Serum γ-Glutamyltransferase and Risk of Metabolic Syndrome and Type 2 Diabetes in Middle-Aged Japanese Men

Noriyuki Nakanishi, md, drph[1]
Kenji Suzuki, scd[2]
Kozo Tatara, md[1]

OBJECTIVE — To investigate the association between serum γ-glutamyltransferase (GGT) and risk of metabolic syndrome and type 2 diabetes in Japanese male office workers.

RESEARCH DESIGN AND METHODS — This study included 2,957 metabolic syndrome–free men and 3,260 nondiabetic men aged 35–59 years who did not have medication for hepatitis, alanine aminotransferase (ALT) levels higher than three times the upper limit of the reference range, or a history of cardiovascular disease at study entry. Subjects were reexamined at periodic annual health examinations over a 7-year period. We used a modified National Cholesterol Education Program definition of metabolic syndrome with BMI instead of waist circumference and the revised criteria of the American Diabetes Association for type 2 diabetes.

RESULTS — With adjustment for age, family history of diabetes, BMI, alcohol intake, cigarette smoking, regular physical activity (fasting plasma glucose for the risk of type 2 diabetes), and white blood cell (WBC) count, the risk of metabolic syndrome and type 2 diabetes increased in correlation with the levels of serum GGT, ALT, aspartate aminotransferase (AST), and alkaline phosphatase. Additional adjustment for all of the other liver enzymes attenuated these associations, but serum GGT remained a significant risk factor for the risk of both metabolic syndrome and type 2 diabetes (*P* for trend <0.001 for both). Top one-fifth versus bottom one-fifth relative risks of metabolic syndrome and type 2 diabetes were 2.23 (95% CI 1.51–3.30) and 2.44 (1.34–4.46), respectively.

CONCLUSIONS — These results indicate that serum GGT may be an important predictor for developing metabolic syndrome and type 2 diabetes in middle-aged Japanese men.

Diabetes Care **27:1427–1432, 2004**

In addition to its diagnostic uses, serum γ-glutamyltransferase (GGT) has substantial epidemiologic significance (1). Prospective studies (2,3) have shown a significant relationship between serum GGT and the development of specific conditions including coronary heart disease (CHD) and stroke. In addition to alcohol, obesity has been found (4) to have a major effect on serum GGT, and there is increasing evidence (4–8) linking raised serum GGT levels with other metabolic disturbances, such as glycemic disorder, hypertension, hypertriglyceridemia, and low HDL cholesterol. Excess deposition of fat in liver, usually termed nonalcoholic fatty liver disease, is closely associated with elevated serum GGT, obesity, insulin resistance, and hyperinsulinemia (9–11). These interrelations between serum GGT, obesity, other metabolic disturbances, and plasma insulin raise the possibility that elevated GGT levels can help predict the development of metabolic syndrome and type 2 diabetes.

The Adult Treatment Panel III of the National Cholesterol Education Program (NCEP) recently proposed a definition of the metabolic syndrome to aid identification of individuals at risk for both CHD and type 2 diabetes (12). The definition incorporates thresholds for five easily measured variables linked to insulin resistance: waist circumference, triglyceride level, HDL cholesterol level, fasting plasma glucose level, and blood pressure. The NCEP-defined metabolic syndrome classification is triggered when predefined limits of any three of these five criteria are exceeded. BMI, which most observers would accept as a satisfactory substitute for waist circumference in middle-aged men, is as effective as waist circumference for predicting the development of type 2 diabetes and other metabolic disturbances (13–15). Indeed, BMI has been recently adopted instead of waist circumference for analyses of metabolic syndrome (16,17).

Using a modified NCEP definition with BMI instead of waist circumference, we examined the association of serum GGT with metabolic syndrome and type 2 diabetes (as diagnosed with the 1997 revised criteria of the American Diabetes Association [18] for epidemiological studies) in Japanese male office workers and performed a longitudinal study to prospectively examine the association of serum GGT with the development of metabolic syndrome and type 2 diabetes. Possible associations between other liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase) and risk of metabolic syndrome and type 2 diabetes were also examined.

From the [1]Department of Social and Environmental Medicine F2, Course of Social Medicine, Osaka University Graduate School of Medicine, Osaka, Japan; and the [2]Japan Labor and Welfare Association, Tokyo, Japan.

