Original Article

Relation of Gamma-Glutamyltransferase and Alcohol Drinking with Incident Diabetes: the HIPOP-OHP Study

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***Aim*: Gamma-glutamyltransferase (GGT) is known to correlate well with alcohol consumption; however, the relation between GGT and diabetes and that between alcohol consumption and diabetes mellitus (DM) is inconsistent. Thus, several questions, such as whether light to moderate drinkers can be considered as low risk for diabetes incidence irrespective of their GGT level, is unresolved. In this study, we investigated the relation of GGT or alcohol drinking with DM incidence considering the body mass index (BMI) in healthy Japanese workers.**

***Methods*: We followed 3095 men who did not have DM at baseline for 4 years. Incident diabetes was defined as a fasting (non-fasting) plasma glucose level of ≥7.0 (11.1) mmol/L, or treatment of diabetes. Multiple adjusted hazard ratios (HR) were calculated using Cox proportional models.**

***Results*: Participants with higher GGT (GGT ≥27 IU/L) showed an increased risk of diabetes incidence even when their BMI level was low. Although a U-shaped relation between alcohol drinking and incident diabetes was observed, the risk to light to moderate drinkers (alcohol < 23 g/day) was not low if they were either overweight (BMI ≥25 kg/m^2) or had higher GGT (HR=2.60, p=0.08) or both overweight and higher GGT (HR=3.16, p=0.07) compared with never drinkers without higher GGT and overweight.**

***Conclusions*: Higher GGT was associated with a higher incidence of DM irrespective of drinking status or obesity. Although a U-shaped relation between alcohol drinking and incident diabetes was observed, the risk to light to moderate drinkers was not low if they were either overweight or had higher GGT.**

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Key words; Diabetes mellitus, Gamma-glutamyltransferase, Alcohol consumption, Prospective studies

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Introduction

Several prospective studies have reported that serum gamma-glutamyltransferase (GGT), which is widely used as a marker of alcohol-induced liver disease and fatty liver, is linearly related to diabetes mellitus (DM) incidence[1-12], which is an important risk

factor of atherosclerosis.

Similarly, several studies have reported a relation between alcohol consumption and the incidence of DM[13-21]; however, most of these studies showed a lower risk for DM among moderate drinkers. Recent meta-analyses of 15 prospective studies showed that the risk of DM incidence was about 30% lower in drinkers who consumed alcohol 12–24 g/day compared with abstainers[21].

Thus, discrepant results were observed between the relation of alcohol consumption to DM and the relation of GGT to DM. This discrepancy might be because GGT is not only affected by alcohol drinking but also by obesity, such as a fatty liver or non-alcoholic fatty liver disease (NAFLD)[1, 22].

Thus, the interpretation of the relation of GGT or alcohol with DM incidence is complicated and several questions, such as whether light to moderate drinkers can be considered at low risk for DM incidence irrespective of GGT or BMI, is unresolved. In this study, we investigated the relation of GGT or alcohol drinking with DM incidence considering the BMI in healthy Japanese workers.

Subjects, Materials and Methods

Study Population

A large intervention trial, the High-Risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) study, was conducted; its details have been published elsewhere[23-28]. The baseline survey was conducted between 1999 and 2000 and the intervention program was performed between 2000 and 2004. This study is a non-randomized control trial of approximately 6500 participants in six intervention and six control companies. Our population strategy is based on three factors, nutrition, physical activity, and smoking. For each factor, a researcher's working team was organized and supported the intervention. A standardized method to obtain comparable data was also been established. Approval for the study was obtained from the Institutional Review Board of Shiga University of Medical Science for ethical issues (No. 10–16).

During 1999–2000, the baseline examination was conducted for 7346 workers. Because very few women (23%) have a drinking habit, we analyzed only men in this study. Among the 5808 men who participated in the baseline survey, we excluded 1735 participants in whom glucose levels were not measured at baseline and 2 participants who did not report the time after their last meal. We also excluded 613 participants for whom no information on GGT, alcohol consumption, or other confounding factors was available. Finally, we excluded 136 participants who had prevalent DM and 229 participants who did not attend a follow-up exam. Thus, 3095 men were eligible for this study.

