Liver Enzymes Compared With Alcohol Consumption in Predicting the Risk of Type 2 Diabetes

The Kansai Healthcare Study

KYOKO KOGAWA SATO, MD, PHD[1]
TOMOSHIGE HAYASHI, MD, PHD[1]
YOSHIKO NAKAMURA, MD, PHD[2]
NOBUKO HARITA, MD[1]
TAKESHI YONEDA, MD[1]
GINJI ENDO, MD, PHD[1]
HIROSHI KAMBE, MD[2]

OBJECTIVE — It has been reported that moderate alcohol consumption decreased the risk of type 2 diabetes but that elevated liver enzymes increased it. The comparative importance of alcohol consumption and liver enzymes as predictors of type 2 diabetes remains unconfirmed.

RESEARCH DESIGN AND METHODS — The participants included 8,576 Japanese men, aged 40–55 years, without type 2 diabetes at entry. Type 2 diabetes was diagnosed if a fasting plasma glucose level was ≥126 mg/dl or if participants were taking oral hypoglycemic medications or insulin.

RESULTS — During the 4-year follow-up period, we confirmed 878 cases. In multivariate models, moderate daily alcohol consumption (16.4–42.6 g ethanol/day) decreased the risk of type 2 diabetes, and higher levels of γ-glutamyltransferase (GGT) and alanine aminotransferase (ALT) increased the risk. In joint analyses of alcohol consumption and liver enzymes, moderate drinkers with the lowest tertile of GGT had the lowest risk of type 2 diabetes. Compared with them, nondrinkers with the highest GGT had the highest risk of type 2 diabetes (odds ratio 3.18 [95% CI 1.75–5.76]). At every level of GGT, moderate or heavy alcohol drinkers (≥42.7 g ethanol/day) had a lower risk of type 2 diabetes than nondrinkers. The relationship of ALT and daily alcohol consumption with the risk of type 2 diabetes was almost the same as that of GGT.

CONCLUSIONS — GGT, ALT, and daily alcohol consumption were independently associated with the risk of type 2 diabetes. Nondrinkers with the highest GGT or ALT had a high risk of type 2 diabetes.

Diabetes Care 31:1230–1236, 2008

The liver has an important role in maintaining basal and postprandial glucose concentrations. The effect of liver enzymes on the incidence of type 2 diabetes has been reported (1–9). Alanine aminotransferase (ALT) is a specific marker of liver pathology, as it is found primarily in the liver. ALT is considered to be the marker most closely correlated to liver fat (10) and reported to be related to hepatic insulin sensitivity (1). On the other hand, γ-glutamyltransferase (GGT) and aspartate aminotransferase (AST) are less specific markers of liver disease, as they are found in other tissues as well as the liver. Although these liver enzymes might have different roles in the pathogenesis of type 2 diabetes, whether these liver enzymes are independently associated with the risk of type 2 diabetes is not known. Only three studies (1–3) have simultaneously measured GGT, ALT, and AST in the same participants to investigate the relationship between all three liver enzymes and the risk of type 2 diabetes, and these results have been inconclusive.

In particular, GGT is well known as a marker of alcohol consumption and correlates to alcohol consumption (11,12). Several epidemiological studies have reported that moderate alcohol consumption was associated with a decreased risk of type 2 diabetes (13); however, some epidemiological studies (2,4–8) have shown that a higher GGT level was associated with an increased risk of type 2 diabetes in a dose-response manner. The comparative importance and joint relationship of these factors to the risk of type 2 diabetes is unclear. Whether daily alcohol consumption can eliminate the effect of the GGT level on the risk of type 2 diabetes is not known. Furthermore, no studies have assessed whether alcohol consumption is associated with a decreased risk of type 2 diabetes independent of GGT, ALT, and AST.

We therefore examined the relationship of liver enzymes (GGT, ALT, and AST) and alcohol consumption with the incidence of type 2 diabetes during a 4-year observation period. Our specific purposes were *1*) to examine whether GGT, ALT, and AST were independently associated with the risk of type 2 diabetes; *2*) to examine whether a combination of alcohol consumption and GGT, ALT, and/or AST were independently associated with the risk of type 2 diabetes in the models that included them simultaneously; and *3*) to evaluate the joint relationship of alcohol consumption and GGT, ALT, or AST with the risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS

The Kansai Healthcare Study

The Kansai Healthcare Study is an ongoing cohort investigation designed to clar-

From the [1]Department of Preventive Medicine and Environmental Health, Osaka City University Graduate School of Medicine, Osaka, Japan; and the [2]Kansai Health Administration Center, Nippon Telegraph and Telephone West Corporation, Osaka, Japan.

