European Heart Journal (2006) **27**, 2170–2176
doi:10.1093/eurheartj/ehl086

Serum gamma-glutamyltransferase predicts non-fatal myocardial infarction and fatal coronary heart disease among 28 838 middle-aged men and women

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Received 22 March 2006; revised 15 May 2006; accepted 19 May 2006; online publish-ahead-of-print 13 June 2006

See page 2145 for the editorial comment on this article (doi:10.1093/eurheartj/ehl151)

KEYWORDS
Gamma-glutamyltransferase;
Myocardial infarction;
Coronary heart disease;
Diabetes;
Oxidative stress

Aims Serum gamma-glutamyltransferase (GGT) concentration may be involved in atherosclerosis. This study examined if serum GGT predicted coronary heart disease (CHD), especially differentiating non-fatal myocardial infarction (MI) and fatal CHD event, among the general population or participants with type-2 diabetes.

Methods and results A prospective study of 28 838 Finnish men and women aged 25–74 years was performed (1467 incident CHD cases; a median follow-up time of 11.9 years). Serum GGT cutpoints were the 25th, 50th, 75th, and 90th sex-specific percentiles. After adjustment for known cardiovascular risk factors, compared with the lowest GGT category, hazard ratios (HR) were 1.15, 1.25, 1.27, and 1.57 among men and 1.03, 1.22, 1.32, and 1.44 among women in other four GGT categories (*P* for trend <0.01, respectively). However, stronger associations were observed among subjects aged <60 and among alcohol drinkers. The strength of association was similar for non-fatal MI and for fatal CHD. Among subjects with type-2 diabetes, the corresponding adjusted HRs were 1.29, 1.57, 1.88, and 1.78 (*P* trend $= 0.03$, men and women combined).

Conclusion This study suggests an independent mechanism linking serum GGT to CHD among general population. Even though the strength of association appeared to be modest among all subjects, stronger associations were observed among subjects aged <60 and among alcohol drinkers. Especially, measurement of serum GGT among type-2 diabetics may be helpful to predict the future risk of CHD.

Introduction

Gamma-glutamyltransferase (GGT) activity, normally found in serum as well as in the plasma membrane of virtually all cells except erythrocytes, catalyzes the first step in the degradation of extracellular glutathione (GSH), allowing for precursor amino acids to be assimilated and reutilized for intracellular GSH synthesis.[1] Thus in this way, GGT activity favours the cellular supply of GSH, the most important non-protein antioxidant of the cell. However, there is also clear evidence that the degradation of GSH can play a pro-oxidant role in selected conditions; low density lipoprotein (LDL) oxidation through GSH/GGT-dependent iron reduction has been suggested as a potential mechanism in atherosclerosis.[2] Experimental work has documented that GGT activity is present in atherosclerotic coronary plaques.[3]

Consistent with experimental findings, several prospective studies have found that serum GGT predicted non-fatal myocardial infarction (MI) or cardiac mortality, especially among patients with previous coronary events.[4–6] Recently, two large prospective cohort studies based on general populations from two European countries showed that serum GGT had a graded positive association with mortality or incidence of coronary heart disease (CHD).[7,8] However, the strengths of associations were substantially different between the two studies. In the study with the outcome of non-fatal MI or fatal CHD event (46.7% of total events were non-fatal MI),[8] the strength of association was quite strong, whereas in the study with the outcome of mortality from acute and subacute forms of CHD,[7] it was modest and even not significant among men. Taken together, these two studies suggest

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that serum GGT may predict non-fatal MI more strongly than fatal CHD.[7,8] As one criticism about using serum GGT in a clinical setting is how much additional value beyond the traditional CVD risk factors serum GGT has in predicting CHD, the strength of association is an important issue.

This study addressed whether the strength of association of serum GGT with CHD in the general population differed depending on whether the case was non-fatal or fatal. Moreover, as serum GGT predicted the risk of microalbuminuria among patients with type-2 diabetes,[9] it may also be interesting to examine whether serum GGT predicts the risk of CHD, a major complication of type-2 diabetes, among patients with type-2 diabetes. Therefore, we performed a prospective study to determine whether serum GGT is an independent predictor of incident non-fatal MI and fatal CHD events among middle-aged Finnish men and women or among participants with type-2 diabetes. We also studied if serum GGT could predict the risk of fatal CHD event among subjects with a history of MI at baseline.