Measurements

In the HIPOP-OHP study, the study group used a common self-administered questionnaire to obtain information within all companies. We used this questionnaire to assess the participants' alcohol drinking (never-drinker, quit drinking, current drinker), smoking (never-smoker, quit smoking, current smoker), and exercise habit (yes, no). Drinking habits for each subject were assessed by a questionnaire common to all companies. The frequency of alcohol consumption during a typical week and the total alcohol intake on each occasion was determined and used to calculate the alcohol intake per week[24]. In this study, we defined one drink as 11.5 g ethanol, a value nearly equal to a 'standard' drink in most countries. Serum GGT was measured using a colorimetric method.

The protocol of the HIPOP-OHP research group standardized physical and laboratory data[23]. Data from the resulting physical examinations, including blood pressure, height, weight, and biological data, such as plasma glucose level and cholesterol, were measured at baseline and thereafter at annual check-ups. DM was defined as a fasting plasma glucose level of ≥7 mmol/L (126 mg/dL), a non-fasting plasma glucose level of ≥11.1 mmol/L (200 mg/dL), or active therapy for DM. The proportion of participants examined under fasting conditions was 88.8% at baseline, 87.5% at the 1-year follow-up, 84.0% at the 2-year follow-up, 85.5% at the 3-year follow-up, and 87.5% at the 4-year follow-up. Borderline hyperglycemia was defined as a plasma glucose level of ≥6.1 mmol/L (110 mg/dL) or a non-fasting plasma glucose level of ≥7.78 mmol/L (140 mg/dL). BMI was calculated as weight (kg) divided by the square of the height (m^2).

Follow-Up Survey

Participants were followed up annually for 4 years except for one company, which was followed up for only 3 years due to a corporate merger. At each visit, a participant's blood glucose level and use of antidiabetic medication were assessed. The date of the exam at which DM was first diagnosed in a participant was considered to be his incident day. The date of the final visit without a diagnosis of DM was considered to be the censored day.

Statistical Analysis

We analyzed cross-sectional data using analysis of variance for continuous variables and the chi-squared test for categorical analyses. We calculated hazard ratio for DM incidence using Cox proportional hazard models adjusted for age, smoking status, BMI, allocated group (intervention or control), walking time (less than 30 min/day vs. more), and family history of DM. For alcohol consumption, drinking groups were separated by never drank, past drinker, current drinker with alcohol consumption of less than one drink per day, 1–2 drinks/day, 2–4 drinks/day, and more than 4 drinks/day. For GGT analyses, quartiles of GGT were used.

To understand whether the risk of incident DM in never drank with higher GGT (GGT ≥27IU/L, median) is high, we assessed the risk of the combination of alcohol drinking and higher GGT. Due to the small sample, we summarized alcohol drinking into 3 categories (never, light to moderate: <2drink/day, and heavy: ≥2 drink/day).

To understand whether leaner participants with a higher GGT or obese participants without a higher GGT are at high risk for DM incidence, we also analyzed the combination of BMI category (BMI <22.8 kg/m^2, BMI 22.8–24.9 kg/m^2, and BMI 25 kg/m^2) and GGT category (below and above median, GGT=27 IU/L). The cut-off of BMI (BMI=22.8) was defined as median BMI of this study population.

Finally, to understand whether the U-shaped association between alcohol consumption and incident DM is observed irrespective of being overweight or having a higher GGT, we also assessed the risk of the combination of GGT (below and above median, GGT=27 IU/L), drinking (never, light to moderate: <2drink/day, and heavy: ≥2 drink/day), and and BMI (normal and overweight) simultaneously. In the analysis, we set never drank with normal BMI and lower GGT as the reference category. We excluded ex-drinkers in these combined analyses.

Because only one company had a program of population strategy program for drinking habit, we analyzed all companies together and adjusted for the information in this study.

Results

The mean age (±standard deviation, SD) of participants in this study was 41.5 (±9.4) years and 62.4% of participants consumed alcohol daily. **Table 1** shows the baseline characteristics of study participants. The mean age was higher in drinkers with greater alcohol consumption. The smoking rate and the proportion of participants who had GGT levels above the median were higher in drinkers with greater alcohol consumption. The proportion of borderline hyperglycemia was smaller in current drinkers who consumed less than one drink per day and those who consumed 1–2 drinks per day. Participants with higher GGT levels were older, consumed more alcohol, were more obese, and were more likely to currently smoke. The proportion of borderline hyperglycemia was linearly associated with the GGT level.

