in Table 1. To stimulate tastes we put a paper 5 millimeters in diameter and moistened with a reagent in the measurement site (Figure 1). Gustatory criteria for 4 tastes (sweet, salty, sour, and bitter) were examined using a 6-point scale (I, II, III, IV, V, and VI). Numbers I, II, and III were standard values (I – minimum standard value, II – the median of the standard value, III – the upper limit of the standard value). Numbers IV, V, and VI were abnormal values (IV – a slight taste disorder, V – a medium taste disorder, VI – a severe taste disorder). Taste disorders were evaluated in the area of the right chorda tympani.

#### Liver function tests

Sera from all 9 patients were used for the following liver function tests: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (Alb), and zinc. Sera were also examined for the presence or absence of HCV or HBV infection. Anti-bodies to HCV (anti-HCV) antibodies and hepatitis B virus surface antigen (HBsAg) were measured by a chemiluminescent enzyme immunoassay (CLEIA) kit and a chemiluminescent immunoassay (CLIA), respectively. Ultrasonography for all subjects was done to examine the shape of the liver and lesions in the liver.

#### Design of the administration of Aminofeel®

Each patient was given one sachet of Aminofeel®, a BCAA-enriched supplement including zinc, after breakfast and another at bedtime for 90 days.

#### Statistical analysis

All data are expressed as mean ± standard error. Differences between two groups were analyzed using the Mann-Whitney U test. Statistical comparisons before administration of the Aminofeel® and after 90 days were done using Wilcoxon's test. All statistical analyses were conducted using JMP Version 6 (SAS Institute, Cary, NC, USA). The level of statistical significance was defined as 0.05.

## RESULTS

The characteristics of the 9 patients studied are shown in Table 2. The diagnosis of liver disease included: chronic hepatitis C (n=5), liver cirrhosis (n=3), and post interferon

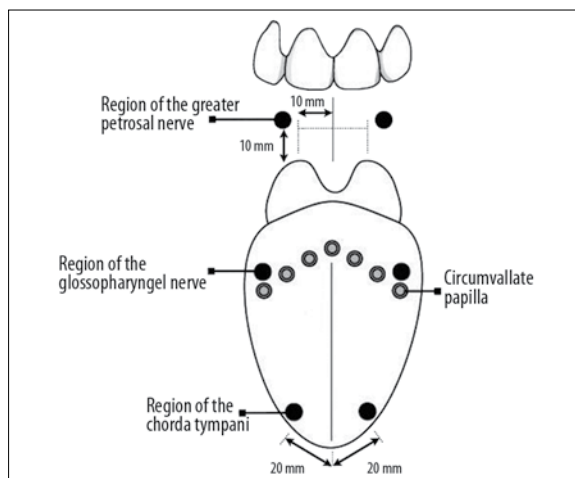
**Table 1.** A gustatory criterion by the kind of test fluid and the concentration.

Taste		I	II	III	IV	V	VI
Sweet taste	(Sucrose)	0.30%	2.50%	10.00%	20.00%	80.0%	Unobservable V
Salty taste	(Sodium chloride)	0.30%	1.25%	5.00%	10.00%	20.00%	Unobservable V
Sour taste	(Acidum tartaricum)	0.02%	0.20%	2.00%	4.00%	8.00%	Unobservable V
Bitter taste	(Quinine)	0.001%	0.02%	0.10%	0.50%	4.00%	Unobservable V

**Table 2.** Characteristics of 9 patients with HCV-related liver diseases before administration of Aminofeel®.

No	Sex	Age	Liver disease	Subjective symptom of taste disorder	Systemic disease	Oral lichen planus		Score of taste				Laboratory data				
						Occurrence	Site	Sweet	Salty	Sour	Bitter	AST	ALT	Alb	PLT	Zinc
												(IU/L)	(IU/L)	(g/dL)	(/mm <sup>3</sup> )	(µg/dL)
1	F	66	LC-C	Negative	Hypertension	Positive	Buccal mucosa	III	III	V	III	92	40	3.54	13.7	71
2	F	78	CH-C	Negative	Negative	Negative		II	I	III	II	45	44	3.88	8.7	73
3	F	56	CH-C	Negative	Hypertension	Negative		II	II	III	II	24	18	3.94	25.0	84
4	M	58	CH-C	Negative	Negative	Negative		II	II	II	II	46	70	3.92	15.8	85
5	F	69	CH-C	Negative	Negative	Negative		I	II	IV	II	46	45	3.99	18.1	71
6	F	54	LC-C	Negative	Negative	Negative		II	II	II	II	33	24	3.88	18.0	126
7	F	72	LC-C	Negative	Hypertension, Hyperlipidemia	Negative		II	II	III	II	34	29	3.87	20.5	93
8	M	51	CH-C	Negative	Diabetes mellitus	Positive	Buccal mucosa and tongue	II	VI	V	V	65	104	3.68	13.8	87
9	M	66	CH-C post IFN (SVR)	Positive	Hypothyroidism	Positive	Buccal mucosa	VI	II	VI	V	21	15	4.3	8.6	67

