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Serum γ-glutamyltransferase is a predictor of incident coronary events in apparently healthy men from the general population

C. Meisinger[a,b,*], A. Döring[b], A. Schneider[b], H. Löwel[b], for the KORA Study Group

[a] *Central Hospital of Augsburg, MONICA/KORA Myocardial Infarction Registry, Stenglinstr. 2, D-86156 Augsburg, Germany*
[b] *GSF National Research Center for Environment and Health, Institute of Epidemiology, Neuherberg, Germany*

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Abstract

Objective: To investigate whether serum γ-glutamyltransferase (GGT) is an independent predictor for incident coronary events in initially healthy men from the general population.
Methods and results: The study was based on 1878 men (aged 25–64 years) who participated in the first MONICA Augsburg survey 1984/1985, and who were free of coronary heart disease at baseline. Up to 2002 a total of 150 incident acute coronary events occurred. Baseline levels of GGT were higher in men who experienced an event than in event-free men (28.4 ± 2.0 units/l versus 22.4 ± 2.1 units/l, p 0.0002). GGT was highly correlated with other cardiovascular risk factors. In a Cox proportional hazards model after age adjustment hazard ratios (HR) for incident myocardial infarction across GGT quartiles (<13, 13 to <20, 20 to <35, and ≥35 units/l) were 1.0, 1.84, 2.02, and 3.08 (p for trend 0.0001). Further adjustment for hypertension, TC/HDL ratio, diabetes, smoking, physical activity, alcohol intake, education years and BMI attenuated the association; comparing the highest versus lowest quartile of GGT the HR for a first-ever coronary event was then 2.34 (95% CI, 1.23–4.44).
Conclusions: Serum GGT is a strong predictor of acute coronary events in apparently healthy men from the general population, independent of other risk factors for cardiovascular disease.
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1. Introduction

Usually, an increase in GGT concentration has been regarded as a marker of alcohol consumption or liver disease [1]. Recently, it has been suggested that serum GGT is an independent prognostic marker for cardiac death and reinfarction, both in unselected populations and in patients with coronary artery disease [2–4]. GGT is located on the external surface of most cells and is responsible of glutathione (GSH) catabolism by hydrolysis of its γ-glutamyl bond between glutamate and cysteine. This reaction produces cysteinyl–glycine moieties, which are usually taken within intracellular milieu by the action of membrane dipeptidases, as precursors for GSH resynthesis [5]. The body of current evidence from studies indicates that GGT may have a role in the pathogenesis of atherosclerosis. GGT activity has been detected in atheromatous plaques of carotid and coronary arteries [6]. Furthermore, cysteinyl–glycine deriving from the hydrolysis of GSH performed by GGT has been found to trigger iron-dependent production of reactive oxygen species (ROS) [7] as well as low-density lipoprotein oxidation in vitro [6]. These facts could provide a pathological basis for the hypothesis of a direct participation of GGT in oxidative processes within the plaque and thus in atherogenesis and coronary artery disease progression. Prior studies have found that serum GGT predicted cardiac mortality or non-fatal myocardial infarction (MI), especially among

* Corresponding author. Tel.: +49 821 400 4373; fax: +49 821 400 2838.
E-mail address: christa.meisinger@gsf.de (C. Meisinger).

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ischaemic patients with established coronary atherosclerosis and previous MI [2,4]. In the present prospective study, we tested the hypothesis whether GGT, possibly as a marker of oxidative stress is an early predictor of incident acute coronary events in initially healthy men aged 25–64 years from the general population in Augsburg, Southern Germany.

2. Methods

The presented data were derived from the first population-based MONICA (Monitoring trends and determinants on cardiovascular diseases) Augsburg (Southern Germany) survey conducted between October 1984 and June 1985. The MONICA Augsburg project was part of the multinational WHO MONICA project and the design of the project has been described in detail elsewhere [8]. Briefly, the cross-sectional survey was carried out in the city of Augsburg and the counties Augsburg and Aichach-Friedberg to estimate the prevalence and distribution of cardiovascular risk factors among men and women. Altogether 4022 persons (2023 men, 1999 women, response 79.3%) aged 25–64 years participated in the cross-sectional study. All subjects were prospectively followed within the framework of the Cooperative Health Research in the Region of Augsburg (KORA).

