0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(11):5410–5414

doi: 10.1210/jc.2004-0505

γ-Glutamyltransferase, Obesity, and the Risk of Type 2 Diabetes: Observational Cohort Study among 20,158 Middle-Aged Men and Women

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Serum γ-glutamyltransferase (GGT) concentration within its normal range has emerged as an important predictor in the pathogenesis of diabetes. We studied serum GGT as a predictor of type 2 diabetes incidence and a possible interaction between obesity and GGT on the development of type 2 diabetes in men and women. A prospective cohort study of 20,158 Finnish men and women aged 25–64 yr who participated in cardiovascular risk-factor surveys carried out in four areas during 10 yr. The average follow-up time was 12.7 yr, and there were 388 incident diabetes cases. Serum GGT cut points were at the 25th, 50th, 75th, and 90th percentiles. Initiation of new diabetes medication defined incidence cases. After adjustment for known risk factors of type 2 diabetes, relative risks for incident diabetes across GGT categories were 1.0, 1.2, 2.3, 3.1, and 3.9 among men and 1.0, 0.8, 1.7, 3.5, and 6.4 among women (*P* for trend < 0.01, respectively). Body mass index appeared to be more strongly associated with type 2 diabetes in both men and women over age 50 yr with GGT median or greater, compared with subjects with GGT less than median. In conclusion, in women as well as men, serum GGT level within its normal range predicted type 2 diabetes and may modify the well-known association between body mass index and type 2 diabetes. (*J Clin Endocrinol Metab* 89: 5410–5414, 2004)

IN PREVIOUS EPIDEMIOLOGICAL studies (1–9), serum γ-glutamyltransferase (GGT) was associated with several cardiovascular risk factors, and it was found to predict hypertension, diabetes, stroke, and coronary heart disease. In particular, there is strong evidence that serum GGT level shows a dose-response relationship with incident diabetes even within its normal range (4, 8, 9), suggesting a biological link with the development of diabetes. Although GGT has been widely used as a marker of alcohol consumption or liver disease (10), neither alcohol nor hepatic dysfunction explained the observed relationships between GGT and diabetes (4, 8, 9). In addition, the well-known associations of obesity and age with diabetes were stronger among subjects with high normal GGT, compared with subjects with low normal GGT, at baseline (8, 9).

Until now, most studies on the association between GGT and diabetes have been performed among men alone (4, 8). In particular, the interaction among obesity, age, and GGT has not been separately investigated among women. Women, compared with men, had a lower serum GGT level (1, 9), and the association in women between GGT and body mass index (BMI) was weaker than that of men (1). Therefore, in women, the interaction among obesity, age, and GGT might possibly be different from that of men. Here we performed a prospective study to determine whether GGT is an independent predictor of incident type 2 diabetes among middle-aged Finnish men and women. In addition, we analyzed whether the relationships of diabetes with obesity and age were modified by baseline GGT level. Although one of the previous studies of these topics (9) included both men and women, the sample size was too small to carry out analyses stratified by gender. Because of the large sample size available in the present study, here we were able to carry out analyses separately in men and in women.

Abbreviations: ALT, Alanine aminotransferase; AST, asparate aminotransferase; BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; GGT, γ-glutamyltransferase; HDL, high-density lipoprotein.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Subjects and Methods

Baseline risk factor surveys were carried out in Kuopio and North Karelia provinces in eastern and the Turku-Loimaa area in southwestern Finland in 1982, 1987, and 1992. The Helsinki capital area was included in the survey in 1992. In each study year, the sample was randomly drawn from the population aged 25–64 yr and was stratified so that in each area at least 250 subjects were chosen from both genders and each 10-yr age group, according to the international World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease project protocol (11). The surveys were independent, *i.e.* study subjects were chosen from the population randomly for each survey, and those who belonged to more than one survey (n = 618) were excluded after their first survey. The study was conducted according to the national data protection legislation and ethical rules of the Finnish National Public Health Institute. In the present study, the data from the four areas and the three study years were combined. The survey samples included 10,438 men and 11,192 women. The participation rate was 78% among men and 85% among women in the pooled data set (12). Of 21,012 participants, 811 were excluded from analyses because of prevalent