Address correspondence and reprint requests to Noriyuki Nakanishi, Department of Social and Environmental Medicine, Course of Social Medicine, Osaka University Graduate School of Medicine F2, 2-2 Yamadaoka, Suita-shi, Osaka 565-0871, Japan. E-mail: noriyuki@pbhel.med.osaka-u.ac.jp.

Received for publication 26 December 2003 and accepted in revised form 15 March 2004.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHD, coronary heart disease; GGT, γ-glutamyltransferase; NCEP, National Cholesterol Education Program; WBC, white blood cell.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

— Our study is an ongoing cohort investigation, designed to clarify risk factors for major diseases, including hypertension, dyslipidemia, and diabetes, among Japanese men who are office workers at one of the biggest building contractors in Japan. A total of 3,681 Japanese males office workers aged 35–59 years participated in cardiovascular risk surveys in May 1994, with a participation rate of 99.6%. The Industrial Safety and Health Law in Japan requires the employer to conduct annual health examinations of all employees. The employee data, which are anonymous, are available for research with the approval of the employer. An institutional review committee approved this study, and all subjects gave their informed consent.

Of 3,681 potential participants, 82 (2.2%) were excluded: 34 (0.9%) were receiving medical treatment for hepatitis, 23 (0.6%) showed ALT levels higher than three times the upper limit of the reference range, and 32 (0.9%) had a past history of either CHD or stroke. Of the 3,599 remaining subjects, 575 (16.0%) were identified as having the metabolic syndrome and 267 (7.4%) as having type 2 diabetes at the initial examination. The metabolic syndrome–free cohort thus comprised 3,024 men and the nondiabetic cohort 3,332 men, and they were reexamined over 7 successive years until May 2001. We also excluded 67 men from the metabolic syndrome–free cohort and 72 men from the nondiabetic cohort who did not participate in consecutive annual health examinations during the follow-up. The final study cohorts for analysis therefore consisted of 2,957 men for development of the metabolic syndrome and 3,260 men for development of type 2 diabetes. They were classified as having the metabolic syndrome or type 2 diabetes when evidence of either of these disorders was found at periodic annual health examinations from May 1995 through May 2001. Sixty-seven participants who started taking medication for diabetes during the observation period were considered to have incidental cases of type 2 diabetes. In view of the age range of the study population, all subjects with type 2 diabetes were diagnosed after 35 years of age.

Study design

Annual health examinations at study entry included medical history, physical examination, a questionnaire on health-related behavior, anthropometric measurements, and biochemical measurements. The participants were asked to fast for at least 8 h and to avoid heavy physical activity for >2 h before the examinations. Medical history and use of prescription drugs were assessed by the examining physicians. A family history of diabetes was defined as having a mother, father, sister, or brother with diagnosed diabetes. As for health-related behavior, data on alcohol intake, smoking habits, and regular physical activity were obtained by interview. The questions about alcohol intake included items about the type of alcoholic beverage, the frequency of alcohol consumption on a weekly basis, and the usual amount consumed daily. Weekly alcohol intake was calculated and then converted to daily alcohol consumption (grams of ethanol per day) by using standard Japanese tables. The questionnaire also asked about smoking habits (never, past, or current smoker); past or current smokers were asked about the number of cigarettes smoked per day and the duration of smoking in years. Participants were asked about the type and frequency on a weekly basis of leisure-time physical activity. Physical exercise was defined as participation in any physical activity, such as jogging, cycling, swimming, or tennis, that was performed long enough to cause sweating. BMI, calculated as weight divided by the square of height in meters, was used as an index of relative weight. After a 5-min rest in a quiet room, systolic and diastolic blood pressures were measured on the right arm by using a standard mercury sphygmomanometer. Blood samples were drawn from an antecubital vein. Serum total cholesterol, HDL cholesterol, and triglyceride levels, fasting plasma glucose level, white blood cell (WBC) count, and enzyme activities for GGT, AST, ALT, and alkaline phosphatase were determined according to standard laboratory procedures (7,19). The five variables used to determine metabolic syndrome status (BMI, blood pressure, triglyceride, HDL cholesterol, and fasting glucose) were also measured at annual health examinations in May from 1995 to 2001. Quality control of the laboratory was internal, and the coefficients of variation within assays for serum triglyceride and HDL cholesterol and plasma glucose were no more than 3% between 1994 and 2001.

