

Effect of *Lactobacillus brevis* SBC8803 on Gamma-Glutamyl Transferase in Japanese Habitual Drinkers: A Double-Blind, Placebo-Controlled Study

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Received February 20th, 2012; revised March 30th, 2012; accepted April 8th, 2012

ABSTRACT

A randomized, double-blind, placebo-controlled clinical trial in Japanese habitual drinkers was conducted to evaluate the efficacy of *Lactobacillus brevis* SBC8803 to alleviate adverse effect of alcohol. Subjects who drank habitually and had moderately higher levels of gamma-glutamyl transferase (GGT) (50 - 100 IU/L) were enrolled. The levels of transaminases in these subjects were almost within normal levels (aspartate transaminase (AST) < 30 IU/L and alanine transaminase (ALT) < 40 IU/L). Either the capsules containing placebo (n = 23) or 130 mg (4.0×10^{10} colony-forming units) of live *L. brevis* SBC8803 (n = 22) per day were administered for the continuous eight weeks (56 days). During the period, the subjects both in test group and placebo groups have kept each drinking behavior as usual. Regarding lipid metabolism, triacylglycerol (TG) levels in the male test group significantly decreased at week 4 as compared with week 0. Biomarkers of hepatocytes-damage; AST and ALT levels showed no significant differences between the placebo and test groups at both weeks 4 and 8. Oxidative stress marker; GGT at weeks 4 was significantly lower in the test group than that in the placebo group (p = 0.017), but not at weeks 8. However, taking a reduced rate of GGT at weeks 8 comparing with that at week 0, that in the test group showed larger value comparing with that in the placebo group. These data about TG and GGT suggest that, although efficacy of *L. brevis* SBC8803 is limited in this study, intake of the probiotic may alleviate alcoholic influence in lipid metabolism and oxidative stress.

Keywords: *Lactobacillus brevis*; Gamma-Glutamyl Transferase; Alcoholic Related Disorder; Double-Blind Placebo-Controlled Study

1. Introduction

The harmful use of alcohol is a worldwide problem resulting in millions of death [1]. It is not only a causal factor in many diseases, but also a precursor to injury and violence. In Japan, recent estimates suggest that 36% of adult males and 6.4% of adult females consume alcohol [2], and 14.7% of out-patients in clinics are considered to be somewhat alcohol-related [3]. One of the best-known target organs is liver, which is eventually damaged by chronic alcohol consumption and resulted in fatty liver, hepatitis, and cirrhosis [4]. As these diseased hepatic conditions are hazardous for human health and socio-economic societies, the prevention to develop such conditions is one of the most important issues for habitual drinkers. It is known that biochemical parameters such as

GGT and TG are increased in serum prior to the development of alcoholic liver diseases, and these parameters are frequently used for monitoring the alcohol consumption and the prediction on the initial manifestation of liver damage [5].

Concerning the increase of GGT, a couple of mechanisms have been postulated. Up until recently, the increase of GGT is chiefly induced by alcohol itself, because this increase is observed in subjects who have not developed alcoholic liver diseases. In both alcoholic and non-alcoholic fatty liver, the increase of GGT was known well and this phenomenon was not considered to be meaningful for further development of these diseases [6]. However, the meaning of elevated GGT is getting more important than thought to be. In the clinical standpoints of view, the risks of future developments of liver diseases, diabetes, and cardiovascular disease are increased

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in several cohort studies when GGT was high [7,8]. In addition, from the biochemical points, the increase of GGT was resulted by the increase of oxidative stresses [9], and the initial manifestation of the oxidative stress-induced diseased conditions including alcoholic liver injury, and non-alcoholic steatohepatitis in patients with metabolic syndrome [10]. Therefore, it is getting more important to monitor GGT as the initial manifestation of alcohol-induced organ injury, in addition to monitoring marker for chronic alcohol consumption.

It is well known that many subjects who habitually have drunk alcohol are suffered from biological effects of chronic alcohol consumption and the production of fatty liver, which is characterized by the accumulation of TG and cholesterol in hepatocytes. The accumulation of TG within the liver is considered to be an early and reversible effect of alcohol consumption. As alcohol increases peripheral lipolysis and alters liver redox potential, which increases fatty acid synthesis, the subsequent increase of fatty acids esterification, will cause TG accumulation [4].