diabetes at baseline identified by the national diabetes registry, which includes subjects receiving reimbursement for their diabetes medication, before the survey and by a survey question about diabetes diagnosed by a physician. Another 43 participants were excluded because of missing data on GGT. A total of 9,771 men and 10,387 women were included in the present analyses. They were followed up through the end of 1997 or until death or the diagnosis of diabetes.

Alcohol drinking, smoking status, and physical activity at baseline were assessed with a set of standardized questions in a self-administered questionnaire mailed to the participants in advance. Alcohol drinking was assessed on the basis of the self-reported number of drinks consumed during the previous week. Physical activity was measured by asking whether the participant practiced leisure time physical activity at least 20–30 min two times or more per week.

At the survey site, specially trained research nurses measured height, weight, and blood pressure by using the standardized World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease protocol (13). Systolic and diastolic blood pressures were measured twice, and the mean of these measurements was used in the analyses. BMI (kilograms per square meter) was used as a measure of relative body weight. A venous blood specimen was taken for biochemical measurements; fasting was not required for all surveys. GGT and cholesterol were determined from fresh serum samples. GGT was determined using a kinetic method (Oy Medix Biochemica AB, Kauniainen, Finland), based on the recommendation of European Committee for Clinical Laboratory Standards. Total and high-density lipoprotein (HDL) cholesterol levels were determined by an enzymatic method (CHOD-PAP, Roche Molecular Biochemicals, Mannheim, Germany). In addition, for a subsample of men and women, fasting glucose (n = 4661) and insulin levels (n = 1617) were determined from frozen plasma. All samples were analyzed in the same central laboratory at the Finnish National Public Health Institute.

Data on the occurrence of new diabetes cases during the follow-up were obtained from the National Social Insurance Institution's register on persons entitled to special reimbursement for diabetes drugs. To receive the special reimbursement, the diagnosis of diabetes is assigned by the person's own physician, usually a general practitioner, internist, or specialist in occupational medicine. The statements documenting the diagnosis are then reviewed by the expert physicians of the Social Insurance Institution. Thus, the register data include diabetes treated with drugs but not diet only. Women with gestational diabetes, who need a short-term drug treatment, are not included in the register. We excluded type 1 diabetes cases by checking the National Hospital Discharge register that provides separate diagnosis codes for types 1 and 2 diabetes. The number of new type 2 diabetes cases during the follow-up was 212 among men and 176 among women.

All analyses were separately performed in men and women. Serum GGT levels were classified into five groups using the 25th, 50th, 75th, and 90th percentiles as cut points. The cut points were 15, 21, 33, and 57 U/liter among men (normal range ≤ 50 U/liter) and 9, 12, 17, and 28 U/liter among women (normal range ≤ 40 U/liter). For calculation of incidence density, length of follow-up was calculated as days from the baseline exam to diabetes diagnosis. Cox proportional hazard models were used to calculate multivariate-adjusted hazard ratios, using the PHREG procedure of the SAS statistical package (14). Deaths were censored at the time of death based on the Mortality Register of Statistics Finland. Covariates were the baseline values of age, BMI, alcohol consumption, cigarette smoking, and physical activity as well as plasma glucose and insulin levels, which were available for a subset only. In addition, we assessed whether the associations among age, BMI, and type 2 diabetes were modified by baseline serum GGT level. The median value of serum GGT level was used as the cut-off point in interaction or stratified analyses.