Methods

Study population

Baseline risk factor surveys were carried out in the Kuopio and North Karelia provinces in eastern Finland and in the Turku-Loimaa area in southwestern Finland, in 1982, 1987, 1992, and 1997. The Helsinki capital area was included in the survey in 1992 and 1997 and Oulu province in northern Finland in 1997. In each study year, the sample was randomly drawn from the population aged 25–64 years and was stratified so that in each area at least 250 subjects were chosen from both genders and each 10-year age group, according to the international WHO MONICA (MONItoring trends and determinants in CArdiovascular disease) project protocol.[10] In 1997, an additional sample of subjects aged 65–74 years were recruited. The surveys were independent, i.e. study subjects were chosen from the population randomly for each survey and only the risk factor findings from their first survey was included when participants were involved in more than one survey. The study was conducted according to the national data protection legislation, the ethical rules of the Finnish National Public Health Institute, and the rules and principles of the Helsinki Declaration. In the present study, the data from the five areas and the four study years were combined. The participation rate was 75% among men and 82% among women in the pooled data set.[11] Of 29 890 participants, 971 were excluded from analyses because they reported the history of MI at baseline. Another 81 participants were excluded because of missing data on GGT. A total of 13 811 men and 15 027 women were included in the present analyses. In the fully adjusted models, 13 802 men and 15 016 women were included due to missing values on some covariates in the rest of subjects.

Measurements

Alcohol drinking, smoking status, physical activity, and diabetes diagnosed by a physician prior to the baseline were assessed with a set of standardized questions in a self-administered questionnaire mailed to the participants in advance. Smoking status was categorized as regular current smokers and former or never smokers. 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 performed 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 using the standardized WHO MONICA protocol.[12] Height and weight were measured in light clothing and without shoes. Height was rounded to the nearest 1 cm and weight to the nearest 100 g. Systolic and diastolic blood pressures were measured twice, and the mean of these measurements was used in the analyses. Body mass index (BMI, kg/m^2) 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, total, and high-density lipoprotein cholesterol were determined from fresh serum samples. GGT was determined using a kinetic method (J.T. Baker Chemicals B.V., Denventer, Holland or Oy Medix Biochemica Ab, Kauniainen, Finland) at 37°C, based on the recommendation of the Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology (1982, 1987, and 1992) or the European Committee for Clinical Laboratory Standards (1997). All GGT analyses were conducted in the same central laboratory in the National Public Health Institute in Helsinki, Finland. HDL-cholesterol was measured after precipitation of apolipoprotein B-containing lipoproteins with dextran sulphate and magnesium chloride. Total and high-density lipoprotein (HDL) cholesterol levels were determined by an enzymatic method (CHOD-PAP, Boehringer Mannheim, Mannheim, Germany).

Fatal CHD events (410–414 in the ICD 8 and 9 classifications and I20–I25 in the ICD 10 classification) as well as non-fatal MI events (410–411 and I21–I22, I24) (according to the criteria used in the FINMONICA MI Register Study) were included in the present study. Non-fatal MI events were derived from the National Hospital Discharge Register, which have shown good validity in Finland.[13] CHD mortality data were obtained from the Central Statistical Office of Finland based on death certificates. The diagnostic criteria for these events have been published.[14] At the National Public Health Institute, the data were further cross-checked with these two registers for completeness. Because of practically free and universal health care system in Finland, the mortality and hospital discharge registers cover virtually the entire Finnish population and thus no loss during the follow-up existed.

Statistical analyses

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 cutpoints (quartiles with the top quartile split), which were used in our previous study with the same dataset on the association between serum GGT and type-2 diabetes.[15] Analyses of serum GGT in quintiles did not yield materially different results. The cutpoints were 16, 24, 38, and 64 U/L among men (normal range: $\leq$50 U/L) and 10, 14, 20, and 32 U/L among women (normal range: $\leq$40 U/L) for the categories of GGT used, respectively. For calculation of the incidence density, length of follow-up was calculated as days from the baseline examination to the date of onset of non-fatal MI or fatal CHD event diagnosis (cases), to death from other causes based on the Mortality Register of Statistics Finland (censored cases) or to the end of the follow-up at 31 December 2003 (non-cases).

Cox proportional hazard models were used to calculate multivariable-adjusted hazard ratios (HRs), using the PHREG procedure of the SAS statistical package. Tests for trend were across the median GGT value in each category. Covariates, selected *a priori* in four models as specified in the tables, were the baseline values of age, study year, study area, BMI, alcohol consumption, cigarette smoking, physical activity, systolic blood pressure (SBP), serum total cholesterol, HDL-cholesterol, and history of diabetes. In each model, variables were entered simultaneously. The proportional hazards assumption was satisfied based on log minus log plots for category of serum GGT. The final multivariable model was validated by plotting the residuals against the fitted values and testing the goodness-of-fit.