Probiotics are defined as live microorganisms that confer a health benefit on the host. Human data suggests an emerging role for probiotic therapy in the treatment of liver diseases, including alcoholic liver disease [11,12]. We have reported that *Lactobacillus brevis* SBC8803 ameliorates ethanol-induced liver injury and fatty liver in C57BL/6N mice fed an ethanol-containing diet [13]. We think that there is a meaningful strategy to alleviate adverse influence of alcohol by the dietary intake of probiotic bacteria. Therefore, in this study, we evaluated the efficacy of *L. brevis* SBC8803 to alleviate adverse effect of alcohol in habitual drinkers whose serum GGT are slightly high levels (50 - 100 IU/L) and, AST and ALT levels are within normal range.

2. Methods

2.1. Subjects

Study subjects were recruited from Ueno Clinic Co., LTA, and the Tokyo Clinical Center in Tokyo, Japan. Selection criteria included subjects between 20 and 64 years with GGT concentrations between 50 and 100 IU/L and who drank habitually. The upper limit of normal in Japanese adult is 50 IU/L in most medical facilities. Subjects were excluded if they were positive for HBs antigen or HCV antibody. Clinical screening (fasting blood tests, urine samples, and medical history) and a dietary questionnaire were further used to select subjects. Sixty-four subjects were selected to participate in this clinical trial and randomly assigned to either the test or placebo group. All subjects were employed Japanese individuals who followed a daily routine. The study was

performed in accordance with the Declaration of Helsinki and regulations of the Ueno Clinic ethics committee for Internal Clinical Studies. All subjects provided written informed consent before participating in the study.

2.2. Test Capsules

The components of the placebo and test sample capsules were shown in **Table 1**. Twelve test capsules contained 4.0×10^{10} colony-forming units (CFUs) (3.3×10^9 CFU/capsule) of *L. brevis* SBC8803. Placebo and test capsules could not be distinguished from each other with the naked eye. These capsules were kept in refrigerators in the subject's house.

2.3. Protocol

Subjects consumed twelve placebo or test capsules daily for eight weeks. These capsules were consumed after one of their three daily meals (breakfast, lunch, or dinner). Subjects maintained their usual alcohol drinking habits throughout the study. Subjects also completed a questionnaire, wherein they specified the quantity and time of capsule intake, daily drinking, and a detailed dietary record for three days before clinical examinations. Data of a subject was excluded if the subject consumed less than one-third or more than three times their weekly pre-observation alcohol intake level during the study.

2.4. Blood Chemistry Analyses

Blood samples were collected from subjects' forearms every four weeks at the clinic using blood collection tubes that did not contain anticoagulants. Participants were instructed to abstain from food and beverages, except water, for 12 h before each of their clinical exami-

Table 1. Placebo and test capsule composition (per 12 capsules).

Constituents (mg)	Placebo capsule	Test capsule
<i>L. brevis</i> SBC8803 ^a	0	130
Maltitol	112	112
Sucrose	48	48
Cellulose	1738	1738
Calcium stearate	120	120
Highly dispersed silicon dioxide	43	43
Starch hydrolysate	339	137
Dextrose	0	72
Total	2400	2400

^aTwelve test capsules contained 4.0×10^{10} CFUs (3.3×10^9 CFU/capsule) of *L. brevis* SBC8803.

Table 2. Characteristics of subjects at baseline (values are mean ± standard deviation).

