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Original Article

Differential Responses of Serum Gamma-glutamyltransferase to Alcohol Intake in Japanese Males

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We studied the association of γ-glutamyltransferase (GGT) and other serum markers of liver injury with daily alcohol consumption in a healthy population of 1,043 Japanese males. A positive correlation between daily alcohol consumption and biochemical markers, such as log GGT (r = 0.432), log AST (r = 0.244) or log LAP (r = 0.246), was seen in all drinkers. However, there was a negative correlation, such as log GGT (r = − 0.434), log AST (r = − 0.424) or log LAP (r = − 0.430), in heavy drinkers who consumed more than 70 g ethanol a day. On the other hand, a positive correlation, such as log GGT (r = 0.426), log AST (r = 0.247) or log LAP (r = 0.216) was found in moderate drinkers who consumed less than 70 g ethanol a day. Interestingly, there was a tendency toward negative association between alcohol consumption and the Tokyo University ALDH2 Phenotype Screening Test (TAST) score in the heavy drinkers, and there was a tendency toward positive association between GGT and TAST score in this group. Our results suggest that there are 2 groups of drinkers, those with elevated GGT (good responders) and those with normal GGT (poor responders) despite heavy drinking.

Key words: gamma-glutamyltransferase (GGT), daily alcohol consumption, good responder and poor responder

Alcohol consumption is generally regarded as the most likely cause of elevated serum levels of gamma-glutamyltransferase (GGT) [1-3]. In Japan, the measurement of serum GGT activity has been commonly used as a screening test for alcoholic liver injury [4]. So far, a number of studies have demonstrated a positive correlation between serum GGT level and the amount of alcohol consumed [5-7]. However, Muto *et al.* reported that high alcohol consumption revealed a negative correlation with GGT activity among chronic alcoholics in a psychiatric hospital, whereas it revealed a positive correlation with GGT among social drinkers who worked at a trading company [8]. Those researchers suggested that the chronic alcoholics with high GGT activity should be considered good responders to alcohol, and the ones with normal GGT activity should be considered poor responders [9]. This unexpected finding has raised the question of whether a negative correlation between the level of alcohol consumption and serum GGT activity exists in a randomly selected population with low to high alcohol consumption. The GGT test is very widely used in health check-ups as well as in clinical examinations. It is therefore important to investigate the existence of 2 or more populations that respond differently to the amount of alcohol consumed in order to evaluate serum GGT elevation as an indicator of alcohol consumption or alcohol-induced liver damage. The aim of the present study is to determine whether there is a subgroup of individuals who

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show normal GGT activity despite high alcohol consumption (poor responders) or a subgroup of individuals who show elevated GGT activity with high alcohol consumption (good responders) among a randomly selected population. The relationship between serum GGT activity and daily alcohol consumption and other life style-related factors was therefore examined in a group of subjects receiving a medical check-up.

Materials and Methods

Subjects. The study population was made up of 1,454 healthy adults including 1,067 men and 387 women, who attended a medical checkup in a local municipality in Japan in October 1994. Subjects who had a past history of chronic liver diseases (chronic hepatitis, liver cirrhosis, hepatitis virus carrier and gall stone) or who had such a disease at the time were excluded from this study. The final analysis was carried out on 1,043 males, since alcohol consumption among the female subjects in the present study was too low to be analyzed.

Methods. Each subject was informed of the purpose of the investigation and asked to fill out a self-administered questionnaire that contained general information on age, gender, drinking and smoking habits, past history and present illness. The questionnaire also included extended questions on drinking habits, such as type of alcoholic beverages, average size of each drink, or the frequency and duration of drinking, and on physical symptoms after alcohol intake so that the subject's alcohol consumption and Tokyo University ALDH2 Phenotype Screening Test (TAST) score could be calculated [10]. Alcohol consumption was converted into pure ethanol using an alcoholic beverage composition table [11]. Daily alcohol consumption, expressed in g per day, and total alcohol consumption, expressed in kg, were computed. The subjects were classified into 3 groups according to their daily alcohol consumption: subjects who had never taken alcohol (nondrinkers), subjects who drank less than 70 g of pure ethanol daily (moderate drinkers) and those who drank 70 g or more of pure ethanol daily (heavy drinkers). Physical symptoms after alcohol intake, such as facial flushing, nausea, or palpitation, were evaluated by TAST and expressed as TAST scores. Subjects with negative TAST scores were considered to be sensitive to alcoholic beverages, and subjects with positive scores were considered not to be sensitive to alcoholic beverages.