The five thresholds used were BMI ≥25 kg/m^2, proposed by the Japan Society for the Study of Obesity (20), systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg, triglyceride level ≥1.69 mmol/l, HDL cholesterol level <1.03 mmol/l, and fasting plasma glucose level ≥6.1 mmol/l. Individuals met the criteria for high blood pressure or high fasting plasma glucose level if they were currently using blood pressure medications or hypoglycemic diabetes control. Individuals with a previous physician diagnosis of hypertension or diabetes who did not report medication use were not allocated to the metabolic syndrome group. Individuals were classified as having metabolic syndrome if they fulfilled three or more of the criteria. Type 2 diabetes was defined according to the criteria of the American Diabetes Association (18) and was defined as a fasting plasma glucose concentration of ≥7.0 mmol/l or treatment with hypoglycemic medications because not every subject was given an oral glucose tolerance test.

Statistical analyses

The χ^2 test and one-way ANOVA were used to analyze the statistical differences among characteristics of the study participants at enrollment in relation to serum GGT levels. Categories of serum GGT comprised the following quintiles: <15, 15–21, 22–31, 32–52, and ≥53 units/l. For calculation of incidence density, person-years of follow-up were calculated from the date of enrollment to the date of the first incidence of the development of the metabolic syndrome or type 2 diabetes or the date of follow-up where either was diagnosed, whichever came first. Cox's proportional hazards models were used to calculate adjusted hazard ratios in separate models for metabolic syndrome or type 2 diabetes. For the risk of incident metabolic syndrome, data were adjusted for family history of diabetes, BMI, alcohol consumption, cigarette smoking, physical activity, WBC count, and liver enzymes. For the risk of incident type 2 diabetes, data were also adjusted for fasting plasma glucose. Potentially confounding factors were treated as categorical variables: age, BMI, WBC count, fasting plasma glucose, GGT, AST, ALT, and alkaline phosphatase (graded from 1 to 5

Table 1—*Characteristics of 3,599 Japanese male office workers in relation to serum GGT levels*

Characteristics	GGT (units/l)					*P* for trend*
	<15	15–21	22–31	32–52	≥53	
n	663	775	712	695	754	
Age (years)	46.5 ± 6.7	47.3 ± 6.4	47.0 ± 6.3	47.6 ± 6.1	47.9 ± 5.7	<0.001
Family history of diabetes	7.7	9.4	9.8	7.5	10.3	0.325
BMI (kg/m^2)	22.2 ± 2.2	23.1 ± 2.4	23.7 ± 2.6	24.2 ± 2.7	24.3 ± 2.8	<0.001
Current drinkers	71.0	81.9	86.7	91.2	93.9	<0.001
Current smokers	43.7	46.3	51.5	53.4	56.4	<0.001
Regular physical activity at least once a week	51.3	52.1	52.1	57.0	53.3	0.143
Systolic blood pressure (mmHg)	122.8 ± 14.8	126.2 ± 14.3	127.7 ± 14.2	130.5 ± 15.1	133.8 ± 15.4	<0.001
Diastolic blood pressure (mmHg)	73.9 ± 10.6	76.5 ± 10.6	78.3 ± 10.4	80.2 ± 11.1	82.4 ± 11.1	<0.001
Total cholesterol (mmol/l)	4.68 ± 0.70	4.95 ± 0.73	5.04 ± 0.81	5.13 ± 0.82	5.28 ± 0.91	<0.001
HDL cholesterol (mmol/l)	1.42 ± 0.30	1.39 ± 0.32	1.37 ± 0.36	1.38 ± 0.36	1.41 ± 0.34	0.035
Triglycerides (mmol/l)	0.86 (0.64–0.19)	1.04 (0.78–1.47)	1.20 (0.85–1.74)	1.35 (1.00–2.04)	1.70 (1.14–2.54)	<0.001
Fasting plasma glucose (mmol/l)	5.03 ± 0.77	5.13 ± 0.65	5.20 ± 0.92	5.27 ± 0.94	5.38 ± 1.05	<0.001
WBC count (10^9 cells/l)	6.12 ± 1.71	6.36 ± 1.58	6.59 ± 1.69	6.68 ± 1.77	6.82 ± 1.67	<0.001
AST (units/l)	17 (15–20)	19 (17–22)	20 (17–24)	22 (20–27)	27 (23–35)	<0.001
ALT (units/l)	14 (11–17)	17 (14–23)	21 (16–28)	24 (18–33)	31 (24–42)	<0.001
Alkaline phosphatase (units/l)	161 (142–183)	161 (143–186)	164 (146–186)	164 (144–188)	172 (151–197)	<0.001
Metabolic syndrome	4.4	9.0	14.6	23.2	28.0	<0.001
Type 2 diabetes	3.2	5.8	7.0	9.5	11.3	<0.001

Data are means ± SD, percent, or median (interquartile range). *Quadratic trend for HDL cholesterol.