We repeated these analyses for non-fatal MI and fatal CHD events as separate outcome variables and also in two subgroups: subjects with history of diabetes at baseline or subjects with history of previous acute MI at baseline. In addition, we performed stratified analyses by age at 60 years and status of alcohol consumption as a

previous study reported a stronger relationship of serum GGT among subjects <60 years and serum GGT has been conventionally used as a marker of alcohol consumption.[7] In subgroup analyses, as the associations between serum GGT and incident CHD were similar between men and women, we presented results combining men and women.

Results

In total, 1467 incident CHD events were registered during a median follow-up time of 11.9 years (interquartile range: 6.9–20.3). At baseline, serum GGT was related to most cardiovascular risk factors (*Table 1*). Age, alcohol consumption, cigarette smoking, BMI, SBP, and DBP were positively associated with baseline serum GGT level in both men and women. Total cholesterol showed a positive association with baseline GGT level among men only, whereas HDL-cholesterol showed an inverse association with it among women only. HDL-cholesterol in men and total cholesterol in women showed U-shaped associations with serum GGT.

Compared with the lowest baseline GGT category, the age-adjusted HRs for incident CHD events adjusted for age were 1.31, 1.56, 1.75, and 2.27 among men and 1.13, 1.49, 1.81, and 2.14 among women in the other four GGT categories, respectively (test for trend $P < 0.01$ in both men and women) (*Table 2*). Additional adjustment for other cardiovascular risk factors (BMI, alcohol consumption, cigarette smoking, physical activity, SBP, total cholesterol, HDL-cholesterol, and history of diabetes) attenuated this relationship, but GGT still remained an independent risk factor for incident CHD events among both genders; multivariable-adjusted HRs were 1.00, 1.15, 1.25, 1.27, and 1.57 (test for trend $P < 0.01$) among men, and 1.00, 1.03, 1.22, 1.32, and 1.44 (test for trend $P < 0.01$) among women in the five GGT categories, respectively. When we separately analyzed non-fatal MI and fatal CHD events, similar associations were observed with the outcome of non-fatal MI as well as with the outcome of fatal CHD event (*Table 3*).

When stratified by age at 60 years, the relationship of serum GGT was only observed among subjects <60 years (*P* for interaction <0.01). After stratification by alcohol drinking, the association between serum GGT and incident CHD was observed in both non-drinkers and drinkers (*Table 4*). However, the association tended to be stronger among drinkers than non-drinkers (*P* for interaction = 0.07). On the other hand, the incidence of CVD events among drinkers was lower than that in non-drinkers in each category of serum GGT.

In addition, serum GGT predicted the future risk of CHD events among 1120 men and women with a history of diabetes at baseline (3.9% of all study subjects) with sex- and multivariable-adjusted HRs of 1.00, 1.29, 1.57, 1.88, and 1.78 (*P* for trend = 0.03) (*Table 5*). The findings were somewhat less clear among 971 patients with a history of acute MI, who were excluded from the other analyses, in that the association found with serum GGT was not graded with fatal CHD; sex- and multivariable-adjusted HRs of 1.00, 1.57, 1.26, 1.36, and 1.59 (*P* for trend = 0.17) (*Table 5*). However, when we dichotomized serum GGT into <25th vs. ≥25th percentiles, sex- and multivariable-adjusted HR for fatal CHD was 1.45 (95% CI: 1.04–2.04).

Discussion

In several previous prospective cohort studies with unselected populations or patients with a history of MI, high

Table 1 Age-adjusted risk factor levels at baseline in 1982, 1987, 1992, or 1997 in men and women aged 25–74 years, by serum GGT level