Results

At baseline, serum GGT was related to most cardiovascular risk factors in both men and women (Table 1). Alcohol consumption, age, cigarette smoking, and BMI were positively associated with baseline serum GGT level. Among clinical variables, systolic and diastolic blood pressure, fast-

TABLE 1. Age-adjusted risk factor levels at baseline in 1982, 1987, or 1992 in men and women aged 25–64 yr, by serum GGT level

	Baseline GGT level					
	<25%	25–<50%	50–<75%	75–<90%	≥90%	*P* for trend
Men	−14 U/liter	15–20 U/liter	21–32 U/liter	33–56 U/liter	≥57 U/liter	
No. of subjects	2381	2391	2558	1454	997	
Age (yr)	42.4	44.0	45.3	45.5	46.2	<0.001
Alcohol (g/wk)	37.9	56.7	69.0	99.1	154.5	<0.001
Current smoker (%)	32.9	37.9	42.4	45.8	48.6	<0.001
Physical activity (%)[a]	45.3	43.1	40.4	36.5	36.0	<0.001
BMI (kg/m^2)	24.8	25.7	27.1	27.8	28.5	<0.001
SBP (mm Hg)	139.1	140.4	142.1	144.0	147.3	<0.001
DBP (mm Hg)	82.8	83.8	86.3	88.4	91.4	<0.001
Fasting plasma glucose (mmol/liter)[b]	4.44	4.59	4.77	4.87	5.34	<0.001
Fasting serum insulin (μU/liter)[c]	5.38	6.80	7.85	9.52	10.61	<0.001
Serum total cholesterol (mmol/liter)	5.73	5.93	6.10	6.26	6.37	<0.001
Serum HDL-C (mmol/liter)	1.29	1.28	1.23	1.22	1.28	<0.001
Women (n = 10387)	−8 U/liter	9–11 U/liter	12–16 U/liter	17–27 U/liter	≥28 U/liter	
No. of subjects	2080	2842	2703	1747	1015	
Age (yr)	40.7	43.3	45.4	47.5	49.4	<0.001
Alcohol (g/wk)	10.1	14.6	22.8	26.2	32.4	<0.001
Current smoker (%)	14.0	18.8	23.9	27.8	31.1	<0.001
Physical activity (%)[a]	39.9	41.3	39.7	40.8	38.0	0.414
BMI (kg/m^2)	24.9	25.0	25.8	27.0	27.8	<0.001
SBP (mm Hg)	134.1	134.8	136.5	138.6	139.6	<0.001
DBP (mm Hg)	79.6	80.1	81.6	82.9	84.1	<0.001
Fasting plasma glucose (mmol/liter)[b]	4.40	4.53	4.59	4.77	4.91	<0.001
Fasting serum insulin (μU/liter)[c]	5.37	6.19	6.91	8.42	9.71	<0.001
Serum total cholesterol (mmol/liter)	5.81	5.86	5.87	5.91	5.94	0.022
Serum HDL-C (mmol/liter)	1.53	1.54	1.52	1.48	1.48	<0.001

[a] Leisure time physical activity two times per week or more.
[b] Fasting plasma glucose was measured among 2205 men and 2456 women.
[c] Fasting serum insulin was measured among 744 men and 873 women.

ing plasma glucose, fasting insulin, and total cholesterol also showed positive associations with baseline GGT level, whereas HDL-cholesterol showed a U-shaped association in men but an inverse association in women.

Compared with the lowest baseline GGT category, the relative risks of incident type 2 diabetes adjusted for age were 1.5, 3.5, 5.7, and 6.7 (test P for trend < 0.01) among men and 1.0, 2.0, 4.7, and 9.0 (test P for trend < 0.01) among women in the other four GGT categories (Table 2). Additional adjustment for BMI, alcohol consumption, cigarette smoking, and physical activity attenuated this relationship, but GGT still remained a strong risk factor for type 2 diabetes among both genders; adjusted relative risks were 1.0, 1.2, 2.3, 3.1, and 3.9 (test P for trend < 0.01) among men and 1.0, 0.8, 1.7, 3.5, and 6.4 (test P for trend < 0.01) among women in the five GGT categories, respectively. Further adjustment for baseline fasting serum glucose did not materially alter the association with GGT. The positive association between baseline GGT and incident type 2 diabetes was observed in both alcohol drinkers and nondrinkers. For example, after adjusting for age, BMI, cigarette smoking, and physical activity, relative risks among nondrinkers were 1.00, 0.87, 1.89, 2.32, and 2.37 (test P for trend < 0.01) among men and 1.00, 0.77, 1.85, 3.65, and 5.67 (test P for trend < 0.01) among women.