Mortality was ascertained by regularly checking the vital status of all participants through the population registries inside and outside the study area; this procedure guaranteed that the vital status of cohort members who had moved out of the study area could also be assessed. The present study was restricted to men because analyses were not feasible in women due to the small number of events. Follow-up information was available for 2023 men. Up to December 31st 2002 altogether 385 men had died. For the present analyses, we excluded persons with prevalent myocardial infarction or with symptoms or signs of stable chronic angina pectoris at baseline ($n = 106$), and all subjects with incomplete data on any of the covariables ($n = 39$). Finally, the prospective analyses comprised 1878 men aged 25–64 years at baseline.

Informed consent was obtained from every participant in the study. The study was approved by an institutional review board.

2.1. Outcome

The outcome variable for the present analysis was a combination of incident fatal or non-fatal acute MI and sudden cardiac death. They were identified through the MONICA/KORA coronary event registry of the 25–74 year old study population and censored at the 75th year of age [9]. Up to 31 December 2000, the diagnosis of a major non-fatal MI was based on the MONICA algorithm taking into account symptoms, cardiac enzymes, and ECG changes [10]. Since 1 January 2001, all patients with MI diagnosed according to ESC and ACC criteria were included [11,12]. Coronary deaths were validated by death certificates, autopsy report, chart review, and information from the coroner or the last treating physician.

2.2. Data collection

Baseline information on sociodemographic variables, medical history, smoking habits, physical activity level, angina pectoris, and alcohol consumption were gathered by trained and certified medical staff (mainly nurses) through a standardized face-to-face interview. The participants were also asked about the awareness, diagnosis and treatment of hypertension. Information concerning medical drug use was obtained. All participants were asked to bring to the interview all medications taken within the last 7 days preceding the examination. In addition they underwent an extensive standardized medical examination including the collection of a blood sample. All study measurements were conducted by a centrally trained staff according to the World Health Organization MONICA protocol using standard instruments. These procedures have been described elsewhere in detail [8]. A quality assurance program was employed in the study to ensure the quality of the data collection over the entire study period.

Hypertension was defined as a measured blood pressure higher than 140/90 mmHg and/or the use of antihypertensive medication, given that the subjects were aware of being hypertensive. Participants were classified as active during leisure time if they regularly participated in sports in summer and winter for atleast 1 h/week in either season.

2.3. Clinical chemical measurements

A non-fasting venous blood sample was obtained from all study participants while sitting. Blood analyses were carried out with an autoanalyser by a clinical laboratory (Central hospital of Augsburg, Germany). Total serum cholesterol analyses were carried out using an enzymatic method (CHOD-PAP; Boehringer Mannheim, Germany). HDL cholesterol was also measured enzymatically after precipitation of the apoprotein B-containing lipoproteins with phosphotungstate/Mg^{2+} (Boehringer Mannheim, Germany). Serum γ-glutamyltransferase was determined by a photometric method (smac, Technicon). Internal and external quality control was performed according to the WHO MONICA Manual [8].

2.4. Statistical analyses

The duration of the follow-up was calculated as the interval between the baseline examination and the occurrence of an incident fatal or non-fatal acute coronary event, death or the date, when the participants were still alive. Means or proportions for baseline demographic and clinical characteristics were computed for men with and without an incident coronary event. The Chi^2-test was used to test the differences

in prevalences. The general linear model was used to compare means (F-test). The study population was stratified into four groups of GGT concentrations with use of cut-points of 13, 20, and 35 units/l (25th, 50th, and 75th percentiles). Relative risks of incident coronary events were computed for quartiles 2–4, as compared with the lowest quartile in Cox proportional hazards models: The first model included GGT and in addition age (continuous). The second model included the previous factors plus education years (</≥ 12 years), hypertension (yes/no), TC/HDL cholesterol ratio (continuous), physical activity (active/inactive), smoking status (regular smoking, that is a subject who smoked atleast one cigarette per day at baseline, yes/no), alcohol intake (0 g/day, 0.1–39.9 g/day, ≥40 g/day), BMI (continuous), and history of diabetes (yes/no and unknown). The TC/HDL cholesterol ratio and GGT were logarithmically transformed before inclusion in analysis as continuous variables since they were not normally distributed. Tests for linear trend across increasing categories of GGT were conducted by assigning the median value within each category to the respective category and by treating the categories as a continuous variable. Furthermore, it was assessed whether GGT would increase the risk of an incident coronary event in men with low and with high alcohol consumption. For this subgroup analyses, the median of the daily alcohol intake (20 g/day) was used as cut-point.