	Baseline GGT level					P_{trend}
	<25%	25 to <50%	50 to <75%	75 to <90%	≥90%	
Men ($n = 13\,811$)	<16 U/L	16 to <24 U/L	24 to <38 U/L	38 to <64 U/L	≥64 U/L	
Number of subjects	3521	3549	3353	2018	1370	
Age (years)	42.7	45.0	47.2	47.2	48.3	<0.01
Alcohol (g/week)	40.5	60.2	76.8	106.6	164.3	<0.01
Current smoker (%)	23.6	29.2	30.8	33.1	37.9	<0.01
Physical activity (%)[a]	49.5	49.8	49.3	45.7	42.7	<0.01
BMI (kg/m^2)	25.0	26.0	27.2	28.1	28.7	<0.01
SBP (mmHg)	139.3	139.4	141.3	142.7	146.7	<0.01
DBP (mmHg)	82.8	83.9	85.8	88.2	90.7	<0.01
Serum total cholesterol (mmol/L)	5.71	5.80	5.91	6.09	6.19	<0.01
Serum HDL-cholesterol (mmol/L)	1.30	1.27	1.22	1.23	1.28	<0.01
Women ($n = 15\,027$)	<10 U/L	10 to <14 U/L	14 to <20 U/L	20 to <32 U/L	≥32 U/L	
Number of subjects	4140	3833	3368	2194	1492	
Age (years)	41.8	44.3	46.4	49.1	51.0	<0.01
Alcohol (g/week)	10.9	20.1	26.1	30.2	40.2	<0.01
Current smoker (%)	9.3	13.9	17.5	19.2	22.3	<0.01
Physical activity (%)[a]	43.6	47.9	49.6	50.8	43.7	<0.01
BMI (kg/m^2)	25.0	25.5	26.1	27.2	28.3	<0.01
SBP (mmHg)	134.9	134.7	134.6	136.1	138.5	<0.01
DBP (mmHg)	80.0	80.6	80.8	82.2	83.8	<0.01
Serum total cholesterol (mmol/L)	5.84	5.78	5.68	5.78	5.81	0.01
Serum HDL-cholesterol (mmol/L)	1.54	1.54	1.52	1.48	1.47	<0.01

[a]Leisure time physical activity two times per week or more.

Table 2 Adjusted HRs and 95% CI for non-fatal MI and fatal CHD associated with serum GGT levels in men and women aged 25–74 years

	Baseline serum GGT level					P_{trend}
	<25%	25 to <50%	50 to <75%	75 to <90%	≥90%	
Men	<16 U/L	16 to <24 U/L	24 to <38 U/L	38 to <64 U/L	≥64 U/L	
Cases/subjects at risk	239/3521	254/3549	255/3353	149/2018	116/1370	
Incidence (per 1000 person–year)	4.19	5.26	6.27	6.29	7.80	
Adjusted HRs (95% CI)						
Model 1	1.0	1.31 (1.09–1.56)	1.56 (1.30–1.87)	1.75 (1.42–2.16)	2.27 (1.81–2.85)	<0.01
Model 2	1.0	1.20 (1.00–1.43)	1.39 (1.15–1.67)	1.53 (1.23–1.90)	1.90 (1.49–2.42)	<0.01
Model 3	1.0	1.14 (0.95–1.36)	1.25 (1.04–1.50)	1.29 (1.04–1.62)	1.63 (1.27–2.09)	<0.01
Model 4	1.0	1.15 (0.96–1.37)	1.25 (1.04–1.51)	1.27 (1.02–1.59)	1.57 (1.22–2.01)	<0.01
Women	<10 U/L	10– < 14 U/L	14 to <20 U/L	20 to <32 U/L	≥32 U/L	
Cases/subjects at risk	98/4140	103/3833	106/3368	80/2194	67/1492	
Incidence (per 1000 person–year)	1.37	1.85	2.56	3.13	4.04	
Adjusted HRs (95% CI)						
Model 1	1.0	1.13 (0.86–1.49)	1.49 (1.13–1.97)	1.81 (1.34–2.45)	2.14 (1.56–2.95)	<0.01
Model 2	1.0	1.07 (0.81–1.42)	1.35 (1.02–1.79)	1.57 (1.15–2.14)	1.85 (1.33–2.57)	<0.01
Model 3	1.0	1.06 (0.80–1.40)	1.25 (0.94–1.66)	1.35 (0.99–1.85)	1.61 (1.15–2.24)	<0.01
Model 4	1.0	1.03 (0.78–1.36)	1.22 (0.92–1.62)	1.32 (0.96–1.80)	1.44 (1.03–2.02)	<0.01

Model 1: Adjustment for age, study year, and study area. Model 2: Model 1 plus adjustment for baseline BMI, cigarette smoking, alcohol consumption, and physical activity. Model 3: Model 2 plus adjustment for SBP, total cholesterol, and HDL-cholesterol. Model 4: Model 3 plus diabetes.