	Placebo group	Test group	P at baseline
Male/female	17/6	17/5	-
Age (year)	43.9 ± 5.2	43.0 ± 7.0	0.655
Body weight (kg)	67.6 ± 7.9	69.4 ± 11.0	0.593
BMI ^a (kg/m ²)	23.7 ± 2.9	24.3 ± 3.1	0.508
GGT (IU/L)	66.1 ± 20.1	73.7 ± 21.8	0.231
AST (IU/L)	22.7 ± 5.8	21.8 ± 3.8	0.512
ALT (IU/L)	23.7 ± 9.4	24.4 ± 8.1	0.787
TG (mg/dL)	114.7 ± 84.6	145.0 ± 95.8	0.267

^aBMI, body mass index. Capsules containing placebo (n = 23) or 130 mg (4.0 × 10¹⁰ colony-forming units) of live *L. brevis* SBC8803 (n = 22) per day were administered for the continuous eight weeks (56 days).

to age, body weight, body mass index, serum GGT, AST, ALT, and TG.

3.2. Capsule Consumption and Alcohol and Dietary Intake

Placebo and test capsule consumption during the trial was >95%. No significant differences were observed between the groups for intake of alcohol (Table 3). There were no significant differences for calorie intake between the placebo (week 4, 2070 ± 603 kcal/day; week 8, 2116 ± 562 kcal/day) and test groups (week 4, 2237 ± 486 kcal/day; week 8, 2194 ± 546 kcal/day).

3.3. Blood Chemistry

GGT, AST, ALT, and TG concentrations are listed in Table 4. At week 4, subjects in the test group showed significantly lower GGT levels as compared with those in the placebo group (p = 0.017). Although no significant changes in GGT levels were observed between the test and placebo groups at week 8, GGT levels in the placebo group were significantly elevated from week 0, while those in the test group remained unchanged. No significant differences were observed for AST, ALT, and TG levels between the placebo and test groups at weeks 4

and 8.

4. Discussion

Chronic and large amount of alcohol consumption significantly correlates detrimental effects as alcohol-related diseases; psychological problems, malnutrition, diseases of central nervous system and peripheral nervous system, cardiovascular disease, liver dysfunction, pancreatitis, increased risk of type 2 diabetes, cancers of head, neck, esophagus, colon and liver. Long-term use of alcohol in excessive quantities is capable of damaging nearly every organ and system in the body both of directly and indirectly. Therefore indirect mechanism of organ damages might be caused by oxidized stress by metabolic changes by alcohol.

During the initial stages of alcoholic liver disease, TG accumulates in hepatocytes leading to the development of steatosis, which is a reversible condition. If alcohol consumption is continued, steatosis can progress to severe fatty liver, fibrosis, cirrhosis, and even hepatocellular carcinoma, particularly in the presence of other comorbid factors [14].

Some effects of probiotics on liver function have been reported. Kirpich *et al.* showed that short-term oral supplementation with *Bifidobacterium bifidum* and *Lactobacillus plantarum* 8PA3 was associated with the restoration of bowel flora and greater recovery from alcohol-induced liver injury than standard therapy alone [11]. However, the early intervention with probiotics is expected to prevent the development of alcoholic liver disease. In this study, we investigate the effect of *L. brevis* in Japanese habitual drinkers without obvious hepatocytes damage by alcohol. They were relatively healthy subjects whose GGT values are from upper limit of normal to 2-fold (50 - 100 IU/L) and, AST and ALT levels are within normal range.

To the best of our knowledge, this is the first investigation regarding the role of probiotics in the improvement of serum GGT for habitual drinkers based on a double-blind, placebo-controlled study. GGT, a well-known biomarker for alcoholic liver damage, is present in hepatocytes and biliary epithelial cells. Although elevated GGT levels initially result from enzyme induction

Table 3. Intake of alcohol in the placebo and test groups (values are mean ± standard deviation).

	Intake of alcohol (g/day)								
	Preobservation (0w)	1 w	2 w	3 w	4 w	5 w	6 w	7 w	8 w
Placebo group	52.2 ± 28.1	45.2 ± 26.5**	44.7 ± 27.4*	44.3 ± 27.3*	43.7 ± 29.9**	43.9 ± 28.2*	46.4 ± 26.3	46.3 ± 32.7	45.9 ± 30.3
Test group	50.6 ± 31.1	47.3 ± 32.2	50.9 ± 36.7	50.8 ± 38.5	49.3 ± 41.0	41.7 ± 24.1**	42.9 ± 23.6*	41.0 ± 23.3*	44.7 ± 24.2

* p < 0.05; ** p < 0.01, changes from pre-observation by t-test.