During the 3.4-year follow-up period, 118 incidents of DM were observed. **Table 2** shows the relation of alcohol consumption to DM incidence. Compared with those who never drank, current drinkers who consumed less than one drink per day showed a lower risk of DM incidence. Otherwise, no apparent associations were observed.

Table 2 also shows the relation of GGT to DM incidence. Compared with the lowest GGT quartile, a significant increased risk of DM was observed in the third quartile. Although the relation was marginal, a linear relation of log transformed GGT to DM incidence remained after adjustment for possible confounding factors.

Fig. 1 shows the relation of the combination of alcohol drinking and GGT with incident DM. Higher GGT participants consistently showed a higher risk of incident DM. Significant risk increase was observed in never drank with higher GGT and heavy drinking with higher GGT.

Fig. 2 shows the relation of the combination of BMI and GGT with incident DM. Participants who had either higher GGT or overweight consistently showed a significant risk increase of incident DM.

Fig. 3 shows the relation of the combination of numbers of higher GGT or overweight and drinking status (never, light to moderate, heavy) with incident DM. A U-shaped relation between alcohol drinking and incident DM was observed in group with either higher GGT or overweight and in the group with both higher GGT and overweight. However, the risks of DM in these light to moderate drinking categories were not low, although these risks did not reach statistical significance (HR=2.60, p=0.08 in either higher GGT or overweight group and HR=3.16, p=0.07 in both higher GGT and overweight group).

Discussion

DM is known as an important risk factor of atherosclerosis. The guideline of the Japanese Atherosclerosis Society for Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases for Japanese catego-

Table 1. Relation of alcohol consumption and risk factors for diabetes mellitus (DM) by drinking status or quartile of gamma-glutamyltransferase (GGT) among men participating in the HIPOP-OHP Study, 1999–2000

	Drinking status							GGT (IU/L)				
	Never drinker	Ex-drinker	Current drinker (drink/day)				*p*-value*	Q1 1–17.9	Q2 18–26.9	Q3 27–44.9	Q4 45–	*p*-value*
			–0.9	1–1.9	2–3.9	4–						
N	923	193	463	488	526	502		723	825	766	781	
Age	39.5	41.0	39.4	42.5	43.2	44.4	<0.01	37.4	41.4	42.8	43.9	<0.01
BMI (kg/m^2)	23.1	23.6	22.9	22.9	23.1	23.2	0.04	21.8	22.7	23.6	24.1	<0.01
Current smoking	50.2%	53.9%	47.3%	52.5%	59.5%	64.7%	<0.01	52.3%	51.1%	56.3%	57.5%	0.05
Group (% control)	65.2%	63.7%	68.3%	62.7%	61.6%	62.5%	0.23	53.7%	70.2%	68.7%	66.6%	<0.01
Alcohol (g/day)	0	0	6.2	16.8	33.6	70.4	<0.01	10.5	16.2	23.0	32.9	<0.01
GGT ≥27 IU/L (Median)	34.2%	45.6%	41.5%	52.0%	62.2%	73.7%	<0.01	0%	0%	100%	100%	<0.01
Family history of DM	17.6%	15.5%	16.8%	16.8%	17.7%	16.8%	0.99	16.1%	17.0%	18.1%	17.0%	0.84
Walking time (% <30 min/day)	17.3%	10.4%	15.8%	15.4%	15.4%	14.4%	0.23	15.9%	13.9%	15.3%	17.8%	0.18
Borderline hyperglycemia	4.3%	6.7%	3.5%	3.7%	6.8%	8.5%	<0.01	2.6%	3.8%	6.9%	7.9%	<0.01

One drink corresponds to alcohol consumption 11.5 g/day
*Analysis of variance for continuous variables and the chi-squared test for categorical analyses.