The association of BMI with incident type 2 diabetes appeared to be modified by GGT. Compared with men with GGT below the median, among men with GGT above the median, BMI was more strongly associated with incident type 2 diabetes (P for interaction $= 0.10$) (Fig. 1). In women, the interaction appeared to be restricted to women aged 50 yr or older (P for the interaction $= 0.24$) (Fig. 2). We stratified women by age 50 yr as a surrogate of menopausal status. On the other hand, the association of age with incident type 2 diabetes was not different, depending on baseline GGT level (data not shown).

Discussion

In the present study, higher serum GGT concentration was directly associated with the increased risk of type 2 diabetes in both genders. The association was strong, graded, and not confounded by BMI and lifestyle factors. Our data are in agreement with results of previous prospective studies in men (4, 8) or pooling findings for men and women (9), which showed that baseline serum GGT level within its normal range was an independent risk factor for the development of diabetes. These studies cover several ethnic groups, including British men selected from lists of general practitioners (4), Korean steelworkers (8), a population-based sample of black and white American men and women (9), and, in the current study, a population-based sample of middle-aged Finnish men and women. In contrast, a study (15) in Pima Indians reported no association of GGT level with incident diabetes; this study is discussed below.

Elevated GGT is conventionally interpreted as a marker of alcohol abuse (10). However, in the previous studies (4, 8, 9),

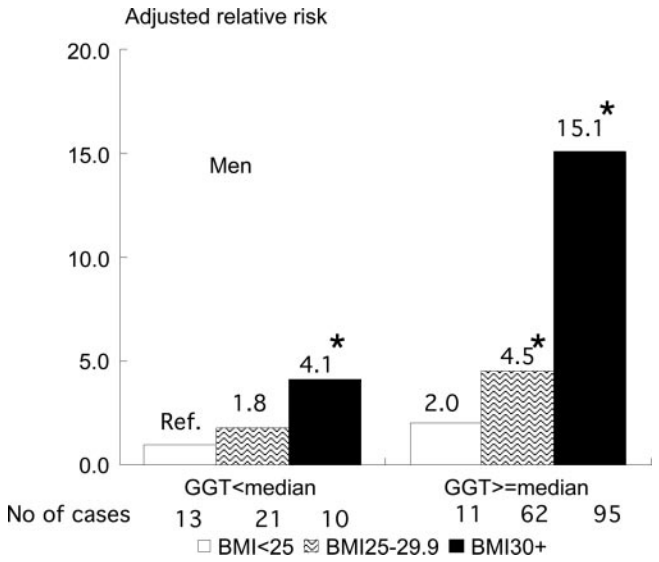

FIG. 1. Interaction between baseline BMI and serum GGT on the risk of incident type 2 diabetes among men. Adjusted for baseline age, alcohol consumption, cigarette smoking, and physical activity. *, 95% confidence interval for the adjusted relative risk does not include 1.

TABLE 2. Hazard ratios of type 2 diabetes associated with serum GGT levels in men and women aged 25–64 yr, adjusting for baseline factors