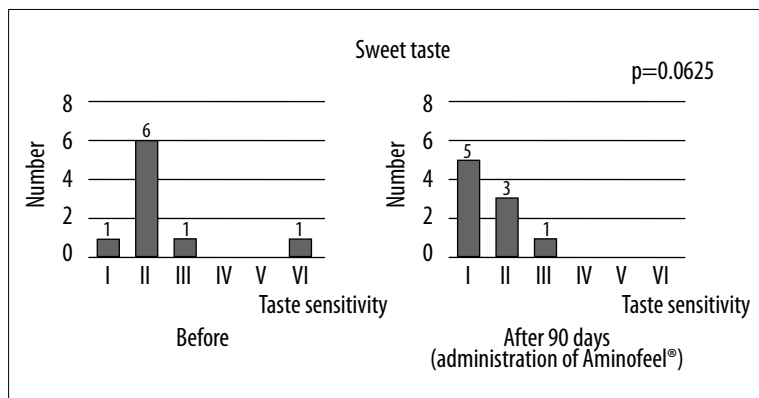
CH-C – chronic hepatitis C; LC-C – HCV-related liver cirrhosis; SVR – Sustained virological response; AST – serum aspartate aminotransferase; ALT – alanine aminotransferase; Alb – albumin; PLT – platelets.



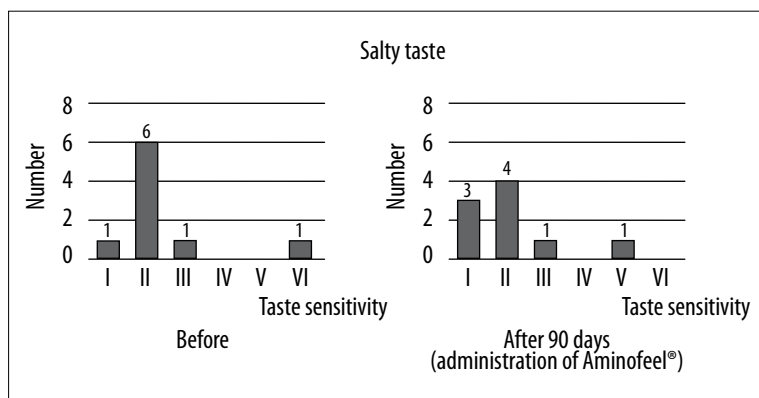
**Figure 1.** Measurement of tastes using a filter-paper disc method.

(IFN) treatment for chronic hepatitis C (n=1). After we succeeded in eliminating HCV by IFN treatment, one patient, a 66 year old man, developed a taste disorder. Of the 9 patients, 3 had oral lichen planus. There was one patient with oral lichen planus of the tongue. The serum zinc value of the 66 year old man with a complaint of a taste disorder was decreased (67 µg/dL).

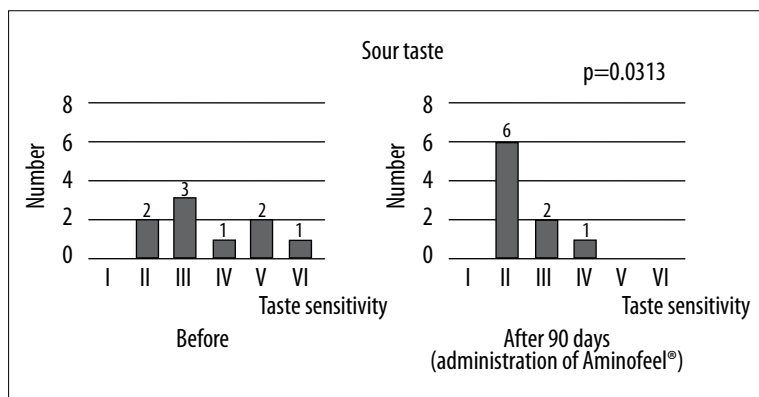
The distributions of gustatory sensitivity before and after administration of Aminofeel® are as shown in Figures 2–5. There was only one patient who was aware of a taste disorder before administration of Aminofeel®, but 4 patients had decreased gustatory sensitivity in the sour taste test, and 2 had it in the bitter taste test. Sensitivity to the sour taste was significantly increased 90 days after the administration of Aminofeel® (P=0.03, Figure 4). Sensitivity to the sweet taste was increased 90 days after the administration of Aminofeel® (P=0.06, Figure 2).



**Figure 2.** The effects of sweet tastes after administration of Aminofeel®. Sensitivity to sweet tastes was increased 90 days after the administration of Aminofeel® (P=0.06).