Table 2. Relation of drinking status or gamma-glutamyltransferase (GGT) with incident diabetes (DM). HIPOP-OHP Study, 4 years of follow-up

		Number of participants	Number of incident DM	HR1	HR2
Drinking status					
Never drinker		923	36	1	1
Ex-drinker		193	10	1.32 (0.65–2.66)	1.26 (0.63–2.55)
Current drinker	–0.9 drinks/day	463	7	0.38 (0.17–0.85)	0.46 (0.20–1.03)
	1–1.9 drinks/day	488	15	0.73 (0.40–1.34)	0.86 (0.47–1.59)
	2–3.9 drinks/day	526	29	1.25 (0.77–2.05)	1.43 (0.87–2.35)
	4– drinks/day	502	21	0.91 (0.53–1.57)	0.96 (0.55–1.66)
GGT					
Quartile 1	1–17.9 IU/L	723	10	1	1
Quartile 2	18–26.9 IU/L	825	24	1.83 (0.87–3.84)	1.51 (0.72–3.18)
Quartile 3	27–44.9 IU/L	766	44	3.51 (1.76–7.02)	2.33 (1.16–4.71)
Quartile 4	45– IU/L	781	40	3.10 (1.54–6.23)	1.88 (0.92–3.83)
	P for linear analyses*	3,095	118	<0.01	0.06

HR1: Age-adjusted hazard ratio
HR2: hazard ratio adjusted for age, body mass index, current smoking, intervention group, walking time, and family history of DM
*Log-transformed GGT was used to calculate the *p*-value.

rized patients with DM as well as those with a history of cerebral infarction or atherosclerosis obliterance as a high-risk group[29]; thus, knowing the risk factors for DM is important for preventing atherosclerosis. In this study, we found a strong correlation between alcohol consumption and the GGT level at baseline; however, the relation of alcohol consumption to incident DM and that of GGT to incident DM was inconsistent, i.e., a U-shaped relation was observed in alcohol consumption analyses and a linear association was observed in GGT analyses. We also found that GGT was associated with DM independent of the BMI category, i.e., higher GGT participants should be treated as high risk for incident DM even if their BMI is within the normal range. We also found that overweight participants had a higher risk of incident DM irrespective of their GGT level. Although the risk to light to moderate drinkers was lower than that to never drank and current drinkers who consumed more than 2 drinks/day, their risk was also substantial if

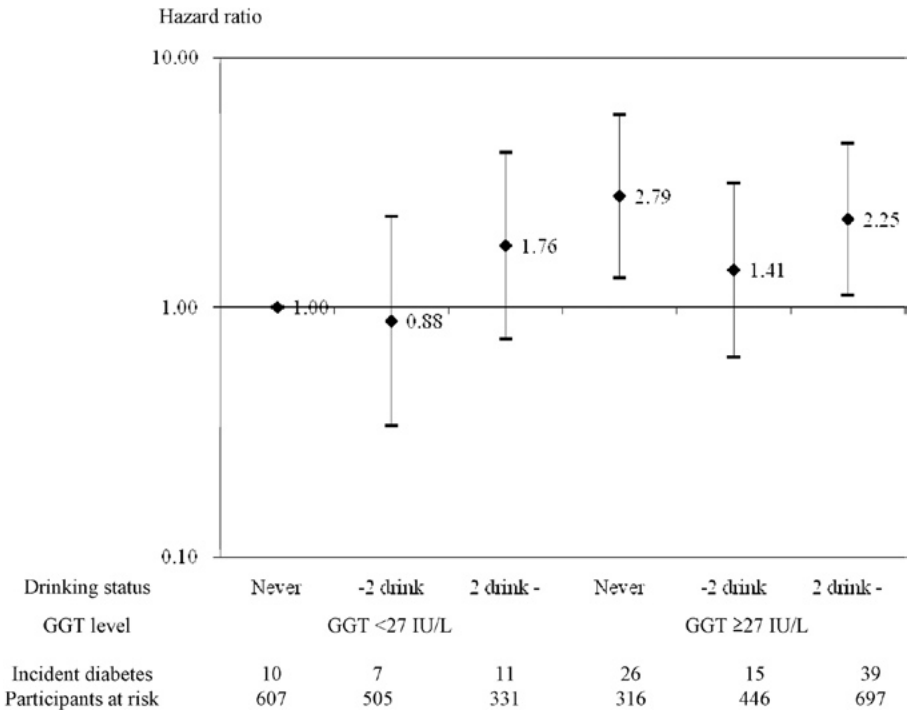

Fig. 1. Relation of combination of gamma-glutamyltransferase (GGT) and drinking with incident diabetes: the HIPOP-OHP study.