[first through fifth quintiles]); family history of diabetes (no or yes); alcohol consumption (graded as 1 [none] or as quartile 1 [grade 2] to quartile 4 [grade 5] for drinkers); cigarette smoking (graded as 1 [none] or as quartile 1 [grade 2] to quartile 4 [grade 5] for current smokers); and regular physical exercise (graded from 1 to 3 [hardly ever, once a week, or twice or more a week]). The linear trends in risks were evaluated by entering the estimated quantitative median value for each category of exposure.

Data were analyzed with the SPSS statistical package for PC (SPSS, Chicago, IL). All reported *P* values are two tailed, and those <0.05 were considered statistically significant.

RESULTS — The characteristics of the study sample in relation to serum GGT levels are shown in Table 1. Tests for differences in characteristics across the five serum GGT level groups were significant except for family history of diabetes and regular physical activity. Age, BMI, current drinking, current cigarette smoking, systolic and diastolic blood pressures, total cholesterol, triglyceride, fasting plasma glucose, WBC count, AST, ALT, and alkaline phosphatase showed a linear trend in relation to serum GGT. The percentage of those who had the metabolic syndrome and type 2 diabetes also increased in correlation with an increase in serum GGT. HDL cholesterol showed a U-shaped association with serum GGT.

Table 2 shows the risk of incidence of the metabolic syndrome among 2,957 metabolic syndrome–free Japanese men during 7 years of follow-up in terms of serum liver enzyme levels. Of these, 608 men developed the metabolic syndrome during 16,758 person-years of follow-up. After adjustment for age, family history of diabetes, BMI, alcohol intake, cigarette smoking, regular physical activity, and WBC count, the relative risks of metabolic syndrome across quintiles of serum GGT were 1.00, 1.49, 1.55, 2.28, and 2.92 (*P* for trend <0.001). The relative risks of metabolic syndrome across quintiles of serum ALT, AST, and alkaline phosphatase were 1.00, 0.99, 1.25, 1.64, and 2.06 (*P* for trend <0.001); 1.00, 1.18, 1.12, 1.70, and 1.75 (*P* for trend <0.001); and 1.00, 1.40, 1.44, 1.82, and 1.66 (*P* for trend <0.001), respectively. Additional adjustment for all of the other liver enzymes attenuated these associations, but serum GGT and alkaline phosphatase remained significant risk factors for the risk of metabolic syndrome (*P* for trend <0.001 and 0.003, respectively). Top one-fifth versus bottom one-fifth relative risks for metabolic syndrome were 2.23 (95% CI 1.51–3.30) for serum GGT and 1.49 (1.13–1.95) for serum alkaline phosphatase.

Table 3 shows the risk of incidence of type 2 diabetes among 3,260 nondiabetic Japanese men during 7 years of follow-up in terms of serum liver enzyme levels. Of these, 276 developed type 2 diabetes during 20,051 person-years of follow-up. After adjustment for age, family history of diabetes, BMI, alcohol intake, cigarette smoking, regular physical activity, fasting plasma glucose, and WBC count, the relative risks of type 2 diabetes across quintiles of serum GGT were 1.00, 1.79, 2.04, 2.68, and 3.06 (*P* for trend <0.001). The relative risks of type 2 diabetes across quintiles of serum ALT, AST, and alkaline phosphatase were 1.00, 1.30, 1.71, 1.71, and 2.47 (*P* for trend <0.001); 1.00, 0.90, 1.28, 1.50, and 1.54 (*P* for trend = 0.002); and 1.00, 1.28, 1.33, 1.38, and 1.73 (*P* for trend = 0.008), respectively. Additional adjustment for all of the other liver enzymes lowered the magnitude of these associations, but the risk of type 2 diabetes increased in a dose-response manner as serum GGT and ALT increased (*P* for trend <0.001 and 0.030, respectively). Top one-fifth versus bottom one-