**Figure 3.** The effects of salty tastes after administration of Aminofeel®.



**Figure 4.** The effects of sour tastes after administration of Aminofeel®. Sensitivity to sour tastes was significantly increased 90 days after the administration of Aminofeel® (P=0.03).

We analyzed for differences before and after the administration of Aminofeel® in AST, ALT, albumin, platelet count and zinc values. These laboratory data are shown in Table 3. The serum zinc value was significantly increased (p=0.02).

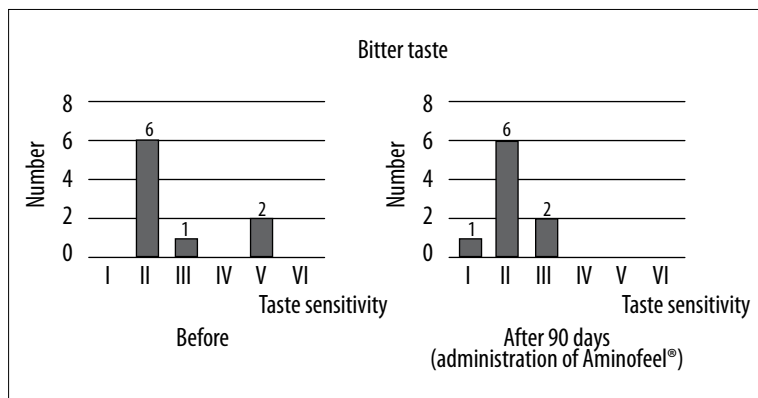
**DISCUSSION**

The number of patients with taste disorders is increasing [1,12]. It is presumed that approximately 240,000/year receive medical treatment for taste disorders from otolaryngologists in Japan [1]. Ikeda et al reported, after administering questionnaires to 1,559 members of the Japan Society of Stomato-pharyngology, that the main treatment used was administration of zinc preparations such as polaprezinc [1]. One reason for the increased number of patients with taste disorders is that the elderly population has increased

year after year [13] and it is believed that taste disorders increase with age.

Taste disorders are symptoms of neurological derangement for which there are many reasons such as use of numerous drugs, idiopathic factors, zinc deficiency, psychogenic factors, systemic diseases, etc [5,6,14]. Zinc is essential for many metabolic and enzymatic functions [15]. A zinc deficiency in man has been found to occur not only as a result of nutritional factors, but also in various disease states, including malabsorption syndromes, acrodermatitis enteropathica, Crohn’s disease, alcoholism and liver cirrhosis [15].

We found that sensitivity to tastes and zinc levels are decreased in patients with HCV-infected liver disease. Some patients had decreased sensitivity of taste despite the fact that they were



**Figure 5.** The effects of bitter tastes after administration of Aminofeel®.

**Table 3.** Laboratory data.

	Before	Administration of Aminofeel®	p value
AST (IU/L) (mean ±SD)	45.1±22.1	44.8±18.3	NS
ALT (IU/L) (mean ±SD)	43.2±28.3	44.0±25.9	NS
Alb (g/dL) (mean ±SD)	3.9±0.2	4.0±0.2	NS
PLT (/mm <sup>3</sup> ) (mean ±SD)	15.8±5.3	15.8±5.8	NS
Zinc (µg/dL) (mean ±SD)	84.1±18.0	108.4±23.5	0.0209

SD – standard deviation; NS – no significance; AST – serum aspartate aminotransferase; ALT – alanine aminotransferase; Alb – albumin; PLT – platelets.

unaware of their taste disorder. In addition, Aminofeel®, a BCAA-enriched supplement, improved sensitivity to tastes and increased zinc levels. Thus, because Aminofeel® contains zinc, it is a useful therapeutic agent for taste disorders. Hayashi et al reported that combination treatment with BCAA and zinc supplements in cirrhotic liver patients with hypoalbuminemia or hypozincemia showed significantly higher efficacy in correcting amino acid imbalances and significantly greater ability to metabolize ammonia than when BCAA was given alone during the 6 months of the study period [16]. There is a report that zinc only treatment did not improve taste disorder in liver cirrhosis [17]. Combination treatment with BCAA and zinc may be useful for improvement of gustatory sensibility, although it is not clear that whether the combination treatment is more effective for sensitivity to tastes in patients with liver diseases than zinc only or not.

Several studies and our previous reports suggest that HCV infection antedates insulin resistance [18,19], and that insulin resistance is associated with extrahepatic manifestations such as lichen planus [20,21]. We have already reported that Aminofeel® improved insulin resistance and β cell function in male patients with chronic liver disease [10]. A post-marketing surveillance study of Aminofeel® confirmed the usefulness of this supplement (data not shown).

**CONCLUSIONS**

Aminofeel® is a supplement that improves the sensitivity to tastes by increasing zinc levels. It also improves insulin resistance in patients with chronic liver disease. It is hoped that this supplement improves the prognosis of liver disease and the quality of life of these patients.

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