Hazard ratios were adjusted for age, current smoking, intervention group, body mass index, walking time, and family history of diabetes.
Vertical lines denote 95% confidence intervals.

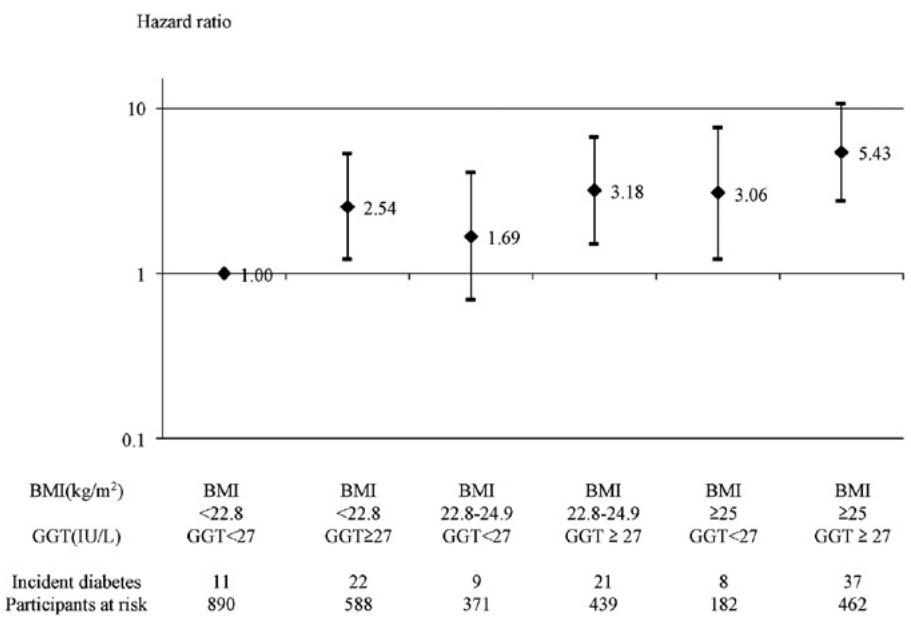

Fig. 2. Relation of combination of gamma-glutamyltransferase (GGT) and body mass index with incident diabetes: the HIPOP-OHP study.

Hazard ratios were adjusted for age, current smoking, intervention group, drinking status, walking time, and family history of diabetes.
Vertical lines denote 95% confidence intervals.