The subjects were also classified by their daily cigarette consumption.

All subjects also underwent a medical examination that included measurement of height, body weight and blood pressure. Body mass index (BMI) was calculated as body weight (kg) / height $(m)^2$.

Blood samples of the subjects were analyzed in the Clinical Research Laboratories of Okayama City Hospital for any activity of GGT, asparatate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), leucine aminopeptidase (LAP) and choline esterase (CHE), and for levels of zinc sulfate turbidity test (ZTT), thymol turbidity test (TTT), total bilirubin (T-Bil), direct bilirubin (D-Bil), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and uric acid (UA).

All data were presented in terms of a median, a minimum and a maximum.

A statistical comparison between groups was undertaken using the nonparametric Mann-Whitney *U* test. A logistic regression analysis was used to analyze how serum GGT activity was affected by age, BMI, daily alcohol consumption, TAST score and smoking in the present study. Pearson's correlation coefficient was calculated to analyze the relationship between daily alcohol consumption and log-transformed data of biochemical markers. All computation was performed with a Windows version of SPSS 8.0 statistical program package (SPSS Inc., IL, USA).

Results

Table 1 summarizes the median, minimum and maximum values of the variables in nondrinkers and drinkers. The values of age, TAST score, smoking index, smoking duration, UA, AST, LDH, T-Bil, D-Bil, LAP, CHE, GGT and HDL-C were significantly higher, and the value of ALP was significantly lower in the drinkers. These results were compatible with those generally accepted. Since the median age of the drinkers was significantly higher than that of the nondrinkers, and age was considered to be a possible confounder of the difference in the biochemical variables, age-matching was carried out one-by-one within a 5-year difference in age between drinkers and nondrinkers. The results are combined in Table 1. After age-matching, the number of variables with significant differences between the 2 groups was reduced to include only the significantly higher values

Table I Median, minimum and maximum values of variables and comparisons between these values before and after age-matching

Variables	Nondrinkers (n = 300)	Drinkers (n = 743)	a	Age-matched D. (n = 300)	b
Age (years)	39 (18 ~ 70)	42 (19 ~ 67)	**	39 (19 ~ 67)	
BMI (kg/m^2)	22.9 (16.4 ~ 33.0)	23.0 (15.1 ~ 32.2)		22.9 (15.1 ~ 31.4)	
Daily alcohol consumption (g/day)	0	19.5 (0.1 ~ 144.3)		17.6 (0.1 ~ 144.3)	
Total alcohol consumption (kg)	0	101.7 (0.3 ~ 1076.8)		71.2 (0.3 ~ 1076.2)	
TAST score	−9.6 (−23.9 ~ 9.4)	6.1 (−18.6 ~ 13.0)	*	6.1 (−17.6 ~ 12.7)	*
Smoking index	0 (0 ~ 4)	1 (0 ~ 4)	*	1 (0 ~ 4)	
Smoking duration (years)	0 (0 ~ 50)	2 (0 ~ 45)	*	1 (0 ~ 40)	
UA (mg/dl)	5.4 (1.0 ~ 8.8)	5.7 (0.7 ~ 9.6)	**	5.8 (0.7 ~ 9.6)	**
ZTT (U)	4.1 (0.6 ~ 19.2)	3.8 (0.5 ~ 17.2)		3.7 (0.5 ~ 12.6)	**
TTT (U)	1.3 (0.2 ~ 10.9)	1.4 (0.1 ~ 14.8)		1.4 (0.1 ~ 9.9)	
AST (IU/l)	17 (8 ~ 49)	19 (8 ~ 102)	**	18 (8 ~ 102)	**
ALT (IU/l)	17 (5 ~ 108)	18 (4 ~ 162)		18 (5 ~ 159)	
ALP (IU/l)	144 (76 ~ 296)	138 (71 ~ 280)	*	138 (71 ~ 272)	
LDH (IU/l)	282 (175 ~ 432)	286 (180 ~ 606)	**	283 (180 ~ 606)	
T-Bil (mg/dl)	0.59 (0.20 ~ 2.52)	0.68 (0.21 ~ 2.37)	**	0.68 (0.25 ~ 2.37)	**
D-Bil (mg/dl)	0.20 (0.09 ~ 0.76)	0.22 (0.09 ~ 0.65)	**	0.22 (0.09 ~ 0.65)	**
LAP (IU/l)	48 (27 ~ 83)	52 (26 ~ 148)	**	51 (26 ~ 115)	**
CHE(IU/l)	292 (136 ~ 480)	303 (137 ~ 632)	*	298 (137 ~ 544)	
GGT(IU/l)	16 (5 ~ 474)	27 (8 ~ 654)	**	25 (8 ~ 315)	**
TG (mg/dl)	125 (33 ~ 758)	136 (29 ~ 930)		125 (29 ~ 830)	
TC (mg/dl)	195 (96 ~ 311)	196 (106 ~ 378)		196 (106 ~ 378)	
HDL-C (mg/dl)	46 (24 ~ 80)	49 (21 ~ 121)	**	50 (21 ~ 109)	**