Kaplan–Meier survival plots of GGT quartiles in relation to incident coronary events were examined. Comparisons between survival curves were performed using log-rank test. Results are presented as hazard ratios (HRs) and 95% confidence intervals (CI). Significance tests were two tailed and p-values less than 0.05 are stated as statistically significant. All analyses were performed using the Statistical Analysis System (Version 8.2, SAS Institute Inc., Cary, NC).

3. Results

In total, 150 incident cases of fatal ($n = 80$) and non-fatal ($n = 70$) coronary events, including sudden cardiac deaths, were registered between 1984 and 2002 (mean follow-up period 15.7 years). Men with an acute coronary event were significantly older, had a higher BMI, higher total cholesterol, and lower HDL cholesterol levels. They had a significantly higher TC/HDL ratio and higher systolic and diastolic blood pressure values. They were more frequently smokers and less frequently physically active. Men with an acute coronary event had also a higher prevalence of diabetes and hypertension. Concentrations of GGT were significantly higher than in those without a coronary event during follow-up. There were no significant differences with regard to education and alcohol consumption between men with an event and men without an event (Table 1).

GGT was positively correlated with age ($p \leq 0.0001$), BMI ($p \leq 0.0001$), systolic blood pressure ($p \leq 0.0001$), total cholesterol ($p \leq 0.0001$), and the TC/HDL ratio ($p \leq 0.0001$), but was not correlated with HDL cholesterol. GGT was also significantly related to physical activity ($p = 0.0005$), smoking ($p \leq 0.0001$), diabetes ($p = 0.0184$), alcohol intake ($p \leq 0.0001$), and education ($p = 0.0010$) (Table 2).

Serum GGT concentration showed a strong relationship with incident coronary events in men (Table 3). GGT levels in the fourth quartile were significantly associated with incident coronary events independent of age (HR 3.08; 95% CI 1.68–5.63) when compared with the first quartile. Further adjustment for hypertension, TC/HDL ratio, diabetes, smoking, physical activity, alcohol intake, education years, and BMI attenuated the association; comparing the highest versus the lowest quartile of GGT the HR for a first-ever coronary event was then 2.34 (95% CI, 1.23–4.44; p for trend

Table 1
Mean (S.D.) and prevalence of demographic and clinical characteristics of men with and without incident coronary event, age 25–64 years

Characteristics	Men with incident coronary event ($n = 150$)	Men without incident coronary event ($n = 1728$)	p-value
Age (years)[a]	52.9 (8.3)	44.0 (11.3)	<0.0001
Body mass index (kg/m^2)[a]	27.9 (3.4)	26.8 (3.5)	0.0003
Systolic blood pressure (mmHg)[a]	139.4 (17.2)	132.8 (16.2)	<0.0001
Diastolic blood pressure (mmHg)[a]	85.5 (10.9)	82.8 (11.3)	0.0044
Hypertension (%)[b]	56.7	37.4	<0.0001
γ-Glutamyltransferase (units/l)[c]	28.4 (2.0)	22.4 (2.1)	0.0002
Total cholesterol (mg/dl)[a]	256.1 (46.1)	234.0 (46.0)	<0.0001
HDL cholesterol (mg/dl)[a]	46.6 (15.5)	51.4 (15.6)	0.0004
Total/HDL cholesterol ratio[c]	5.7 (1.4)	4.7 (1.4)	<0.0001
Physical activity (%)	26.0	45.4	<0.0001
Regular smoker (%)	49.3	33.3	<0.0001
History of diabetes (%)	9.3	2.0	<0.0001
Alcohol intake			
0 g/day (%)	16.7	12.4	0.0693
0.1–39.9 g/day (%)	37.3	46.5	
≥40 g/day (%)	46.0	41.1	
Education <12 years (%)	74.0	68.4	0.1556

[a] Mean (S.D.), p-value from t-test.
[b] Blood pressure values ≥140/90 mmHg and/or use of antihypertensive medication.
[c] Geometric mean, p-value from t-test for log-transformed characteristic.