Table 3 Adjusted HRs and 95% CI of non-fatal MI and fatal CHD associated with serum GGT levels in men and women aged 25–74 years

	Baseline serum GGT level					P_{trend}
	<25%	25 to <50%	50 to <75%	75 to <90%	≥90%	
Outcome: non-fatal MI						
Men						
Cases/subjects at risk	165/3521	171/3549	165/3353	97/2018	74/1370	
Adjusted HRs (95% CI)						
Model 1	1.0	1.28 (1.03–1.59)	1.48 (1.19–1.85)	1.65 (1.27–2.12)	2.11 (1.59–2.79)	<0.01
Model 2	1.0	1.12 (0.90–1.39)	1.16 (0.92–1.46)	1.16 (0.88–1.53)	1.45 (1.06–1.97)	0.04
Women						
Cases/subjects at risk	66/4140	77/3833	80/3368	60/2194	41/1492	
Adjusted HRs (95% CI)						
Model 1	1.0	1.26 (0.91–1.76)	1.69 (1.22–2.36)	2.02 (1.41–2.89)	1.97 (1.32–2.93)	<0.01
Model 2	1.0	1.17 (0.84–1.63)	1.42 (1.02–1.99)	1.53 (1.06–2.22)	1.40 (0.92–2.13)	0.02
Outcome: fatal CHD						
Men						
Cases/subjects at risk	110/3521	123/3549	131/3353	76/2018	57/1370	
Adjusted HRs (95% CI)						
Model 1	1.0	1.37 (1.06–1.78)	1.73 (1.34–2.24)	2.06 (1.53–2.77)	2.58 (1.86–3.58)	<0.01
Model 2	1.0	1.21 (0.93–1.57)	1.42 (1.09–1.86)	1.48 (1.07–2.03)	1.66 (1.16–2.37)	<0.01
Women						
Cases/subjects at risk	50/4140	43/3833	48/3368	37/2194	41/1492	
Adjusted HRs (95% CI)						
Model 1	1.0	0.90 (0.60–1.35)	1.27 (0.85–1.89)	1.65 (1.07–2.54)	2.50 (1.64–3.82)	<0.01
Model 2	1.0	0.79 (0.52–1.19)	0.98 (0.65–1.47)	1.08 (0.69–1.70)	1.48 (0.94–2.33)	0.05

Model 1: Adjusted for age, study year, and study area. Model 2: Additionally adjusted for BMI, cigarette smoking, alcohol consumption, physical activity, SBP, total cholesterol, HDL-cholesterol, and diabetes.

levels of serum GGT predicted CVD events or CHD mortality after adjusting for other known CVD risk factors as well as alcohol consumption.[4–8] This prospective cohort study also presented a positive association of serum GGT with the risk of CHD, showing in a single dataset that this elevated risk is present for both non-fatal MI and fatal CHD events and exists in both men and women, especially those with age <60 and alcohol drinkers. Despite a general consistency in finding statistical significance of CHD risk elevated in those with high normal GGT, strength of association varied between studies. Relative risks may be important in deciding whether measurement of serum GGT would be useful in clinical practice. In our study (number of study subjects: 28 838) and the prospective study from Austria (number of

Table 4 Adjusted HRs and 95% CI of non-fatal MI and fatal CHD associated with serum GGT levels stratified by age or alcohol consumption

	Baseline serum GGT level					P_{trend}
	<25%	25 to <50%	50 to <75%	75 to <90%	≥90%	
Age <60 years						
Cases/subjects at risk	215/6934	245/6410	225/5536	152/3402	125/2279	
Adjusted HRs (95% CI)						
Model 1	1.0	1.39 (1.15–1.67)	1.67 (1.39–2.02)	2.02 (1.64–2.49)	2.60 (2.08–3.26)	<0.01
Model 2	1.0	1.23 (1.02–1.48)	1.35 (1.11–1.63)	1.48 (1.19–1.85)	1.84 (1.44–2.35)	<0.01
Age ≥60 years						
Cases/subjects at risk	120/727	112/972	136/1,185	77/810	58/583	
Adjusted HRs (95% CI)						
Model 1	1.0	1.01 (0.78–1.31)	1.31 (1.02–1.68)	1.39 (1.03–1.86)	1.64 (1.19–2.28)	<0.01
Model 2	1.0	0.89 (0.68–1.16)	1.05 (0.81–1.36)	1.04 (0.76–1.42)	1.11 (0.78–1.56)	0.37
Non-drinkers						
Cases/subjects at risk	220/4232	203/3471	187/2758	98/1575	78/1008	
Adjusted HRs (95% CI)						
Model 1	1.0	1.17 (0.97–1.42)	1.59 (1.31–1.94)	1.67 (1.31–2.13)	2.25 (1.72–2.93)	<0.01
Model 2	1.0	1.02 (0.84–1.24)	1.24 (1.01–1.51)	1.13 (0.88–1.46)	1.43 (1.08–1.90)	<0.01
Drinkers						
Cases/subjects at risk	110/3335	148/3755	164/3763	125/2469	104/1733	
Adjusted HRs (95% CI)						
Model 1	1.0	1.45 (1.13–1.85)	1.59 (1.24–2.02)	2.07 (1.60–2.69)	2.64 (2.01–3.47)	<0.01
Model 2	1.0	1.28 (1.00–1.64)	1.28 (1.00–1.64)	1.54 (1.18–2.03)	1.85 (1.37–2.49)	<0.01

Model 1: Adjusted for age, sex, study year, and study area. Model 2: Additionally adjusted for BMI, cigarette smoking, alcohol consumption, physical activity, SBP, total cholesterol, HDL-cholesterol, and diabetes.