a, Nondrinkers *vs*. drinkers; b, Nondrinkers *vs*. age-matched drinkers; $*P < 0.05$; $**P < 0.01$ (Mann-Whitney *U* test). ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; CHE, Choline esterase; D-Bil, Direct bilirubin; GGT, Gamma-glutamyltransferase; HDL-C, High density lipoprotein cholesterol; LAP, Leucine aminopeptidase; LDH, Lactate dehydrogenase; TAST score, Tokyo University ALDH2 Phenotype Screening Test score; T-Bil, total bilirubin; TC, Total cholesterol; TG, Triglycerides; TTT, Thymol turbidity test; UA, Uric acid; ZTT, Zinc sulfate turbidity test.

of the TAST scores, UA, AST, T-Bil, D-Bil, LAP, GGT and HDL-C, and the lower value of ZTT.

In order to determine if there is dose-response in those variables, their values were compared between moderate and heavy drinkers (Table 2). Heavy drinkers showed significantly higher values of daily alcohol consumption, total alcohol consumption, TAST score, UA, AST, LAP and GGT as compared with moderate drinkers. Heavy drinkers were then further divided into 2 groups according to the GGT level, one with a normal GGT level ($\leqq 50$ IU/l) and the other with an elevated GGT level (> 50 IU/l). There was no significant difference between the 2 groups in the median values of age, BMI, drinking habit (daily and total alcohol consumption), TAST score and UA. But the median values of AST, LAP and GGT for the group with elevated GGT were significantly higher than those for the group with normal GGT (Table 3).

Although there were no significant differences in daily alcohol consumption or total alcohol consumption between the groups with normal and elevated GGT, the values of UA, AST, LAP and GGT were analyzed for their correlation with the amount of daily alcohol consumption in 3 groups: all drinkers, moderate drinkers and heavy drinkers. Since the values of liver function tests in a population generally show log-normal distribution, correlation coefficients were calculated after logarithmic transformation of the variables. TAST score was excluded because it was a categorical score. There was a positive correlation between daily alcohol consumption and log-transformed (log) UA, log AST, log LAP and log GGT in all drinkers. Similar results were obtained in moderate drinkers except for log UA, which became insignificant. However, in heavy drinkers, no positive correlation was obtained for any of the parameters analyzed. Instead, a significant negative correlation was found between daily alcohol consumption and log AST, log LAP or log GGT. Thus, in heavy drinkers, there was a negative correlation between alcohol consumption and the biochemical variables that reflect liver injury. Scatter-grams of the