Table 2—*The risk of incidence of the metabolic syndrome among 2,957 metabolic syndrome–free Japanese men during 7 years of follow-up in relation to serum liver enzyme levels*

	Liver enzyme					
Outcome	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend
GGT (units/l)	<14 (*n* = 526)	14–19 (*n* = 602)	20–28 (*n* = 638)	29–48 (*n* = 594)	≥49 (*n* = 597)	
Cases/person-years	42/3,235	96/3,557	118/3,669	161/3,213	191/3,085	
Incidence density (per 1,000 person-years)	13.0	27.0	32.2	50.1	61.9	
Adjusted relative risk (95% CI)						
Model 1*	1.0 (referent)	2.05 (1.43–2.95)	2.44 (1.72–3.47)	3.74 (2.66–5.25)	4.56 (3.26–6.37)	<0.001
Model 2†	1.0 (referent)	1.49 (1.03–2.15)	1.55 (1.08–2.22)	2.28 (1.61–3.25)	2.92 (2.05–4.17)	<0.001
Model 3‡	1.0 (referent)	1.37 (0.95–1.98)	1.35 (0.93–1.95)	1.91 (1.31–2.77)	2.23 (1.51–3.30)	<0.001
ALT (units/l)	<14 (*n* = 560)	14–16 (*n* = 457)	17–21 (*n* = 692)	22–28 (*n* = 631)	≥29 (*n* = 617)	
Cases/person-years	59/3,384	54/2,704	116/4,014	160/3,491	219/3,165	
Incidence density (per 1,000 person-years)	17.4	20.0	28.9	45.8	69.2	
Adjusted relative risk (95% CI)						
Model 1*	1.0 (referent)	1.13 (0.78–1.63)	1.63 (1.19–2.23)	2.58 (1.91–3.47)	3.87 (2.90–5.16)	<0.001
Model 2†	1.0 (referent)	0.99 (0.68–1.43)	1.25 (0.91–1.71)	1.64 (1.21–2.22)	2.06 (1.54–2.77)	<0.001
Model 3‡	1.0 (referent)	0.89 (0.61–1.30)	1.07 (0.76–1.49)	1.27 (0.89–1.80)	1.42 (0.95–2.11)	0.093
AST (units/l)	<17 (*n* = 511)	17–18 (*n* = 455)	19–21 (*n* = 743)	22–25 (*n* = 624)	≥26 (*n* = 624)	
Cases/person-years	68/3,070	74/2,664	129/4,332	159/3,370	178/3,322	
Incidence density (per 1,000 person-years)	22.1	27.8	29.8	47.2	53.6	
Adjusted relative risk (95% CI)						
Model 1*	1.0 (referent)	1.24 (0.90–1.73)	1.33 (0.99–1.79)	2.07 (1.56–2.75)	2.34 (1.77–3.10)	<0.001
Model 2†	1.0 (referent)	1.18 (0.84–1.63)	1.12 (0.83–1.50)	1.70 (1.27–2.27)	1.75 (1.32–2.32)	<0.001
Model 3‡	1.0 (referent)	1.00 (0.71–1.40)	0.85 (0.62–1.17)	1.04 (0.73–1.48)	0.92 (0.63–1.34)	0.774
Alkaline phosphatase (units/l)	<140 (*n* = 583)	140–155 (*n* = 586)	156–170 (*n* = 590)	171–191 (*n* = 578)	≥192 (*n* = 620)	
Cases/person-years	84/3,433	121/3,334	122/3,348	131/3,225	150/3,419	
Incidence density (per 1,000 person-years)	24.5	36.3	36.4	40.6	43.9	
Adjusted relative risk (95% CI)						
Model 1*	1.0 (referent)	1.47 (1.11–1.94)	1.48 (1.12–1.96)	1.64 (1.25–2.16)	1.76 (1.35–2.30)	<0.001
Model 2†	1.0 (referent)	1.40 (1.06–1.86)	1.44 (1.09–1.90)	1.82 (1.38–2.40)	1.66 (1.27–2.18)	<0.001
Model 3‡	1.0 (referent)	1.39 (1.05–1.84)	1.41 (1.06–1.86)	1.73 (1.31–2.28)	1.49 (1.13–1.95)	0.003

*Model 1: adjustment for age; †model 2: model 1 plus adjustment for family history of diabetes, BMI, alcohol intake, cigarette smoking, regular physical activity, and WBC count; ‡model 3: model 2 plus adjustment for all of the other liver enzymes.

fifth relative risks for type 2 diabetes were 2.44 (95% CI 1.34–4.46) for serum GGT and 2.07 (1.07–3.98) for serum ALT.