Table 4. Baseline GGT, AST, ALT, and TG levels in the placebo and test groups (values are mean \pm standard deviation).

			Baseline	Week 4	Week 8
All subjects (Placebo, n = 23; Test, n = 22)	GGT (IU/L)	Placebo	66.1 \pm 20.1	76.5 \pm 48.4 [†]	76.7 \pm 36.1*
		Test	73.7 \pm 21.8	69.3 \pm 27.0	78.6 \pm 34.7
	AST (IU/L)	Placebo	22.7 \pm 5.8	24.8 \pm 6.9	25.7 \pm 7.7*
		Test	21.8 \pm 3.8	24.0 \pm 4.3**	24.5 \pm 4.2**
	ALT (IU/L)	Placebo	23.7 \pm 9.4	25.1 \pm 11.5	26.3 \pm 9.9
		Test	24.4 \pm 8.1	25.9 \pm 9.3	27.7 \pm 10.1*
TG (mg/dL)	Placebo	114.7 \pm 84.6	94.6 \pm 44.4	116.4 \pm 60.8	
	Test	145.0 \pm 95.8	111.0 \pm 57.0	122.5 \pm 70.8	
Male subjects (Placebo, n = 17; Test, n = 17)	GGT (IU/L)	Placebo	70.9 \pm 20.9	83.5 \pm 54.8 [†]	82.8 \pm 40.0
		Test	72.8 \pm 17.4	68.0 \pm 23.2	76.7 \pm 29.1
	AST (IU/L)	Placebo	21.8 \pm 5.1	24.9 \pm 7.3*	24.8 \pm 6.9*
		Test	22.2 \pm 3.9	23.9 \pm 4.0	24.9 \pm 4.0*
	ALT (IU/L)	Placebo	24.5 \pm 10.0	26.7 \pm 12.2	27.5 \pm 10.5
		Test	26.8 \pm 7.6	27.0 \pm 9.7	29.6 \pm 9.6
TG (mg/dL)	Placebo	123.6 \pm 97.1	100.6 \pm 48.8	111.3 \pm 58.6	
	Test	163.0 \pm 98.9	115.5 \pm 58.3*	130.5 \pm 72.8	
Female subjects (Placebo, n = 6; Test, n = 5)	GGT (IU/L)	Placebo	52.7 \pm 9.6	56.8 \pm 7.4	59.3 \pm 10.9
		Test	76.8 \pm 35.5	73.6 \pm 40.3	85.2 \pm 53.4
	AST (IU/L)	Placebo	25.3 \pm 7.4	24.5 \pm 6.4	28.2 \pm 9.9
		Test	20.2 \pm 3.1	24.6 \pm 5.7	22.8 \pm 5.0
	ALT (IU/L)	Placebo	21.3 \pm 8.0	20.7 \pm 8.5	23.0 \pm 7.9
		Test	16.4 \pm 2.9	22.2 \pm 7.6	21.4 \pm 10.1
TG (mg/dL)	Placebo	89.5 \pm 15.9	77.3 \pm 24.0	131.0 \pm 70.3	
	Test	83.6 \pm 54.3	95.4 \pm 55.7	95.2 \pm 62.6	

[†]p < 0.05. Analysis of covariance was applied for primary outcomes (measured serum GGT) between the two groups. To compare secondary outcomes (AST, ALT, and TG) between the two groups, unpaired *t*-tests were used. *p < 0.05, **p < 0.01, changes from baselines by *t*-test.

by alcohol and not from hepatic damage, a continual increase in GGT generally indicates that the liver is being damaged. In this study, subjects showed normal AST and ALT levels, indicating that the liver of these subjects is not levels that would indicate alcoholic liver disease. We assumed that the administration of *L. brevis* SBC8803 would help in reducing alcohol-related liver damage before the development of alcoholic liver disease. Then at week 4, subjects in the test group showed significantly lower GGT levels ($p = 0.017$) as compared with those in the placebo group.