Table 2 Comparison of variables between moderate and heavy drinkers

Variables	Moderate drinkers (n = 718)	Heavy Drinkers (n = 25)	
	DAC < 70	DAC ≧ 70	
Age (years)	42 (19 ～ 67)	38 (23 ～ 56)	
BMI (kg/m²)	23.0 (15.1 ～ 32.2)	24.0 (19.0 ～ 28.7)	
Daily alcohol consumption (g/day)	18.7 (0.1 ～ 69.8)	81.9 (70.2 ～ 144.3)	**
Total alcohol consumption (kg)	92.6 (0.3 ～962.2)	521.9 (73.5 ～1076.2)	**
TAST score	6.1 (−18.6 ～ 13.0)	6.2 (−16.3 ～ 12.9)	*
UA (mg/dl)	5.7 (0.7 ～ 9.6)	6.1 (3.6 ～ 8.3)	*
ZTT (U)	3.7 (0.5 ～ 17.2)	4.1 (2.0 ～ 6.9)	
AST (IU/l)	19 (8 ～ 82)	21 (13 ～ 102)	*
T-Bil (mg/dl)	0.67 (0.21～ 2.37)	0.64 (0.35～ 1.03)	
D-Bil (mg/dl)	0.22 (0.09～ 0.65)	0.23 (0.14～ 0.45)	
LAP (IU/l)	51 (26 ～148)	61 (41 ～ 131)	**
GGT(IU/l)	27 (8 ～458)	65 (23 ～ 654)	**
HDL-C (mg/dl)	49 (21 ～121)	49 (34 ～ 85)	

All data are presented as median (minimum～maximum). DAC, daily alcohol consumption (g). *, **, AST, BMI, D-Bil, GGT, HDL-C, LAP, TAST score, T-Bil, UA, ZTT; see legend to Table 1.

Table 3 Comparison of variables between heavy drinkers with normal and elevated gamma-glutamyl-transferase

Variables	GGT		
	≦ 50 IU/l (n = 10)	> 50 IU/l (n = 15)	
Age (years)	38 (23 ～ 45)	38 (32 ～ 56)	
BMI (kg/m²)	24.4 (19.4～ 27.0)	23.8 (19.0～ 28.7)	
Daily alcohol consumption (g/day)	95.4 (70.2～ 144.3)	80.2 (70.4～ 102.0)	
Total alcohol consumption (kg)	507.6 (102.5～ 730.0)	524.8 (73.5～ 1076.2)	
TAST score	− 1.3 (− 16.3～ 12.7)	9.0 (− 9.6～ 12.9)	
UA (mg/dl)	5.7 (4.7～ 7.1)	6.5 (3.6～ 8.3)	
AST (IU/l)	17 (13 ～ 26)	28 (15 ～ 102)	*
LAP (IU/l)	55 (41 ～ 65)	76 (42 ～ 131)	**
GGT(IU/l)	33 (23 ～ 47)	92 (59 ～ 654)	***

All data are presented as median (minimum～maximum). ***, $P < 0.001$. *, **, AST, BMI, GGT, LAP, TAST score, UA; see legend to Table 1.

individual values of log GGT, log AST and log LAP in all drinkers, moderate drinkers and heavy drinkers are shown in Fig. 1.

In order to determine whether the heavy drinkers with negative TAST scores are related to those with elevated GGT levels, we examined the relationship between TAST score and serum GGT level in heavy drinkers, and the scatter-gram is shown in Fig. 2. Fisher's exact probability test showed the tendency for the serum GGT level of the group with positive TAST scores to be higher than that of the group with negative TAST scores ($P = 0.052$).