Table 5 Adjusted HRs and 95% CI of serum GGT levels with non-fatal MI and fatal CHD among subjects with diabetes at baseline, or fatal CHD among subjects with history of MI

	Baseline serum GGT level					P_{trend}
	<25%	25 to <50%	50 to <75%	75 to <90%	≥90%	
Subjects with diabetes						
Cases/subjects at risk	22/173	34/240	40/242	37/220	35/245	
Adjusted HRs (95% CI)						
Model 1	1.0	1.28 (0.74–2.22)	1.79 (1.04–3.06)	2.04 (1.18–3.54)	2.17 (1.23–3.81)	<0.01
Model 2	1.0	1.29 (0.74–2.26)	1.57 (0.89–2.75)	1.88 (1.04–3.40)	1.78 (0.96–3.30)	0.03
Subjects with history of MI						
Cases/subjects at risk	50/179	73/233	42/207	44/195	33/157	
Adjusted HRs (95% CI)						
Model 1	1.0	1.50 (1.04–2.15)	1.18 (0.77–1.78)	1.43 (0.94–2.16)	1.53 (0.97–2.41)	0.12
Model 2	1.0	1.57 (1.08–2.29)	1.26 (0.81–1.96)	1.36 (0.87–2.11)	1.59 (0.97–2.62)	0.17

Model 1: Adjusted for age, sex, study year, and study area. Model 2: Additionally adjusted for BMI, cigarette smoking, alcohol consumption, physical activity, SBP, total cholesterol, HDL-cholesterol, and diabetes.

study subjects: 163 944),[7] the strength of association was relatively modest, but the small study from Germany (number of study subjects: 1878)[8] showed a stronger association. As the major difference between the previous two studies[7,8] appeared to be whether non-fatal MI was included in the outcome or not, we separately evaluated the association of serum GGT with non-fatal MI and fatal CHD events. However, we found no risk difference between non-fatal MI and fatal CHD events. The other difference among three studies was whether subjects with angina or history of MI at baseline were excluded or not. The study from Germany[8] excluded subjects with history of MI or angina, but our study excluded only subjects with history of MI because information on history of angina was not available. On the other hand, the study from Austria[7] did not exclude subjects with history of MI or angina. As the baseline risk in the study population is lower by excluding participants with angina in addition to those with MI, the stronger association shown in the German study may be partly explained by the difference in the exclusion criteria.

In addition, this study showed that serum GGT was positively associated with CHD among subjects with diabetes at baseline; the strength of association was somewhat stronger than in the general population. However, the association among subjects with a history of acute MI at baseline was not as strong as among subjects with diabetes.

Our study together with other studies suggests that an independent mechanism may link GGT to CHD, beyond its strong associations with known CVD risk factors. Serum GGT also significantly contributed to the estimated risk of CVD mortality as determined by a new risk scoring system for CVD risk in clinical practice in Europe developed by the SCORE project group,[16] independent of the major risk factors for CVD mortality.[17] Compared with known CVD risk factors such as smoking or serum cholesterol, however, the strength of the association appeared to be modest.

While previous studies report greater prognostic value of serum GGT on the risk of CHD among subjects with prevalent heart problems when compared with subjects without,[4,6] the prognostic value of serum GGT in this study seemed to be clearest among subjects with diabetes at baseline. Among subjects with a history of MI, serum GGT levels were elevated in subjects who had another CHD event and the association with serum GGT was significant when it was dichotomized into values $<$25th vs. $>$25th percentile, but it did not show a dose-response relation. This may be related to the variety of clinical conditions among subjects with history of acute MI, despite adjustment for known CVD risk factors.