	Baseline serum GGT level					P of trend
	<25%	25–<50%	50–<75%	75–<90%	≥90%	
Men	−14 U/liter	15–20 U/liter	21–32 U/liter	33–56 U/liter	≥57 U/liter	
No. of cases	18	26	67	57	44	
Adjusted relative risk						
Model 1	1.0	1.5 (0.8–2.7)	3.5 (2.1–5.9)	5.7 (3.4–9.8)	6.7 (3.9–11.6)	<0.01
Model 2	1.0	1.2 (0.6–2.1)	2.3 (1.4–4.0)	3.1 (1.8–5.4)	3.9 (2.2–7.0)	<0.01
Model 3	1.0	0.8 (0.2–3.5)	3.4 (1.0–11.5)	2.6 (0.7–9.6)	4.6 (1.2–17.0)	<0.01
Women	−8 U/liter	9–11 U/liter	12–16 U/liter	17–27 U/liter	≥28 U/liter	
No. of cases	10	16	34	55	61	
Adjusted relative risk						
Model 1	1.0	1.0 (0.5–2.2)	2.0 (1.0–4.0)	4.7 (2.4–9.4)	9.0 (4.6–17.8)	<0.01
Model 2	1.0	0.8 (0.3–1.8)	1.7 (0.8–3.5)	3.5 (1.8–7.0)	6.4 (3.2–12.7)	<0.01
Model 3	1.0	0.7 (0.1–4.1)	2.4 (0.5–10.6)	2.2 (0.5–9.8)	5.9 (1.3–25.8)	<0.01

Model 1, Adjustment for age.

Model 2, Model 1 plus adjustment for baseline BMI, cigarette smoking, alcohol consumption, and physical activity.

Model 3, Model 2 plus adjustment for baseline fasting plasma glucose (measured among 2205 men and 2456 women). Thus, this model was restricted to these 4661 subjects.

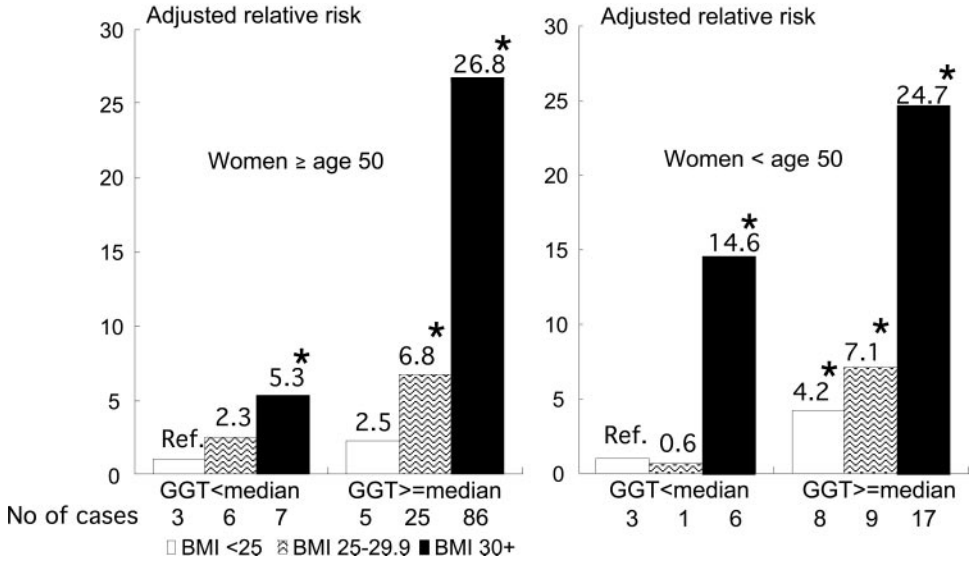

FIG. 2. Interaction between baseline BMI and serum GGT on the risk of incident type 2 diabetes among women. Adjusted for baseline age, alcohol consumption, cigarette smoking, and physical activity. *, 95% confidence interval for the adjusted relative risk does not include 1.

alcohol consumption could not explain the association between GGT and incident diabetes. Again, in our study, the association of GGT with incident type 2 diabetes was independent of alcohol intake and existed among nondrinkers as well. Recently because fatty liver has been linked to the insulin resistance syndrome and/or type 2 diabetes (16, 17), GGT might be interpreted as a marker for hepatic steatosis and hepatic insulin resistance in the pathogenesis of type 2 diabetes (4). The present data had no information on more liver-specific enzymes such as alanine aminotransferase (ALT) or asparate aminotransferase (AST). However, our previous two studies (8, 9) showed that the dose-response relationship between GGT level and incidence of diabetes was also observed among subjects within the normal range of ALT or AST. In addition, the associations between ALT or AST and diabetes were weaker than those of GGT and were mostly restricted to abnormal levels of liver enzymes (4, 8, 9).