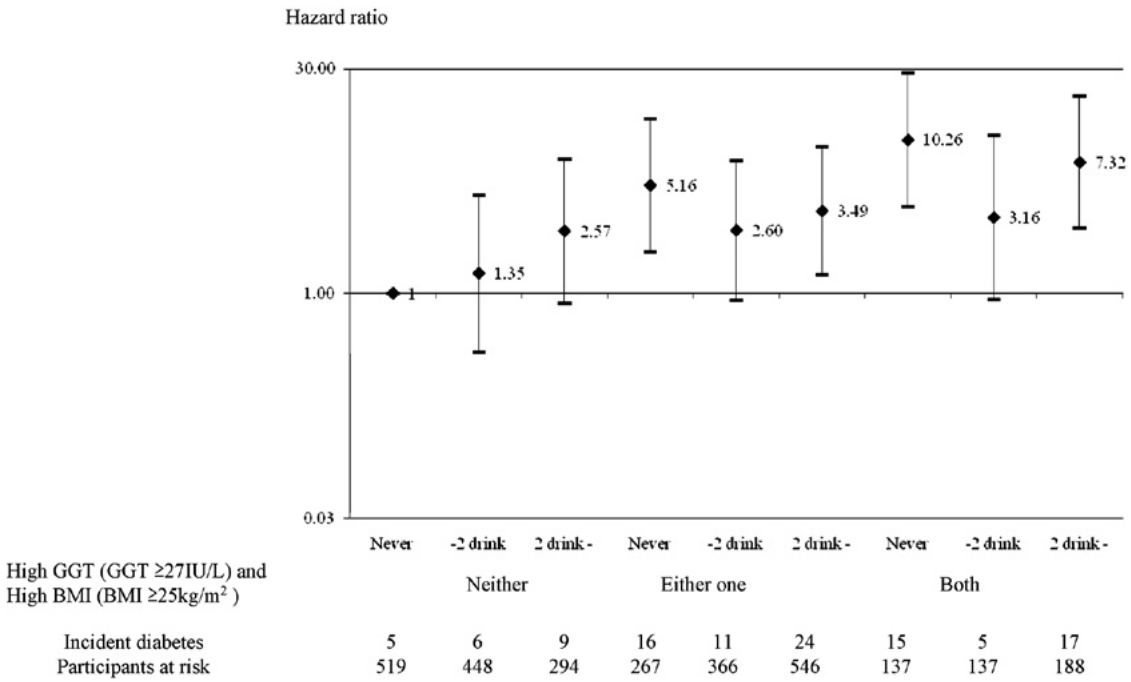

Fig. 3. Relation of combination of gamma-glutamyltransferase (GGT), body mass index, and drinking status with incident diabetes: the HIPOP-OHP study.

Hazard ratios were adjusted for age, current smoking, intervention group, walking time, and family history of diabetes. Vertical lines denote 95% confidence intervals.

they were overweight or had higher GGT.

The strength of this study was in using a precise questionnaire to assess alcohol consumption. Another was the similar socioeconomic status among participants. Because the participants were employees of relatively large companies, they could be considered to be healthy workers with a relatively high socioeconomic status. Finally, in this study, we distinguished between those who had never drunk throughout their lifetime and ex-drinkers.

In this study, we found a risk reduction in current drinkers who consumed less than one drink per day. This finding was consistent with the meta-analyses of 15 original prospective cohort studies[21]. Several mechanisms have been proposed to explain the protective effect of moderate alcohol consumption on DM. One is the inverse relation of alcohol consumption to insulin or high-density lipoprotein cholesterol. Wannamethee *et al.* reported that these factors explained the protective effect of alcohol on DM for 20% of the population[17]. Other researchers reported that the protective effect might be due to the anti-inflammatory effect of alcohol consumption[21]. In our data, the U-shaped relation was apparent in participants with higher GGT or higher BMI. Since both GGT and BMI were strongly related to the inflammation level, such as CRP[30], our finding also suggests that the protective effect of light to moderate drinking might be due to the anti-inflammatory effect. However, the most recent study reported that the U-shaped relation was observed even in the lowest GGT tertiles[11]. Further studies might be required to confirm the effect modification between alcohol intake and GGT or BMI for incident DM.

We found that participants with higher GGT showed a higher risk of incident DM irrespective of the BMI. This finding is consistent with previous studies that reported a higher risk of GGT for DM with a lower BMI[2, 5, 10]. **Fig. 2** clearly shows that participants with higher GGT should be treated as high-risk participants even if they have normal BMI. The figure also shows that overweight participants also should be treated as high risk even if their GGT is lower. The increased risk of higher GGT or higher BMI was also observed even in light to moderate drinkers. Participants who were overweight or had higher GGT should be treated as being at high risk of their DM incidence irrespective of drinking status.

Several limitations of this study should be noted. This study had a follow-up period of 3.4 years with

only 118 cases of incident DM; thus, some risks did not reach statistical significance. However, even in this short period of follow-up, we made several important findings, such as that higher GGT participants should be carefully followed even if they are not overweight. Second, this study was the prospective analysis of a controlled trial of lifestyle modification. Although, as we reported previously, no differences in trend between the intervention group and control group regarding BMI and alcohol consumption were observed[25], lifestyle changes, such as nutrition, physical activity, and smoking might affect other risk factors for DM. To control for these effects, we adjusted for groups (intervention and control) and found that groups (intervention and control) did not alter the findings, and stratified analyses between the control group and intervention group revealed similar results. Thus, we considered that this did not largely affect our results; however, we should mention that these lifestyle changes might underestimate the strength of the relation of alcohol, GGT, and BMI with DM incidence. Third, in this study, lower BMI participants with GGT ≥27 IU/L clearly showed a higher risk for DM than lower BMI participants with GGT <27 IU/L; however, due to the smaller numbers of events, it is difficult to define the threshold level of GGT in this study. Thus, larger prospective studies will be required to define the cut-off point of GGT for light drinkers (with non-obese participants) in clinical practice.