As TAST score was shown to be an important determinant of serum GGT level in relation to alcohol consumption, biochemical variables in all drinkers were compared between 2 groups of subjects, those with negative TAST scores and those with positive TAST scores. The results showed that daily and total alcohol consumption, UA, AST, ALT and GGT levels were significantly higher, and CHE was significantly lower in the group with positive TAST scores than in the group with negative TAST scores (Table 4). For further analysis to determine whether TAST score has any effect on the relationship between serum GGT level and daily

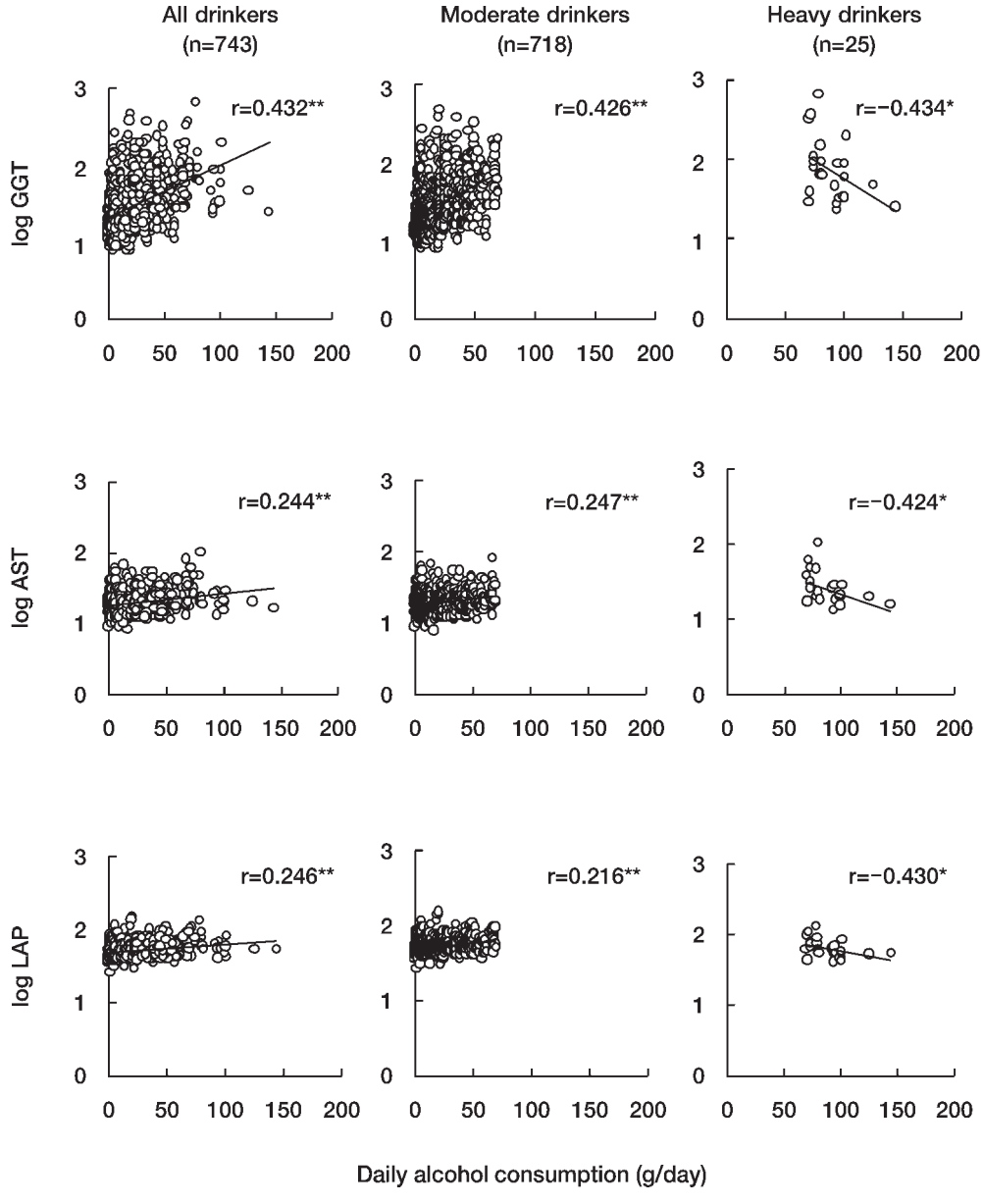

Fig. 1 Scattered diagrams of the relationship between daily alcohol consumption and log-transformed biochemical markers that differ significantly depending on the amount of alcohol consumed daily. $*P < 0.05$, $**P < 0.01$ (r, Pearson's correlation coefficient).