Corresponding author: Kyoko Kogawa Sato, MD, PhD, Preventive Medicine and Environmental Health, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka 545-8585, Japan. E-mail: ksato@med.osaka-cu.ac.jp.

Received for publication 16 November 2007 and accepted in revised form 20 February 2008.

Published ahead of print at http://care.diabetesjournals.org on 4 March 2008. DOI: 10.2337/dc07-2184.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FPG, fasting plasma glucose; GGT, γ-glutamyltransferase.

ify the risk factors for cardiometabolic diseases (14). Between April 2000 and March 2001, 12,647 male employees of a company in the area of Kansai, Japan, aged 40–55 years at entry and considered to be involved in sedentary jobs, were enrolled in this study. All employees in this company aged ≥40 years underwent annual detailed medical check-ups. The protocol for this research was reviewed by the Human Subjects Review Committee, Osaka City University.

For current analysis, study participants consisted of 11,073 Japanese men aged 40–55 years at entry with a fasting plasma glucose (FPG) <126 mg/dl and not taking oral hypoglycemic medication or insulin. A 4-year follow-up examination after baseline was conducted between April 2004 and March 2005. We excluded 53 men because of death and 2,016 men because of loss to follow-up. Another 428 individuals who completed follow-up but had missing information were also excluded. Thus, the study population consisted of 8,576 men.

Data collection and measurements

The clinical examination consisted of a medical history; a physical examination; anthropometric measurements; self-administered questionnaires on lifestyle characteristics, such as regular leisure-time physical activity, smoking habit, and daily alcohol consumption; and measurement of FPG, GGT, ALT, and AST levels. Trained nurses took all measurements. Blood samples were drawn after an overnight 12-h fast. AST and ALT were measured using the International Federation of Clinical Chemistry–recommended method (15). GGT was measured using the Japanese Society of Clinical Chemistry–transferable method (16). This method was reported to have a strong correlation with the International Federation of Clinical Chemistry–recommended method ($r = 0.998$) (16). BMI was calculated as the weight in kilograms divided by the square of the height in meters.

The question about the duration of the walk to work as commuting physical activity was "How long does it take you to walk to this office?" The questionnaire had five possible answers (0–10, 11–20, 21–30, 31–40, or ≥41 min). As only 5.5% of men reported a walk of ≥31 min, we combined them into the category of a walk of 21–30 min. The single-item questionnaire regarding leisure-time physical activity had three possible answers: rarely, sometimes, or regular (at least once weekly). Participants were classified as engaging in regular leisure-time physical activity at least once weekly or less than once weekly. The validations of these questionnaires measured as above were described in detail previously (14). In a voluntary sample ($n = 219$) of this cohort, a detailed questionnaire was administered about the types of leisure-time physical activities participants took part in (described as light, moderate, or vigorous in accordance with the Centers for Disease Control and Prevention), their weekly activity frequency, and time spent in each activity. Participants were classified as engaging in regular leisure-time physical activity at least once weekly if they reported that they engaged in moderate- or vigorous-intensity activities at least once weekly and spent ≥30 min doing so weekly. Cohen's κ between simple and detailed questionnaires was 0.59 ($P < 0.001$) (14).

Regarding smoking habits, participants were classified as nonsmokers, past smokers, or current smokers. Questions about alcohol intake included the weekly frequency of alcohol consumption and the usual amount of alcohol consumed on a daily basis. Alcohol intake was converted to total alcohol consumption (in grams of ethanol per day) using standard Japanese tables.

Diagnosis of type 2 diabetes

Type 2 diabetes at baseline and follow-up examination was diagnosed if an FPG level was ≥126 mg/dl or if participants were taking oral hypoglycemic medications or insulin (17). Due to the age range of the study population, all cases of diabetes were diagnosed after the age of 40 years and were therefore classified as type 2 diabetes.

Statistical analysis

We used multiple logistic regression analysis to estimate the odds ratio (OR) for the incidence of type 2 diabetes in relation to baseline variables. We evaluated nonlinear effects of all continuous independent variables by using quadratic and log transformations. The presence of effect modification was tested by the insertion of first-order interaction terms into appropriate regression models. We calculated the 95% CI for each OR. *P* values were two tailed. Statistical analyses were performed using SPSS, version 15.0 (SPSS, Chicago, IL) and Stata, SE version 9.0 (Stata, College Station, TX).