However, one prospective study (15) in Pima Indians has reported that higher ALT, but not GGT, predicted type 2 diabetes. Their baseline mean values of ALT, AST, and GGT were above the upper limit of normal range: about 2 times higher than those of the previous studies (4, 8, 9) in which GGT was more strongly associated with diabetes. Because clinical studies (18, 19) have consistently reported an association between several pathologic liver conditions and type 2 diabetes, the results in Pima Indians might reflect the association between liver damage and type 2 diabetes.

Although the mechanisms underlying the above association remain largely unknown, certain mechanisms related to oxidative stress might play a role. There is clear evidence that cellular GGT level is closely related to oxidative stress indicators *in vivo*, either as an antioxidant or a prooxidant, depending on circumstances (20–26). Although the relation between cellular and serum GGT is unclear, supporting a role of cellular GGT in the oxidative stress, our previous studies (9, 27–29) in Coronary Artery Risk Development in Young Adults (CARDIA) subjects have consistently shown that serum GGT within its normal range might be related to oxidative stress.

Consistent with our previous findings (8, 9), we observed that BMI was a stronger risk factor for incident type 2 diabetes among subjects with high normal GGT than in those with low normal GGT. Even though the interaction was observed among both genders, in women it was mostly shown among women aged 50 yr or older; most of whom were probably postmenopausal. A possible interpretation of this interaction between BMI and GGT is that obese subjects with high normal GGT have already suffered subclinical pathological changes due to obesity, whereas obese subjects with low normal GGT are at an earlier stage of pathogenesis. According to this interpretation, serum GGT level might be an intervening factor in the association between obesity and diabetes. If this is true, an adjustment for GGT should have attenuated the association between BMI and type 2 diabetes. However, the adjustment for GGT did not materially change the association between BMI and the incidence of type 2 diabetes.

In our previous study of Korean men (8), age was a strong risk factor for diabetes only among subjects with high normal GGT; however, both CARDIA (9) and Finnish data failed to show an interaction between GGT and age. In our previous paper (9), we interpreted that a young age distribution in the CARDIA cohort might explain the different result between Korean and CARDIA data because the interaction with age in the Korean study was largely restricted to participants who were 45 yr old or more. However, the present data did not show the interaction between age and GGT, despite similarity of age distribution with Korean data, suggesting that our previous finding might have been due to chance. On the other hand, racial difference or leanness of Korean men might explain the different result.

Our study has several limitations. First, there was a possibility of underdiagnosis of incident type 2 diabetes because only drug-treated diabetes was regarded as the outcome. However, the underdiagnosis might attenuate the strength of association because there is a clear positive association between serum GGT and fasting serum glucose. Second, even though we interpreted that our finding might not relate to liver disease, that judgment was made based on our previous studies (8, 9), not the present results.

In conclusion, this study suggests that serum GGT is a strong and independent predictor of type 2 diabetes in both genders, irrespective of alcohol consumption. We speculate that it might be involved in the pathogenesis in diabetes through a mechanism related to oxidative stress. In addition, the well-known associations of BMI with diabetes may be modified by serum GGT level. For the prediction of type 2 diabetes in obese subjects, it may be useful to determine serum GGT because it is easy and inexpensive to measure and strongly modifies the obesity related type 2 diabetes risk.

Acknowledgments

Received March 15, 2004. Accepted August 6, 2004.

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This work was supported by the Academy of Finland, Research Council for Health (Grants 46558 and 53585), and YALTA (National Institutes of Health/National Heart, Lung, and Blood Institute Grant R01 HL53560).

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