alcohol consumption, the slopes of the regression lines for positive and negative TAST scores were compared between the 2 groups (Fig. 3). Serum GGT level and daily alcohol consumption showed a significantly positive correlation in both of the groups, with similar correlation coefficients and parameters of regression lines (TAST score < 0; $r = 0.422$, GGT $= 25.44 + 0.43 \times$ daily alcohol consumption, TAST score $\geqq 0$; $r = 0.474$, GGT $= 24.78 + 1.0 \times$ daily alcohol consumption). Thus, the negative correlation between alcohol consumption and serum GGT was shown only in the group of heavy drinkers.

Discussion

The results obtained in all subjects showed that

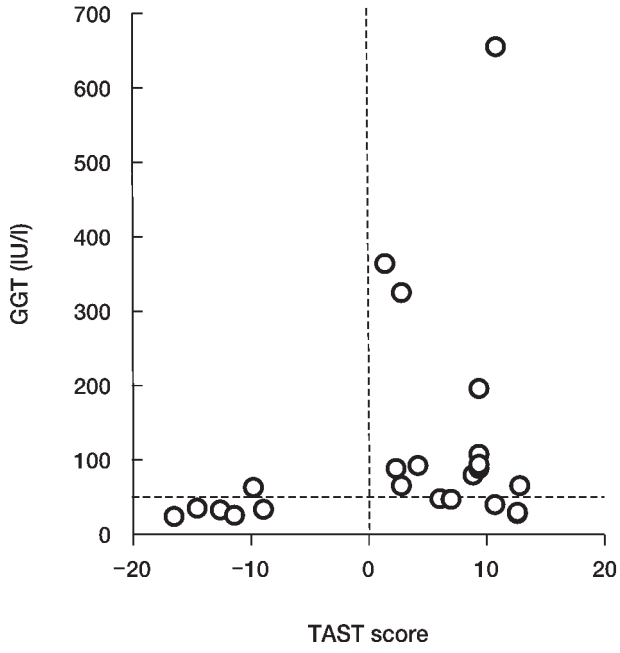

Fig. 2 Scattered diagram of the relationship between TAST score and serum GGT among the heavy drinkers. Two cases are not represented because the TAST scores were unavailable.

age-adjusted values of GGT and other biochemical markers in drinkers were higher than those in nondrinkers, and those in heavy drinkers were higher than those in moderate drinkers. These results are compatible with those generally accepted [1, 3]. However, in the group of heavy drinkers, there was a negative correlation between the level of alcohol consumption and the serum GGT level.

Muto *et al.* showed a negative correlation between serum GGT activity and the amount of alcohol consumed in a group of chronic alcohol-dependent patients [8, 9]. Those researchers used total alcohol consumption, instead of daily alcohol consumption, as an index of alcohol intake. Our study using daily alcohol consumption as an index of alcohol intake also showed a similar result. There was a positive association between the amount of daily alcohol consumed and the serum level of GGT in moderate drinkers (less than 70 g per day) and a negative association in heavy drinkers (70 g or more per day). Thus, the results of the present study of heavy drinkers among the alcohol-consuming normal population confirmed the negative association between alcohol consumption and serum GGT levels, which was shown in chronic alcoholics by Muto *et al.* [8, 9].