RESULTS

— Among the eligible 8,576 men followed for 4 years, 878 developed type 2 diabetes. The baseline characteristics of this study population are summarized in Table 1. Study participants overall were not obese, with a mean BMI of 23.4 kg/m^2. Although participants who developed type 2 diabetes during follow-up tended to have a higher BMI than those who did not, both mean values of BMI were <25 kg/m^2.

In multiple logistic regression analysis, because age, FPG, daily alcohol consumption, GGT, and AST showed a nonlinear association with the incidence of type 2 diabetes in the models of Table 2, we fit a model using these categorized variables to make it easily understood. Age was divided into three categories: 40–44, 45–49, and 50–55 years old. The FPG level was also divided into three categories: <100, 100–109, and 110–125 mg/dl. Participants, except nondrinkers, were classified into tertiles of daily alcohol consumption levels: light drinkers (0.1–16.3 g ethanol/day), moderate drinkers (16.4–42.6 g ethanol/day), and heavy drinkers (≥42.7 g ethanol/day). We fit a model using GGT, ALT, and AST categorized by tertiles. We examined the significance of the first-order interaction terms in all models of Table 2 between daily alcohol consumption and GGT, ALT, or AST. None of these interactions was significant.

We tested a number of regression models to assess the effects of liver enzymes and daily alcohol consumption on the incidence of type 2 diabetes (Table 2). GGT, ALT, or AST was independently associated with the risk of type 2 diabetes after adjusting for daily alcohol consumption, age, BMI, smoking habit, parental history of diabetes, walk to work, regular leisure-time physical activity, and FPG level (models 1–3 of Table 2). Next, we assessed the models, including two of three liver enzymes. Both GGT and ALT were associated with an increased risk of type 2 diabetes in all models of models 4–6 of Table 2, but AST was not significantly associated with the risk of type 2 diabetes after adjusting for GGT or ALT (models 5 and 6 of Table 2). In addition, we examined the model that included all three liver enzymes simultaneously. Similarly, higher GGT and ALT, not AST, independently increased the risk of type 2 diabetes (model 7 of Table 2). Moderate daily alcohol consumption was associated with a decreased risk of type 2 diabetes in all models (models 1–7 of Table 2).

Table 1—*Characteristics of study participants at baseline according to whether type 2 diabetes developed after the 4-year follow-up*

Characteristics	Total	Type 2 diabetes status after follow-up	
		No diabetes	Diabetes
n	8,576	7,698	878
Age (years)	47.8 ± 4.2	47.7 ± 4.1	48.7 ± 4.1
BMI (kg/m^2)	23.4 ± 2.9	23.3 ± 2.8	24.6 ± 3.2
FPG (mg/dl)	97.6 ± 9.5	96.3 ± 8.5	109.1 ± 9.8
AST (IU/l)	25.8 ± 14.0	25.3 ± 12.9	30.0 ± 21.0
ALT (IU/l)	29.3 ± 19.8	28.5 ± 18.7	37.0 ± 26.4
GGT (IU/l)	65.1 ± 82.4	62.3 ± 76.3	89.6 ± 120.5
Drinking habit (%)	84.4	84.5	83.8
Daily alcohol consumption (g ethanol)	25.2 ± 21.9	25.1 ± 21.9	25.8 ± 22.3
Smoking habit (%)			
Nonsmokers	21.5	21.6	20.4
Past smokers	22.4	22.2	24.4
Current smokers	56.1	56.2	55.2
Walk to work (%)			
0–10 min	19.8	19.6	21.6
11–20 min	52.4	52.3	52.7
≥21 min	27.8	28.1	25.6
Regular leisure-time physical activity (%)	18.1	18.2	16.6
Parental history of diabetes (%)	12.9	12.0	21.0

Data are means ± SD or percent.

The joint analyses of daily alcohol consumption and liver enzymes in association with the risk of type 2 diabetes are shown in Table 3. Moderate drinkers with the lowest tertile of GGT had the lowest risk of type 2 diabetes (model 1 of Table 3). Compared with them, nondrinkers or light drinkers with the highest GGT had the highest risk of type 2 diabetes. Within each category of GGT, moderate or heavy daily alcohol consumption was associated with a decreased risk of type 2 diabetes (model 1 of Table 3). We also examined the combined effects of other liver enzymes and alcohol consumption on the incidence of type 2 diabetes (models 2 and 3 of Table 3). The relationship of ALT or AST and daily alcohol consumption with the risk of type 2 diabetes was almost the same as that of GGT. Nondrinkers with the highest tertile of ALT or AST level had the highest risk of type 2 diabetes, but the multiple-adjusted ORs of the highest level of ALT and AST among nondrinkers or light drinkers for the risk of type 2 diabetes were lower than those of GGT.