In our previous study with largely the same FIN-MONICA dataset,[15] serum GGT within its reference range had a strong dose-response relation with incident type-2 diabetes in both men and women, the risk in the highest category being about five times higher than that of the lowest category. This study extends that finding, showing that serum GGT also predicts CHD complications among diabetic patients. However, the strength of association with CHD was weaker than that with the risk of diabetes. Ruttmann *et al*.[7] suggested cut-off values of serum GGT which were related to the increased risk of CVD mortality through analyses of sensitivities and specificities for selected threshold values of GGT, but in our study serum GGT showed graded associations with various clinical outcomes or CVD risk factors. It suggests that setting any artificial cutpoints to divide normal vs. abnormal GGT in this respect may lose information and therefore not be appropriate. In addition, in the CARDIA study with young white and black men and women, serum GGT levels within its reference range positively predicted the future risk of microalbuminuria among subjects with hypertension or diabetes.[9] Thus, our current and previous studies consistently suggest that serial measurement of serum GGT among diabetic patients may be useful to predict the risk of complications in diabetic patients.

In this study, the stronger association of serum GGT with incident CHD observed in alcohol drinkers, compared with non-drinkers, may need further discussion as serum GGT has been conventionally used as an objective indicator of excess alcohol consumption. This observation led us to suspect that the strong association between serum GGT and non-fatal MI or fatal CHD event in the Germany study[8] may be partly explained by the high proportion of alcohol drinkers among study subjects; about 80% of study subjects were drinkers. Interestingly, we reported a similar interaction between serum GGT and alcohol consumption with the risk of hypertension.[18] The dose-response relationship generally seen is that the mean GGT increases as the amount of self-reported alcohol consumption increases.[19] Nevertheless, a wide variation in GGT levels exists among subjects who report the same amount of alcohol consumption.[19] Our results may be related to the inaccuracy of information on self-reporting alcohol consumption; drinkers with low serum GGT might drink less alcohol than drinkers with high serum GGT. However, under this interpretation, it may be difficult to explain the dose-response relation of serum GGT across all categories with CHD risk because moderate alcohol consumption is usually associated with decreased CHD risk. Furthermore, it should be noted that the graded association between GGT levels and CHD was similar in both sexes, and yet Finnish women reported much lower amounts of alcohol drinking when compared with men, despite the range of GGT in women was by far lower than in men. Rather than this interpretation, our results may suggest that subjects whose serum GGT increases after alcohol consumption may be more susceptible to the risk of CHD than subjects who do not increase serum GGT after the same amount of alcohol consumption. At present, it is unclear which factors can influence inter-individual variation in the changes of serum GGT after alcohol consumption. Genetic factors may explain elevation of serum GGT after alcohol consumption.[20] Further studies on factors which influence increases of serum GGT after alcohol consumption may be helpful to elucidate the mechanism of serum GGT affecting atherosclerosis.

Compelling evidence for the importance of inflammation and atherosclerosis at both the basic and clinical level has evolved in parallel.[21,22] In this context, the finding in the CARDIA study that serum GGT predicted future concentrations of inflammation markers such as C-reactive protein or fibrinogen in a dose-response manner could be of substantial interest.[23] This finding was also confirmed in the NHANES representative sample of the US population.[24] In addition, serum GGT predicted the future levels of F_2-isoprostanes, an oxidative damage product of arachidonic acid in the CARDIA subjects.[23] These associations suggest that graded higher serum GGT activity was associated with both inflammation and oxidative stress, both of which are proposed as key mechanisms of atherosclerosis.

In conclusion, even after adjusting for known CVD risk factors, there was a modest dose-response relation between serum GGT levels and the risk of both non-fatal MI and fatal CHD event. However, this relation was more pronounced among subjects aged $<$60, alcohol drinkers, and those with type-2 diabetes at baseline. The determination of serum GGT, usually considered as a marker of alcohol consumption or hepatobiliary diseases but equally considered as a marker of oxidative stress, may have important clinical implications for prediction of CHD, diabetes, and complications among diabetics, identifying a subset at high risk of events who require specific and enhanced therapeutic effort.

Acknowledgements

This study is funded by Academy of Finland, Research Council for Health (Grant Nos. 46558, 53585, 108297, 204274, 205657), YALTA (Grant No. NIH/NHLBI R01 HL53560), and the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea. (A050349).

Conflict of interest: none declared.