CONCLUSIONS — Results of this study showed that the risk of incidence of the metabolic syndrome and type 2 diabetes increased in correlation with an increase in serum GGT. Other liver enzymes, such as serum AST, ALT, and alkaline phosphatase, were also significantly associated with the risk of the metabolic syndrome and type 2 diabetes, but the increase in the risks associated with these liver enzymes was substantially lower than that related to serum GGT. Our results suggest that liver enzymes are closely associated with the risk of metabolic syndrome and type 2 diabetes and that among these enzymes serum GGT is the most powerful risk indicator for developing the metabolic syndrome and type 2 diabetes.

Our results are consistent with those of previous studies (5–8,21) and indicate that elevated serum GGT is associated with an increased risk of the metabolic syndrome and type 2 diabetes. However, the mechanism of how liver enzymes increase the risks of metabolic syndrome and diabetes remains to be elucidated. One explanation for our findings is that the elevation of liver enzymes could be expression of excess deposition of fat in liver, which is regarded as a feature of the insulin resistance syndrome (9–11). This hypothesis is supported by the finding that increased serum GGT levels are strongly associated with an increased risk of developing type 2 diabetes. Another possible pathophysiological mechanism is that elevated liver enzymes may reflect inflammation, which impairs insulin signaling both in the liver and systemically (11,22,23). In this population, mean WBC count increased with an increase in serum GGT. Because WBCs, a major component of the inflammatory process, are activated by cytokines, especially interleukin-6 and interleukin-8 (24), elevated GGT could reflect subclinical inflammation, which would represent the underlying mechanism. In addition, certain mechanisms related to oxidative stress

Table 3—*The risk of incidence of type 2 diabetes among 3,260 nondiabetic Japanese men during 7 years of follow-up in relation to serum liver enzyme levels*

	Liver enzyme					
Outcome	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend
GGT (units/l)	<15 (*n* = 625)	15–20 (*n* = 595)	21–30 (*n* = 709)	31–52 (*n* = 679)	≥53 (*n* = 652)	
Cases/person-years	18/3,984	40/3,713	58/4,353	77/4,091	83/3,909	
Incidence density (per 1,000 person-years)	4.5	10.8	13.3	18.8	21.2	
Adjusted relative risk (95% CI)						
Model 1*	1.0 (referent)	2.31 (1.33–4.03)	2.89 (1.70–4.90)	4.01 (2.40–6.70)	4.42 (2.65–7.36)	<0.001
Model 2†	1.0 (referent)	1.79 (1.02–3.13)	2.04 (1.19–3.51)	2.68 (1.57–4.57)	3.06 (1.77–5.30)	<0.001
Model 3‡	1.0 (referent)	1.55 (0.88–2.72)	1.77 (1.01–3.08)	2.08 (1.18–3.66)	2.44 (1.34–4.46)	<0.001
ALT (units/l)	<14 (*n* = 568)	14–17 (*n* = 717)	18–22 (*n* = 575)	23–30 (*n* = 700)	≥31 (*n* = 700)	
Cases/person-years	23/3,577	40/4,451	48/3,566	59/4,319	106/4,138	
Incidence density (per 1,000 person-years)	6.4	9.0	13.5	13.7	25.6	
Adjusted relative risk (95% CI)						
Model 1*	1.0 (referent)	1.36 (0.81–2.27)	2.07 (1.26–3.40)	2.15 (1.33–3.49)	4.07 (2.59–6.39)	<0.001
Model 2†	1.0 (referent)	1.30 (0.78–2.17)	1.71 (1.04–2.81)	1.71 (1.05–2.81)	2.47 (1.54–3.95)	<0.001
Model 3‡	1.0 (referent)	1.23 (0.72–2.07)	1.55 (0.90–2.67)	1.52 (0.85–2.72)	2.07 (1.07–3.98)	0.030
AST (units/l)	<17 (*n* = 512)	17–19 (*n* = 749)	20–21 (*n* = 519)	22–26 (*n* = 813)	≥27 (*n* = 667)	
Cases/person-years	29/3,227	42/4,705	40/3,276	84/4,879	81/3,964	
Incidence density (per 1,000 person-years)	9.0	8.9	12.2	17.2	20.4	
Adjusted relative risk (95% CI)						
Model 1*	1.0 (referent)	0.97 (0.67–1.56)	1.33 (0.83–2.15)	1.84 (1.20–2.80)	2.20 (1.44–3.37)	<0.001
Model 2†	1.0 (referent)	0.90 (0.56–1.44)	1.28 (0.79–2.07)	1.50 (0.98–2.31)	1.54 (1.00–2.38)	0.002
Model 3‡	1.0 (referent)	0.73 (0.45–1.19)	0.92 (0.55–1.55)	0.89 (0.52–1.51)	0.75 (0.41–1.36)	0.659
Alkaline phosphatase (units/l)	<140 (*n* = 632)		≥193 (*n* = 670)			
Cases/person-years	38/3,954	50/3,992	52/4,155	56/3,919	80/4,031	
Incidence density (per 1,000 person-years)	9.6	12.5	12.5	14.3	19.8	
Adjusted relative risk (95% CI)						
Model 1*	1.0 (referent)	1.30 (0.85–1.99)	1.32 (0.87–2.01)	1.49 (0.99–2.25)	2.04 (1.39–3.00)	<0.001
Model 2†	1.0 (referent)	1.28 (0.84–1.96)	1.33 (0.88–2.03)	1.38 (0.91–2.10)	1.73 (1.16–2.59)	0.008
Model 3‡	1.0 (referent)	1.24 (0.81–1.90)	1.23 (0.81–1.88)	1.25 (0.82–1.90)	1.48 (0.99–2.23)	0.084