CONCLUSIONS — These prospective data demonstrated that both daily alcohol consumption and GGT were independently associated with the risk of type 2 diabetes. Moderate alcohol consumption was associated with a decreased risk of type 2 diabetes. A higher level of GGT was associated with an increased risk of type 2 diabetes. Moderate alcohol drinkers with the lowest GGT had the lowest risk of type 2 diabetes. The effect of ALT or AST and daily alcohol consumption on the risk of type 2 diabetes was almost same as that of GGT. These finding were independent of age (40–44, 45–49, or 50–55 years), BMI, FPG (<100, 100–109, or 110–125 mg/dl), smoking habit, parental history of diabetes, walk to work, and regular leisure-time physical activity. However, no association was found between AST and the risk of type 2 diabetes after adjustment for other liver enzymes.

Many prospective studies have shown the effect of moderate alcohol consumption on the reduced risk of type 2 diabetes, but in all of these studies, the models were not adjusted for liver enzymes (13). On the other hand, without few exceptions, previous epidemiological studies have shown that a higher GGT increased the risk of type 2 diabetes after adjusting for daily alcohol consumption but have not shown the effect of daily alcohol consumption on the risk of type 2 diabetes (2,4–8). Only two studies (3,9) showed the associations of ALT or AST and alcohol consumption with the risk of type 2 diabetes. ALT (9) or AST (3) was associated with an increased risk of type 2 diabetes. The effect of alcohol consumption on the risk of type 2 diabetes was inconsistent (3,9).

Furthermore, a few reports (1–3) have estimated the association of three liver enzymes (GGT, ALT, and AST) with the incidence of type 2 diabetes among the same participants, but their results were inconsistent. Vozarova et al. (1) reported in Pima Indians that high ALT, but neither AST nor GGT, predicted the development of type 2 diabetes in the model not including alcohol consumption. Only AST remained related to the incidence of type 2 diabetes in the Mexico City Diabetes Study (3). The different independent variables in their models, the number of participants, or the incidence rate of type 2 diabetes might explain these different results. In contrast, Nakanishi et al. (2) showed that GGT and ALT, not AST, independently increased the risk of type 2 diabetes, but they did not show the results of alcohol consumption.

We did not identify the reason why no alcohol consumption or light alcohol consumption and elevated GGT or ALT independently increased the risk of type 2 diabetes, and nondrinkers with high GGT or ALT had the highest risk of it. Two studies (18,19) reported that a higher GGT level was related to insulin resistance. On the other hand, moderate alcohol consumption has been reported to be associated with improved insulin sensitivity (20–22). Therefore, the relationship between GGT, alcohol consumption, and incidence of type 2 diabetes may be partly mediated by insulin resistance. In

Table 2—*Multivariate model of the incidence of type 2 diabetes in relation to baseline of daily alcohol consumption and liver enzymes