Higashikawa *et al.* reported that *L. plantarum* SN13T improved serum total cholesterol level in healthy adults in normal range [12]. In the test group of this study, se-

rum TG levels tended to decrease at weeks 4 and 8 as compared with week 0. Furthermore, in the male test group, TG levels significantly decreased at week 4 as compared with week 0. Generally increasing of serum TG is reversible effect of lipid metabolism by alcohol consumption, so serum TG is useful as one of biomarker for chronic alcohol consumption. Regarding with mechanism of increasing TG, Alcohol metabolism contributes to lipid metabolism by the multiple steps; increasing substrate supply, increasing fat esterification to TG. Generally alcohol increases lipolysis of peripheral adipose fat and the altered liver redox state increases fatty acid synthesis. When alcohol and acetaldehyde dehydrogenases catalyze the oxidation of alcohol via acetaldehyde to

acetate, the cofactor nicotinamide adenine dinucleotide (NAD) is converted to its reduced form NADH. The resulting increase in the ratio of NADH/NAD is responsible for metabolic imbalance and alteration of redox state in hepatocytes. This increase in substrate supply (glycerol and free fatty acids) enhances the rate of esterification of glycerol-3-phosphate. Furthermore alcohol consumption activates the sterol regulatory element-binding protein (SREBP)-1 that induces genes involved in lipid biosynthesis. Conversely, alcohol consumption down-regulates the transcription factor peroxisome proliferator-activated receptor- α (PPAR- α) that regulates enzymes involved in fatty acid oxidation and prevents fatty acid import into the mitochondria [15]. In addition, the pro-oxidants are generated from alcohol metabolism or from activated phagocytes, resulting lipid peroxidation.

L. brevis SBC8803 could improve the lipid metabolism in habitual drinkers. It may be important meaning that the both of GGT and TG increased in this study as the postulated mechanisms. Recently, the meaning of elevated GGT is getting more important for the risks of future developments of liver diseases, type 2 diabetes and cardiovascular disease are increased in several cohort studies when GGT was high [7,8]. In addition, from the biochemical points, the increase of GGT was resulted by the oxidized stresses [9], and the initial manifestation of oxidized stress-induced diseased conditions including alcoholic liver injury, and non-alcoholic steatohepatitis in patients with metabolic syndrome [10]. Therefore, it is getting more important to monitor GGT as the initial manifestation of alcohol-induced organ injury, in addition to monitoring marker for chronic alcohol consumption.

In our previous study involving C57BL/6N mice that had been fed an ethanol-containing diet, *L. brevis* SBC8803 ameliorated fatty liver and ethanol-induced liver injury by suppressing the upregulation of TNF- α as well as SREBP-1 and SREBP-2 in the liver [13]. Alcohol increases SREBP-1 activity by decreasing the activities of AMP-activated protein kinase and sirtuin-1; TNF- α produced in response to alcohol exposure causes fatty liver by upregulating SREBP-1 activity [15,16]. We speculate that *L. brevis* SBC8803 also may influence the regulation of TNF- α and SREBPs in habitual drinkers without obvious hepatocytes damage by alcohol, following the changing of lipid metabolism and oxidized stress condition.

In this study, the preferable effect of lactic acid bacteria for serum GGT and TG seemed to be felt in the 4th week. We have to consider compliance of administration in habitual drinkers for more suitable amount per administration and number of uses. Additionally the storage condition of probiotics might be important. The capsules

for eight weeks were packed in an aluminum pouch. The live *L. brevis* of capsules used in this study were kept though the trail in our laboratory. However, there is still a possibility that live *L. brevis* decreased because of change of temperature by movement of pouch of capsules from the refrigerator at the intake time. We have a speculation that the decrease of live lactic acid bacteria might influence the efficacy of capsules in 8 weeks period. Therefore, we started the improvement of the technology for storing live *L. brevis* until use, or an alternative use of killed *L. brevis* [17] or an isolated active substance, polyphosphate derived from *L. brevis* [18]. Further studies are needed to adapt these alternatives.

In conclusion, the intake of *L. brevis* SBC8803 may alleviate alcoholic liver damage in humans. Further research is required to clarify the degree of efficacy and the mechanisms by which probiotics affect liver function.

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