In conclusion, participants with higher GGT should be treated as being at high risk for incident DM irrespective of their BMI, i.e., GGT should be assessed even if their BMI is within the normal range. Although a U-shaped relation between drinking status and incident DM was observed, their risk was high if they were overweight or had higher GGT. Thus, the DM risk of light to moderate drinkers should not be overlooked if they have higher GGT or are obese. Since DM is an important risk factor for atherosclerotic diseases, further studies, targeting the relation of alcohol, GGT with progression of subclinical atherosclerosis or incident cardiovascular diseases, might be required.

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References

1) Perry IJ, Wannamethee SG, Shaper AG: Prospective study of serum gamma-glutamyltransferase and risk of NIDDM. Diabetes Care, 1998; 21: 732-737
2) 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, 2003; 46: 359-364
3) 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, 2003; 49: 1358-1366
4) Nakanishi N, Nishina K, Li W, Sato M, Suzuki K, Tatara K: Serum gamma-glutamyltransferase and development of impaired fasting glucose or type 2 diabetes in middle-aged Japanese men. J Intern Med, 2003; 254: 287-295
5) Lee DH, Silventoinen K, Jacobs DR Jr, Jousilahti P, Tuomileto J: gamma-Glutamyltransferase, obesity, and the risk of type 2 diabetes: observational cohort study among 20,158 middle-aged men and women. J Clin Endocrinol Metab, 2004; 89: 5410-5414
6) Nakanishi N, Suzuki K, Tatara K: Serum gamma-glutamyltransferase and risk of metabolic syndrome and type 2 diabetes in middle-aged Japanese men. Diabetes Care, 2004; 27: 1427-1432
7) 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, 2005; 28: 2913-2918
8) Meisinger C, Löwel H, Heier M, Schneider A, Thorand B; KORA Study Group: Serum gamma-glutamyltransferase and risk of type 2 diabetes mellitus in men and women from the general population. J Intern Med, 2005; 258: 527-535
9) Nannipieri M, Gonzales C, Baldi S, Posadas R, Williams K, Haffner SM, Stern MP, Ferrannini E; Mexico City diabetes study. Liver enzymes, the metabolic syndrome, and incident diabetes: the Mexico City diabetes study. Diabetes Care, 2005; 28: 1757-1762
10) Doi Y, Kubo M, Yonemoto K, Ninomiya T, Iwase M, Tanizaki Y, Shikata K, Iida M, Kiyohara Y: Liver enzymes as a predictor for incident diabetes in a Japanese population: the Hisayama study. Obesity (ilver spring). 2007; 15: 1841-1850
11) Sato KK, Hayashi T, Nakamura Y, Harita N, Yoneda T, Endo G, Kambe H: Liver enzymes compared with alcohol consumption in predicting the risk of type 2 diabetes: the Kansai Healthcare Study. Diabetes Care, 2008; 31: 1230-1236
12) Ford ES, Schulze MB, Bergmann MM, Thamer C, Joost HG, Boeing H: Liver enzymes and incident diabetes: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Diabetes Care, 2008; 31: 1138-1143