	n	Case [*n* (%)]	Multiple-adjusted OR (95% CI)	*P*
Model 1 variables				
GGT (IU/l)				
Tertile 1 (5–29)	2,910	204 (7.0)	1.00	
Tertile 2 (30–58)	2,817	276 (9.8)	1.11 (0.89–1.38)	0.361
Tertile 3 (59–1,357)	2,849	398 (14.0)	1.64 (1.31–2.05)	<0.001
Daily alcohol consumption				
Nondrinkers	1,334	142 (10.6)	1.00	
Light drinkers	1,657	164 (9.9)	0.91 (0.69–1.19)	0.475
Moderate drinkers	3,002	291 (9.7)	0.65 (0.50–0.83)	0.001
Heavy drinkers	2,583	281 (10.9)	0.66 (0.50–0.86)	0.002
Model 2 variables				
ALT (IU/l)				
Tertile 1 (3–19)	2,967	193 (6.5)	1.00	
Tertile 2 (20–30)	2,804	272 (9.7)	1.21 (0.97–1.50)	0.088
Tertile 3 (31–271)	2,805	413 (14.7)	1.63 (1.31–2.02)	<0.001
Daily alcohol consumption				
Nondrinkers	1,334	142 (10.6)	1.00	
Light drinkers	1,657	164 (9.9)	0.95 (0.72–1.25)	0.727
Moderate drinkers	3,002	291 (9.7)	0.76 (0.59–0.97)	0.025
Heavy drinkers	2,583	281 (10.9)	0.82 (0.64–1.05)	0.107
Model 3 variables				
AST (IU/l)				
Tertile 1 (8–20)	3,139	265 (8.4)	1.00	
Tertile 2 (21–26)	2,777	247 (8.9)	1.02 (0.83–1.25)	0.882
Tertile 3 (27–284)	2,660	366 (13.8)	1.41 (1.15–1.72)	0.001
Daily alcohol consumption				
Nondrinkers	1,334	142 (10.6)	1.00	
Light drinkers	1,657	164 (9.9)	0.94 (0.71–1.23)	0.645
Moderate drinkers	3,002	291 (9.7)	0.73 (0.57–0.93)	0.011
Heavy drinkers	2,583	281 (10.9)	0.78 (0.60–1.00)	0.046
Model 4 variables				
GGT (IU/l)				
Tertile 1 (5–29)	2,910	204 (7.0)	1.00	
Tertile 2 (30–58)	2,817	276 (9.8)	1.03 (0.82–1.29)	0.824
Tertile 3 (59–1357)	2,849	398 (14.0)	1.39 (1.08–1.79)	0.010
ALT (IU/l)				
Tertile 1 (3–19)	2,967	193 (6.5)	1.00	
Tertile 2 (20–30)	2,804	272 (9.7)	1.13 (0.90–1.41)	0.302
Tertile 3 (31–271)	2,805	413 (14.7)	1.40 (1.10–1.78)	0.006
Daily alcohol consumption				
Nondrinkers	1,334	142 (10.6)	1.00	
Light drinkers	1,657	164 (9.9)	0.93 (0.70–1.22)	0.582
Moderate drinkers	3,002	291 (9.7)	0.68 (0.53–0.88)	0.003
Heavy drinkers	2,583	281 (10.9)	0.70 (0.53–0.92)	0.010
Model 5 variables				
GGT (IU/l)				
Tertile 1 (5–29)	2,910	204 (7.0)	1.00	
Tertile 2 (30–58)	2,817	276 (9.8)	1.08 (0.86–1.35)	0.490
Tertile 3 (59–1357)	2,849	398 (14.0)	1.51 (1.18–1.94)	0.001
AST (IU/l)				
Tertile 1 (8–20)	3,139	265 (8.4)	1.00	
Tertile 2 (21–26)	2,777	247 (8.9)	0.94 (0.76–1.17)	0.599
Tertile 3 (27–284)	2,660	366 (13.8)	1.19 (0.95–1.48)	0.127

(continued)

Table 2—*Continued*

	n	Case [*n* (%)]	Multiple-adjusted OR (95% CI)	*P*
Daily alcohol consumption				
Nondrinkers	1,334	142 (10.6)	1.00	
Light drinkers	1,657	164 (9.9)	0.91 (0.69–1.20)	0.507
Moderate drinkers	3,002	291 (9.7)	0.66 (0.51–0.84)	0.001
Heavy drinkers	2,583	281 (10.9)	0.66 (0.51–0.87)	0.002
Model 6 variables				
ALT (IU/l)				
Tertile 1 (3–19)	2,967	193 (6.5)	1.00	
Tertile 2 (20–30)	2,804	272 (9.7)	1.24 (0.98–1.56)	0.077
Tertile 3 (31–271)	2,805	413 (14.7)	1.58 (1.19–2.11)	0.002
AST (IU/l)				
Tertile 1 (8–20)	3,139	265 (8.4)	1.00	
Tertile 2 (21–26)	2,777	247 (8.9)	0.87 (0.69–1.10)	0.244
Tertile 3 (27–284)	2,660	366 (13.8)	1.05 (0.80–1.37)	0.730
Daily alcohol consumption				
Nondrinkers	1,334	142 (10.6)	1.00	
Light drinkers	1,657	164 (9.9)	0.95 (0.72–1.25)	0.725
Moderate drinkers	3,002	291 (9.7)	0.75 (0.59–0.96)	0.024
Heavy drinkers	2,583	281 (10.9)	0.81 (0.63–1.04)	0.102
Model 7 variables				
GGT (IU/l)				
Tertile 1 (5–29)	2,910	204 (7.0)	1.00	
Tertile 2 (30–58)	2,817	276 (9.8)	1.04 (0.82–1.30)	0.767
Tertile 3 (59–1357)	2,849	398 (14.0)	1.40 (1.08–1.81)	0.011
ALT (IU/l)				
Tertile 1 (3–19)	2,967	193 (6.5)	1.00	
Tertile 2 (20–30)	2,804	272 (9.7)	1.17 (0.92–1.49)	0.189
Tertile 3 (31–271)	2,805	413 (14.7)	1.44 (1.07–1.94)	0.016
AST (IU/l)				
Tertile 1 (8–20)	3,139	265 (8.4)	1.00	
Tertile 2 (21–26)	2,777	247 (8.9)	0.85 (0.67–1.07)	0.167
Tertile 3 (27–284)	2,660	366 (13.8)	0.97 (0.73–1.27)	0.804
Daily alcohol consumption				
Nondrinkers	1,334	142 (10.6)	1.00	
Light drinkers	1,657	164 (9.9)	0.93 (0.71–1.22)	0.590
Moderate drinkers	3,002	291 (9.7)	0.69 (0.53–0.89)	0.004
Heavy drinkers	2,583	281 (10.9)	0.71 (0.54–0.93)	0.012