References

1. Whitfield JB. Gamma glutamyl transferase. *Crit Rev Clin Lab Sci* 2001;**38**:263–355.
2. Emdin M, Pompella A, Paolicchi A. Gamma-glutamyltransferase, atherosclerosis, and cardiovascular disease: triggering oxidative stress within the plaque. *Circulation* 2005;**112**:2078–2080.
3. Paolicchi A, Emdin M, Ghliozeni E, Ciancia E, Passino C, Popoff G, Pompella A. Atherosclerotic plaques contain gamma-glutamyl transpeptidase activity. *Circulation* 2004;**109**:1140.
4. Wannamethee G, Ebrahim S, Shaper AG. Gamma-glutamyltransferase: determinants and association with mortality from ischaemic heart disease and all causes. *Am J Epidemiol* 1995;**142**:699–708.
5. Karlson BW, Wiklund O, Hallgren P, Sjolin M, Lindqvist J, Herlitz J. 10-year mortality amongst patients with a very small or unconfirmed acute myocardial infarction in relation to clinical history, metabolic screening and signs of myocardial ischaemia. *J Intern Med* 2000;**247**:449–456.
6. Emdin M, Passino C, Michelassi C, Titta F, L'abbate A, Donato L, Pompella A, Paolicchi A. Prognostic value of serum gamma-glutamyl transferase activity after myocardial infarction. *Eur Heart J* 2001;**22**:1802–1807.
7. Ruttmann E, Brant LJ, Concin H, Diem G, Rapp K, Ulmer H; Vorarlberg Health Monitoring Promotion Program Study Group. Gamma-glutamyltransferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163 944 Austrian adults. *Circulation* 2005;**112**:2130–2137.
8. Meisinger C, Doring A, Schneider A, Lowel H; for the KORA Study Group. Serum gamma-glutamyltransferase is a predictor of incident coronary events in apparently healthy men from the general population. *Atherosclerosis* 2006; Published online ahead of print.
9. Lee DH, Jacobs DR Jr, Gross M, Steffes M. Serum gamma glutamyltransferase was differently associated with microalbuminuria by status of hypertension or diabetes: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Clin Chem* 2005;**51**:1185–1191.
10. Tunstall-Padoe H; for the WHO MONICA Project. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. *J Clin Epidemiol* 1988;**41**:105–114.
11. Vartiainen E, Jousilahti P, Alfthan G, Sundvall J, Pietinen P, Puska P. Cardiovascular risk factor changes in Finland, 1972–1997. *Int J Epidemiol* 2000;**29**:49–56.
12. Pajak A, Kuulasmaa K, Tuomilehto J, Ruokokoski E. The WHO MONICA Project. Geographical variation in the major risk factors of coronary heart disease in men and women aged 25–64 years. *World Health Stat Q* 1988;**41**:115–140.
13. Mahonen M, Salomaa V, Brommels M, Molarius A, Miettinen H, Pyorala K, Tuomilehto J, Arstila M, Kaarsalo E, Ketonen M, Kuulasmaa K, Lehto S, Mustaniemi H, Niemela M, Palomaki P, Torppa J, Vuorenmaa T. The validity of hospital discharge register data on coronary heart disease in Finland. *Eur J Epidemiol* 1997;**13**:403–415.
14. Palomaki P, Miettinen H, Mustaniemi H, Lehto S, Pyorala K, Mahonen M, Tuomilehto J. Diagnosis of acute myocardial infarction by MONICA and FINMONICA diagnostic criteria in comparison with hospital discharge diagnosis. *J Clin Epidemiol* 1994;**47**:659–666.
15. 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.
16. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM; SCORE Project Group. Estimation of 10-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;**24**:987–1003.
17. Ulmer H, Kollerits B, Kelleher C, Diem G, Concin H. Predictive accuracy of the SCORE risk function for cardiovascular disease in clinical practice: a prospective evaluation of 44 649 Austrian men and women. *Eur J Cardiovasc Prev Rehabil* 2005;**12**:433–441.
18. Lee DH, Ha MH, Kim JR, Gross M, Jacobs DR Jr. Gamma-glutamyltransferase, alcohol, and blood pressure. A 4-year follow-up study. *Ann Epidemiol* 2002;**12**:90–96.
19. Poikolainen K, Karkkainen P, Pikkarainen J. Correlations between biological markers and alcohol intake as measured by diary and questionnaire in men. *J Stud Alcohol* 1985;**46**:383–387.
20. Whitfield JB, Zhu G, Nestler JE, Heath AC, Martin NG. Genetic covariation between serum gamma-glutamyltransferase activity and cardiovascular risk factors. *Clin Chem* 2002;**48**:1426–1431.
21. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;**105**:1135–1143.
22. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation* 2003;**107**:363–369.
23. Lee DH, Jacobs DR, Gross M, Kiefe CI, Roseman J, Lewis CE, Steffes M. Gamma glutamyltransferase is a predictor of incident diabetes and hypertension: the CARDIA Study. *Clin Chem* 2003;**49**:1358–1366.
24. Lee DH, Jacobs DR Jr. Association between serum gamma-glutamyltransferase and C-reactive protein. *Atherosclerosis* 2005;**178**:327–330.