13) Tsumura K, Hayashi T, Suematsu C, Endo G, Fujii S, Okada K: Daily alcohol consumption and the risk of type 2 diabetes in Japanese men: the Osaka Health Survey. Diabetes Care, 1999; 22: 1432-1437
14) Ajani UA, Hennekens CH, Spelsberg A, Manson JE: Alcohol consumption and risk of type 2 diabetes mellitus among US male physicians. Arch Intern Med, 2000; 160: 1025-1030
15) Wei M, Gibbons LW, Mitchell TL, Kampert JB, Blair SN: Alcohol intake and incidence of type 2 diabetes in men. Diabetes Care, 2000; 23: 18-22
16) Conigrave KM, Hu BF, Camargo CA Jr, Stampfer MJ, Willett WC, Rimm EB: A prospective study of drinking patterns in relation to risk of type 2 diabetes among men. Diabetes, 2001; 50: 2390-2395
17) Wannamethee SG, Shaper AG, Perry IJ, Alberti KG: Alcohol consumption and the incidence of type II diabetes. J Epidemiol Community Health, 2002; 56: 542-548
18) Nakanishi N, Suzuki K, Tatara K: Alcohol consumption and risk for development of impaired fasting glucose or type 2 diabetes in middle-aged Japanese men. Diabetes Care, 2003; 26: 48-54
19) Wannamethee SG, Camargo CA Jr, Manson JE, Willett WC, Rimm EB: Alcohol drinking patterns and risk of type 2 diabetes mellitus among younger women. Arch Intern Med, 2003; 163: 1329-1336
20) Carlsson S, Hammar N, Grill V, Kaprio J: Alcohol consumption and the incidence of type 2 diabetes: a 20-year follow-up of the Finnish twin cohort study. Diabetes Care, 2003; 26: 2785-2790
21) Koppes LL, Dekker JM, Hendriks HF, Bouter LM, Heine RJ: Moderate alcohol consumption lowers the risk of type 2 diabetes: a meta-analysis of prospective observational studies. Diabetes Care, 2005; 28: 719-725
22) Chang Y, Ryu S, Sung E, Jang Y: Higher concentrations of alanine aminotransferase within the reference interval predict nonalcoholic fatty liver disease. Clin Chem, 2007; 53: 686-692
23) Okamura T, Tanaka T, Babazono A, Yoshita K, Chiba N, Takebayashi T, Nakagawa H, Yamato H, Miura K, Tamaki J, Kadowaki T, Okayama A, Ueshima H; HIPOP-OHP Research Group. The high-risk and population strategy for occupational health promotion (HIPOP-OHP) study: study design and cardiovascular risk factors at the baseline survey. J Hum Hypertens, 2004; 18: 475-485
24) Okamura T, Tanaka T, Yoshita K, Chiba N, Takebayashi T, Kikuchi Y, Tamaki J, Tamura U, Minai J, Kadowaki T, Miura K, Nakagawa H, Tanihara S, Okayama A, Ueshima H; HIPOP-OHP research group. Specific alcoholic beverage and blood pressure in a middle-aged Japanese population: the High-risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) Study. J Hum Hypertens, 2004; 18: 9-16
25) Naito M, Nakayama T, Okamura T, Miura K, Yanagita M, Fujieda Y, Kinoshita F, Naito Y, Nakagawa H, Tanaka T, Ueshima H; HIPOP-OHP Research Group. Effect of a 4-year workplace-based physical activity intervention program on the blood lipid profiles of participating employees: The high-risk and population strategy for occupational health promotion (HIPOP-OHP) study. Atherosclerosis, 2008; 197: 784-790
26) Tamura U, Tanaka T, Okamura T, Kadowaki T, Yamato H, Tanaka H, et al: Changes in weight, cardiovascular risk factors and estimated risk for coronary heart disease following smoking cessation in Japanese male workers: HIPOP-OHP Study. J Atheroscler Thromb, in press
27) Hayashino Y, Fukuhara S, Okamura T, Yamato H, Tanaka H, Tanaka T, Kadowaki T, Ueshima H; HIPOP-OHP Research Group. A prospective study of passive smoking and risk of diabetes in a cohort of workers: the High-risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) Study. Diabetes Care, 2008; 31: 732-734
28) Kamon Y, Okamura T, Tanaka T, Hozawa A, Yamagata Z, Takebayashi T, Kusaka Y, Urano S, Nakagawa H, Kadowaki T, Miyoshi Y, Yamato H, Okayama A, Ueshima H; HIPOP-OHP Research Group: Marital Status and Cardiovascular Risk Factors among Middle-aged Japanese Male Workers: The High-risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) Study. J Occup Health, 2008; 50: 348-356
29) Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, Daida H, Biro S, Hirobe K, Funahashi T, Yokote K, Yokode M: Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. J Atheroscler Thromb, 2007; 14: 45-50
30) Lee DH, Jacobs DR Jr: Association between serum gammaglutamyltransferase and C-reactive protein. Atherosclerosis, 2005; 178: 327-330