*Adjusted for age (40–44, 45–49, and 50–55 years), BMI, FPG level (<100, 100–109, and 110–125 mg/dl), smoking habit (nonsmokers, past smokers, and current smokers), parental history of diabetes, walk to work (0–10, 11–20, and ≥21 min), and regular leisure-time physical activity.

addition, ALT is a well-known specific marker of liver pathology and of nonalcoholic fatty liver disease. Insulin resistance has been reported to be common in those with nonalcoholic fatty liver disease (23,24). The pathogenesis of the association between high ALT among nondrinkers and light drinkers and the risk of type 2 diabetes might be in part due to nonalcoholic fatty liver disease and insulin resistance.

The present study had some limitations. First, we included in the models daily alcohol consumption, liver enzymes, age, BMI, FPG, smoking habit, parental history of diabetes, walk to work, and regular leisure-time physical activity. However, other unmeasured or unknown confounding variables such as fasting plasma insulin level, dietary factors, and genetic factors might explain the associations that we observed between liver enzymes, daily alcohol consumption, and the incidence of type 2 diabetes. Second, because all participants were registered employees of the same company and a single ethnic group, our results may not be representative of the general population but may apply to Japanese-American men and also possibly other Asian-American and native Asian men. Thus, future studies need to focus on the effect of liver enzymes, alcohol consumption, and insulin resistance on the incidence of type 2 diabetes, taking account of genetic factors in other ethnicities or the general population. Third, we could not administer the oral glucose tolerance test to diagnose type 2 diabetes because of excessive cost and demands on the participants' time, although the American Diabetes Association has recommended that, for epidemiological studies, estimates of diabetes incidence should be based on an FPG level of ≥126 mg/dl (17).

In conclusion, men with elevated GGT or ALT who are nondrinkers or light drinkers should be considered at high risk for the development of type 2 diabetes. In a meta-analysis of a population-based study, GGT was reported to be positively

Table 3—*Multivariate ORs of the incidence of type 2 diabetes according to joint categories of daily alcohol consumption and liver enzymes**