Table 4 Median, minimum and maximum of variables and those comparisons between 2 groups of drinkers classified by TAST score

Variables	TAST score ≦ 0 (n = 233)	TAST score > 0 (n = 363)	
Age (years)	43 (21 ~ 65)	39 (20 ~ 67)	
BMI (kg/m^2)	22.9 (16.4 ~ 32.0)	23.3 (15.2 ~ 32.2)	
Daily alcohol consumption (g/day)	17.9 (0.1 ~ 144.2)	21.2 (0.5 ~ 125.6)	**
Total alcohol consumption (kg)	92.3 (0.3 ~ 1076.2)	131.3 (1.3 ~ 962.1)	**
TAST score	−9.8 (−18.6 ~ −1.6)	9.4 (0.3 ~ 13.0)	**
UA (mg/dl)	5.6 (0.7 ~ 8.1)	5.8 (0.8 ~ 9.6)	*
ZTT (U)	3.8 (0.5 ~ 17.2)	3.8 (0.8 ~ 15.9)	
TTT (U)	1.4 (0.2 ~ 10.0)	1.4 (0.1 ~ 14.8)	
AST (IU/l)	18 (9 ~ 62)	19 (8 ~ 68)	**
ALT (IU/l)	16 (4 ~ 159)	21 (4 ~ 111)	**
ALP (IU/l)	138 (80 ~ 272)	137 (71 ~ 280)	
LDH (IU/l)	283 (180 ~ 424)	288 (201 ~ 606)	
T-Bil (mg/dl)	0.65 (0.29 ~ 2.07)	0.66 (0.21 ~ 2.37)	
D-Bil (mg/dl)	0.22 (0.09 ~ 0.61)	0.22 (0.09 ~ 0.65)	
LAP (IU/l)	51 (30 ~ 115)	52 (30 ~ 148)	
CHE(IU/l)	309 (185 ~ 632)	300 (137 ~ 438)	*
GGT(IU/l)	24 (8 ~ 220)	31 (8 ~ 654)	**
TG (mg/dl)	128 (31 ~ 642)	141 (36 ~ 930)	
TC (mg/dl)	193 (96 ~ 294)	196 (106 ~ 378)	
HDL-C (mg/dl)	48 (26 ~ 101)	50 (21 ~ 109)	

*, **, ALP, ALT, AST, BMI, CHE, D-Bil, GGT, HDL-C, LAP, LDH, TAST score, T-Bil, TC, TG, TTT, UA, ZTT; see legend to Table 1.

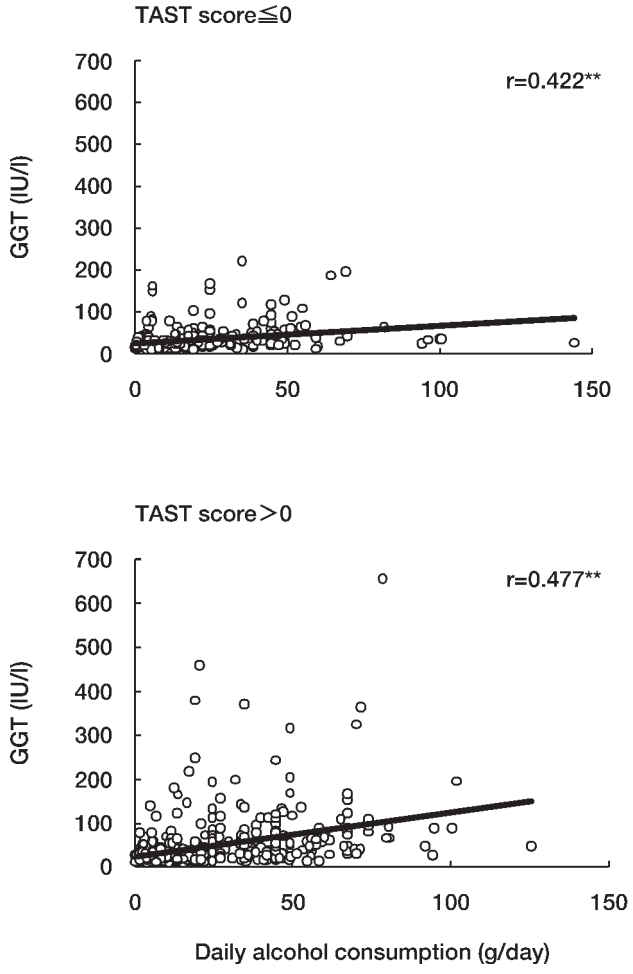

Fig. 3 Scattered diagrams of the relationship between daily alcohol consumption and gamma-glutamyltransferase (GGT) among drinkers classified into 2 groups by TAST score. $^{**}P < 0.01$.