*Model 1: adjustment for age; †model 2: model 1 plus adjustment for family history of diabetes, BMI, alcohol intake, cigarette smoking, regular physical activity, fasting plasma glucose level, and WBC count; ‡model 3: model 2 plus adjustment for all of the other liver enzymes.

might play a role because cellular GGT has a central role in glutathione homeostasis by initiating the breakdown of extracellular glutathione, a critical antioxidant defense for the cell (1,25). Increases in serum GGT activity may be a response to oxidative stress, making increased transport of glutathione into cells. Supporting a role of serum GGT in the inflammation and oxidative stress, serum GGT level predicted future levels of inflammation and oxidative stress markers, such as fibrinogen, uric acid, C-reactive protein, and F_2-isoprostanes, in a dose-response manner (8).

Our study has several limitations. First, serum GGT during follow-up was not included in the analysis. In this study, serum GGT at study entry was strongly associated with that at the date of diagnosis of metabolic syndrome and type 2 diabetes or at the end of follow-up (Spearman's rank correlation coefficient 0.751 and 0.750, respectively; $P < 0.001$ for both). This indicates that those who had the higher serum GGT at study entry tended to continue to do so during follow-up. The observed associations between serum GGT at baseline and the increased risk of metabolic syndrome and type 2 diabetes may thus reflect the effects of serum GGT during a given observation period.

Second, bias in case finding could have occurred. Specifically, men with high serum GGT levels are more likely to visit a doctor for reasons other than metabolic syndrome and diabetes, so the metabolic syndrome and diabetes could have been found by chance. However, because all incidental cases were found during periodic annual screenings in our study, such a bias is unlikely to have occurred.

Finally, we could not include several confounding variables in this study, such as waist circumference and fasting insulin level. The central pattern of distribution, with its higher weighting of waist circumference, is associated with more insulin resistance than the peripheral pattern of distribution (26). Some data (13,15) show that waist circumference predicts diabetes marginally better than BMI. Nevertheless, most physicians routinely as-

sess BMI, whereas the value of waist measurements in clinical practice has not been thoroughly examined and may require modification for different ethnic groups. A number of investigations (13–15) have also shown that BMI can predict the development of type 2 diabetes and other metabolic disturbances as robustly as waist circumference. Moreover, the use of BMI versus waist measurements has been favorably evaluated (16,17) as a determinant of the metabolic syndrome and type 2 diabetes.

Despite these potential limitations, our findings, which were obtained from a cohort of middle-aged Japanese men, support the conclusion that elevated, although still normal, serum GGT is associated with a higher risk of the metabolic syndrome and type 2 diabetes.

Acknowledgments— This study was supported in part by a grant-in-aid from the Smoking Research Foundation, Tokyo, Japan.