		Daily alcohol consumption		
	Nondrinkers	Light drinkers	Moderate drinkers	Heavy drinkers
Model 1 GGT				
Case/*n* (%)				
Tertile 1	63/796 (7.9)	64/841 (7.6)	50/872 (5.7)	27/401 (6.7)
Tertile 2	52/402 (12.9)	59/541 (10.9)	102/1,072 (9.5)	63/802 (7.9)
Tertile 3	27/136 (19.9)	41/275 (14.9)	139/1,058 (13.1)	191/1,380 (13.8)
OR (95% CI)				
Tertile 1	1.65 (1.07–2.52)	1.49 (0.97–2.29)	1.00	1.17 (0.69–2.01)
Tertile 2	1.67 (1.05–2.67)	1.63 (1.04–2.54)	1.31 (0.88–1.94)	1.08 (0.71–1.66)
Tertile 3	3.18 (1.75–5.76)	2.44 (1.47–4.04)	1.63 (1.12–2.39)	1.81 (1.26–2.60)
Model 2 ALT				
Case/*n* (%)				
Tertile 1	34/489 (7.0)	46/605 (7.6)	59/1,044 (5.7)	54/829 (6.5)
Tertile 2	37/413 (9.0)	45/529 (8.5)	101/998 (10.1)	89/864 (10.3)
Tertile 3	71/432 (16.4)	73/523 (14.0)	131/960 (13.6)	138/890 (15.5)
OR (95% CI)				
Tertile 1	1.69 (1.05–2.72)	1.77 (1.13–2.76)	1.00	1.16 (0.77–1.76)
Tertile 2	1.75 (1.09–2.82)	1.47 (0.93–2.30)	1.54 (1.07–2.23)	1.47 (1.01–2.15)
Tertile 3	2.37 (1.55–3.62)	2.31 (1.53–3.50)	1.83 (1.27–2.63)	2.09 (1.46–2.99)
Model 3 AST				
Case/*n* (%)				
Tertile 1	62/650 (9.5)	62/746 (8.3)	88/1,083 (8.1)	53/660 (8.0)
Tertile 2	31/385 (8.1)	48/513 (9.4)	80/1,008 (7.9)	88/871 (10.1)
Tertile 3	49/299 (16.4)	54/398 (13.6)	123/911 (13.5)	140/1,052 (13.3)
OR (95% CI)				
Tertile 1	1.71 (1.17–2.51)	1.29 (0.88–1.89)	1.00	0.95 (0.64–1.40)
Tertile 2	0.98 (0.61–1.60)	1.39 (0.91–2.11)	1.03 (0.72–1.46)	1.27 (0.90–1.80)
Tertile 3	2.02 (1.30–3.14)	1.83 (1.20–2.78)	1.48 (1.06–2.05)	1.48 (1.08–2.04)

*Adjusted for age (40–44, 45–49, and 50–55 years), BMI, FPG level (<100, 100–109, and 110–125 mg/dl), smoking habit (nonsmokers, past smokers, and current smokers), parental history of diabetes, walk to work (0–10, 11–20, and ≥21 min), and regular leisure-time physical activity.

associated with incidence of coronary heart disease or stroke independent of alcohol consumption (25). Therefore, liver enzymes might be a useful maker to evaluate the risk of type 2 diabetes or cardiovascular diseases in clinical practice, as it is convenient and easily available. The mechanism by which GGT, ALT, or alcohol consumption is associated with incidence of type 2 diabetes remains to be determined. To confirm these findings, further research on these associations is needed.

Acknowledgments— This work was supported by a grant-in-aid for Health and Labor Sciences Research Grants (Research on Occupational Safety and Health H14-03) from the Ministry of Health Labor and Welfare of Japan and for Scientific Research (17390177) from the Ministry of Education, Culture, Sports, Science, and Technology, as well as by facilities and services provided by Kansai Health Administration Center at Nippon Telegraph and Telephone West Corporation. The funding sources had no role in the collection of the data or in the decision to submit the manuscript for publication.

We thank the participants in the Kansai Healthcare Study for their dedication.

References

1. Vozarova B, Stefan N, Lindsay RS, Saremi A, Pratley RE, Bogardus C, Tataranni PA: High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes* 51:1889–1895, 2002
2. Nakanishi N, Suzuki K, Tatara K: Serum γ-glutamyltransferase and risk of metabolic syndrome and type 2 in middle-aged Japanese men. *Diabetes Care* 27: 1427–1432, 2004
3. Nannipieri M, Gonzales C, Baldi S, Posadas R, Williams K, Haffner SM, Stern MP, Ferrannini E: Liver enzymes, the metabolic syndrome, and incident diabetes: the Mexico City Diabetes Study. *Diabetes Care* 28:1757–1762, 2005
4. Perry IJ, Wannamethee SG, Shaper AG: Prospective study of serum γ-glutamyltransferase and risk of NIDDM. *Diabetes Care* 21:732–737, 1998
5. Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, Steffes M, Blomhoff R, Jacobs DR Jr: Gamma-glutamyltransferase and diabetes: a 4 year follow-up study. *Diabetologia* 46:359–364, 2003
6. Lee DH, Jacobs DR Jr, Gross M, Kiefe CI, Roseman J, Lewis CE, Steffes M: Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Clin Chem* 49:1358–1366, 2003
7. Meisinger C, Lowel H, Heier M, Schneider A, Thorand B, the KORA Study Group: Serum gamma-glutamyltransferase and risk of type 2 diabetes mellitus in men and women from the general population. *J Intern Med* 258:527–535, 2005
8. Wannamethee SG, Shaper AG, Lennon L, Whincup PH: Hepatic enzymes, the metabolic syndrome, and the risk of type 2 diabetes in older men. *Diabetes Care* 28: 2913–2918, 2005
9. Sattar N, Scherbakova O, Ford I, O'Reilly DS, Stanley A, Forrest E, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J: Elevated alanine aminotransferase predicts