There was a negative correlation not only between alcohol consumption and serum GGT level but also between alcohol consumption and other serum markers of liver injury, such as AST and LAP. When we divided the heavy drinkers into 2 groups, one with GGT > 50 IU/l and the other with GGT ≦ 50 IU/l, the subjects in the group with higher serum GGT levels showed significantly higher values of AST and LAP, even though the level of alcohol consumption did not differ significantly between the 2 groups. Those results indicated that elevated GGT level is not a marker of alcohol consumption but a marker of liver injury or the susceptibility of the liver to alcohol consumption in terms of liver damage.

Thus, whether an individual is a responder or nonresponder to alcohol consumption was not only related to GGT but also to AST and LAP, which are considered to be serum markers of alcoholic liver injury.

Interestingly, TAST score also showed a tendency to be negatively associated with alcohol consumption in heavy drinkers (data are not shown). This suggests that TAST score should correlate positively with GGT; and, in fact, the heavy drinkers with positive TAST scores tended to have GGT levels higher than 50 IU/l. This result was rather unexpected and difficult to explain, because individuals with greater negative TAST scores in heavy drinkers might produce more acetaldehyde, an active chemical reactor that would cause liver injury. On the contrary, what we can suspect from this result is that acetaldehyde is not a major substance that leads to the release of GGT, AST and LAP from injured hepatocytes.

GGT activity is increased by multiple factors. Aging [6], obesity [12, 13], alcohol intake [1–3, 5–7] and smoking habit [14, 15] are considered to be the factors that elevate serum GGT activity, and coffee intake [6, 15, 16] and exercise [6, 12, 13] as the factors that reduce GGT activity. In our study, age, BMI and smoking habit were ruled out as the confounders of serum GGT difference between nondrinkers and age-matched drinkers because the medians of age, BMI and smoking index and duration did not differ significantly between the 2 groups. The logistic regression analysis in all drinkers demonstrated that daily alcohol consumption was the factor that most affected serum GGT elevation (data are not shown).

The mechanism of the different responses to alcohol intake between good and poor responders is still unknown. Recently, many studies on the genotypes of aldehyde dehydrogenase 2 (ALDH2) have been reported. There is a significant difference in alcohol consumption among the groups that had different genotypes of ALDH2 [17], and alcoholic liver disease develops even with moderate amounts of alcohol intake in heterozygotes of the ALDH2 genes, in which the acetaldehyde metabolism in the liver is impaired [18], although this conflicts with our previous conclusion. Of interest is a recent finding that both AST and ALT activities were significantly higher in the ALDH2*1/*1 group than in the ALDH2*1/*2 group among moderate and heavy drinkers [19]. Yan *et al.* and Nagata *et al.* reported that

patients with alcoholic liver injury with the ALDH2*1/*2 genotype had milder liver damage than the patients with the ALDH2*1/*1 genotype [20, 21]. Higher concentrations of acetaldehyde in the ALDH2*1/*2 genotype may lead to an increased production of prostaglandins, resulting in vasodilatation and improvement of microcirculation in the liver [22], or may lead to the abrogation of necrosis and inflammation through the preservation of IκBα and inhibition of NF-κB activity, followed by down-regulation of TNFα and COX-2 [23]. Thus, follow-up studies are very important to determine whether the higher production of acetaldehyde is preventive for alcohol-induced liver injury or not.

In the present study of alcohol drinkers in the normal population, we can conclude that there was a negative correlation between daily alcohol consumption and serum GGT level among heavy drinkers, thus confirming the previous finding that there are 2 groups that respond differently to alcohol intake, namely the group with elevated GGT (good responders) and the group with normal GGT despite heavy drinking (poor responders). The results of our study emphasize that serum GGT activity is useful in the clinical assessment of alcoholic liver injury, but it is not useful in assessment of the amount of alcohol consumed.

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