References

1. Whitfield JB: Gamma-glutamyl transferase. *Crit Rev Clin Lab Sci* 38:263–355, 2001
2. Wannamethee G, Ebrahim S, Shaper AG: Gamma-glutamyltransferase: determinants and association with mortality from ischemic heart disease and all causes. *Am J Epidemiol* 142:699–708, 1995
3. Bots ML, Salonen JT, Elwood PC, Nikitin Y, Freire de Concalves A, Inzitari D, Sivenius J, Trichopoulou A, Tuomilehto J, Koudstaal PJ, Grobbee DE: Gamma-glutamyltransferase and risk of stroke: the EUROSTROKE project. *J Epidemiol Community Health* 56 (Suppl. 1):I25–I29, 2002
4. Nilssen O, Førde OH, Brenn T: The Tromsø Study: distribution and population determinants of gamma-glutamyltransferase. *Am J Epidemiol* 132:318–326, 1990
5. Perry IJ, Wannamethee SG, Shaper AG: Prospective study of serum γ-glutamyltransferase and risk of NIDDM. *Diabetes Care* 21:732–737, 1998
6. Rantala AO, Lilja M, Kauma H, Savolainen MJ, Reunanen A, Kesäniemi YA: Gamma-glutamyl transpeptidase and the metabolic syndrome. *J Intern Med* 248:230–238, 2000
7. 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* 254:287–295, 2003
8. 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
9. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, McCullough AJ, Natale S, Forlani G, Melchionda N: Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes* 50: 1844–1850, 2001
10. Marchesini G, Forlani G: NASH: from liver diseases to metabolic disorders and back to clinical hepatology. *Hepatology* 35:497–499, 2002
11. Malnick SD, Beergabel M, Knobler H: Non-alcoholic fatty liver: a common manifestation of a metabolic disorder. *QJM* 96: 699–709, 2003
12. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001
13. Wei M, Gaskill SP, Haffner SM, Stern MP: Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans: a 7-year prospective study. *Obes Res* 5:16–23, 1997
14. Sattar N, Tan CE, Han TS, Forster L, Lean ME, Shepherd J, Packard CJ: Associations of indices of adiposity with atherogenic lipoprotein subfractions. *Int J Obes Relat Metab Disord* 22:432–439, 1998
15. Stevens J, Couper D, Pankow J, Folsom AR, Duncan BB, Nieto FJ, Jones D, Tyroler HA: Sensitivity and specificity of anthropometrics for the prediction of diabetes in a biracial cohort. *Obes Res* 9:696–705, 2001
16. Ridker PM, Buring JE, Cook NR, Rifai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. *Circulation* 107:391–397, 2003
17. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J: Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* 108:414–419, 2003
18. 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
19. 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* 26:48–54, 2003
20. Matsuzawa Y, Inoue S, Ikeda Y, Sakata T, Saito Y, Sato Y, Shirai K, Ohno M, MiyazakiS, Tokunaga K, Fukunaga K, Yamanouchi K, Nakamura T: New definition of obesity and diagnostic criteria for high-risk obesity [in Japanese]. *Himan Kenkyu (Researches on Obesity)* 6:18–28, 2000
21. Cucuianu M: Serum γ-glutamyltransferase and/or serum cholinesterase as markers of the metabolic syndrome (Letter). *Diabetes Care* 22:1381–1382, 1999
22. Hotamisligil GS: Inflammatory pathways and insulin action. *Int J Obes Relat Metab Disord* 27 (Suppl. 3):S53–S55, 2003
23. Hsueh WA, Quinones MJ: Role of endothelial dysfunction in insulin resistance. *Am J Cardiol* 92:10J–17J, 2003
24. van Oostrom AJ, Sijmonsma TP, Verseyden C, Jansen EH, de Koning EJ, Rabelink TJ, Castro Cabezas M: Postprandial recruitment of neutrophils may contribute to endothelial dysfunction. *J Lipid Res* 44: 576–583, 2003
25. Stark AA: Oxidative metabolism of glutathione by gamma-glutamyl transpeptidase and peroxisome proliferation: the relevance to hepatocarcinogenesis: a hypothesis. *Mutagenesis* 6:241–245, 1991
26. Krotkiewski M, Bjorntorp P, Sjostrom L, Smith U: Impact of obesity on metabolism in men and women: importance of regional adipose tissue distribution. *J Clin Invest* 72:1150–1162, 1983