new-onset type 2 diabetes independently of classical risk factors, metabolic syndrome, and C-reactive protein in the west of Scotland Coronary Prevention Study. *Diabetes* 53:2855–2860, 2004
10. Westerbacka J, Corner A, Tiikkainen M, Tamminen M, Vehkavaara S, Hakkinen AM, Fredriksson J, Yki-Jarvinen H: Women and men have similar amounts of liver and intra-abdominal fat, despite more subcutaneous fat in women: implications for sex differences in markers of cardiovascular risk. *Diabetologia* 47: 1360–1369, 2004
11. Teschke R, Brand A, Strohmeyer G: Induction of hepatic microsomal gamma-glutamyltransferase activity following chronic alcohol consumption. *Biochem Biophys Res Commun* 75:718–724, 1977
12. Shaper AG, Pocock SJ, Ashby D, Walker M, Whitehead TP: Biochemical and haematological response to alcohol intake. *Ann Clin Biochem* 22:50–61, 1985
13. Howard AA, Arnsten JH, Gourevitch MN: Effect of alcohol consumption on diabetes mellitus: a systematic review. *Ann Intern Med* 140:211–219, 2004
14. Sato KK, Hayashi T, Kambe H, Nakamura Y, Harita N, Endo G, Yoneda T: Walking to work is an independent predictor of incidence of type 2 diabetes in Japanese men: the Kansai Healthcare Study. *Diabetes Care* 30:2296–2298, 2007
15. Bergmeyer HU, Hørder M, Rej R: International Federation of Clinical Chemistry (IFCC) Scientific Committee, Analytical Section: approved recommendation (1985) on IFCC methods for the measurement of catalytic concentration of enzymes. Part 2. IFCC method for aspartate aminotransferase (L-aspartate: 2-oxoglutarate aminotransferase, EC 2.6.1.1). *J Clin Chem Clin Biochem* 24:481–510, 1986
16. Committee on Enzyme, Japan Society of Clinical Chemisty: Recommended method for measurement of enzymes in human serum-γ-glutamyltransferase (γ-GT). *Japanese J Clin Chem* 24:106–121, 1995
17. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
18. Wallace TM, Utzschneider KM, Tong J, Carr DB, Zraika S, Bankson DD, Knopp RH, Kahn SE: Relationship of liver enzymes to insulin sensitivity and intra-abdominal fat. *Diabetes Care* 30:2673–2678, 2007
19. Fraser A, Ebrahim S, Smith GD, Lawlor DA: A comparison of associations of alanine aminotransferase and gamma-glutamyltransferase with fasting glucose, fasting insulin, and glycated hemoglobin in women with and without diabetes. *Hepatology* 46:158–165, 2007
20. Mayer EJ, Newman B, Quesenberry CP Jr, Friedman GD, Selby JV: Alcohol consumption and insulin concentrations: role of insulin in associations of alcohol intake with high-density lipoprotein cholesterol and triglycerides. *Circulation* 88:2190–2197, 1993
21. Kiechl S, Willeit J, Poewe W, Egger G, Oberhollenzer F, Muggeo M, Bonora E: Insulin sensitivity and regular alcohol consumption: large, prospective, cross sectional population study (Bruneck study). *BMJ* 313:1040–1044, 1996
22. Lazarus R, Sparrow D, Weiss ST: Alcohol intake and insulin levels: the Normative Aging Study. *Am J Epidemiol* 145:909–916, 1997
23. Utzschneider KM, Kahn SE: Review: the role of insulin resistance in nonalcoholic fatty liver disease. *J Clin Endocrinol Metab* 91:4753–4761, 2006
24. Tarantino G, Saldalamacchia G, Conca P, Arena A: Non-alcoholic fatty liver disease: further expression of the metabolic syndrome. *J Gastroenterol Hepatol* 22:293–303, 2007
25. Fraser A, Harris R, Sattar N, Ebrahim S, Smith GD, Lawlor DA: Gamma-glutamyltransferase is associated with incident vascular events independently of alcohol intake: analysis of the British Women's Heart and Health Study and meta-analysis. *Arterioscler Thromb Vasc Biol* 27:2729–2735, 2007