Table 2
Association between γ-glutamyltransferase and other cardiovascular risk factors by Pearson correlation coefficient *r* and mean (S.D.) with *p*-values

	γ-Glutamyltransferase	
	Pearson correlation coefficient	*p*-value
Age[a]	0.11	<0.0001
BMI[a]	0.27	<0.0001
Total cholesterol[a]	0.30	<0.0001
HDL cholesterol[a]	−0.03	0.1909
Total/HDL cholesterol ratio[a]	0.23	<0.0001
Systolic blood pressure[a]	0.26	<0.0001
	Geometric mean (S.D.)	*p*-value
Hypertension[b]		
No	19.8 (2.0)	<0.0001
Yes	28.5 (2.1)	
Regular smoker[b]		
No	21.2 (2.1)	<0.0001
Yes	26.1 (2.2)	
Physical activity[b]		
No	24.1 (2.1)	0.0005
Yes	21.3 (2.1)	
History of diabetes[b]		
No	22.6 (2.1)	0.0184
Yes	31.2 (2.5)	
Education[b]		
<12 years	21.0 (2.0)	0.0010
≤12 years	23.7 (2.2)	
Alcohol intake[b]		
0 g/day	17.7 (1.9)	<0.0001
0.1–39.9 g/day	19.2 (1.9)	
≥40 g/day	29.8 (2.2)	

[a] Pearson correlation coefficient.
[b] Geometric mean (S.D.) of γ-glutamyltransferase, *p*-value from *t*-test and *F*-test, respectively.

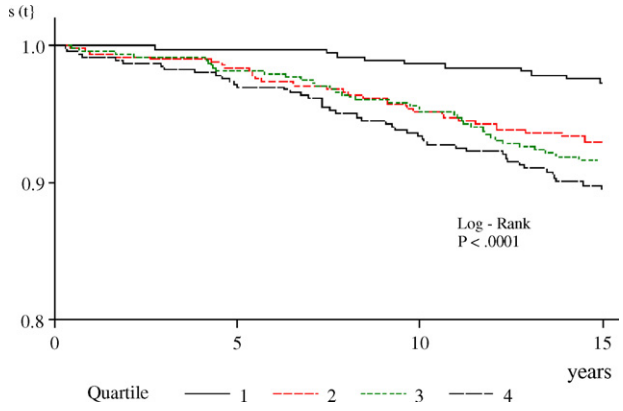

Fig. 1. Association of GGT quartiles with incident coronary events.

0.0219). Table 3 further describes the observed crude incidence rates of coronary events by GGT categories. Incidence of coronary events increased with increasing GGT levels from 19.9/10,000 person-years in the first quartile to 77.2/10,000 person-years in the fourth quartile.

To assess whether GGT levels increase the risk of a first-ever coronary event for men with low alcohol intake (<20 g daily) and men with high alcohol intake (≥20 g daily), the impact of GGT on the incidence of coronary events was analyzed separately for the two groups. In the subgroup with low alcohol intake the HR was 2.63 (95% CI, 1.01–6.84) for men in the fourth GGT quartile when compared with men in the first quartile after multivariable adjustment. Comparing the highest versus lowest quartile of GGT the HR for an incident coronary event was 2.12 (95% CI, 0.88–5.13) among men with a high alcohol intake.

Fig. 1 shows the Kaplan–Maier curves for incident coronary events by GGT categories. With increasing GGT concentrations coronary event rates increased significantly over the more than 15 years of follow-up (log-rank test $p \leq 0.0001$). The event curves for the men with GGT concentrations in the second, third and fourth quartile begin to separate from the first quartile very early during follow-up, and separate to a greater extent with increasing follow-up time.

4. Discussion

In this prospective cohort study, the relative risk of a first-ever coronary event associated with serum GGT concentrations in initially healthy men from the general population was investigated. Serum GGT concentrations were elevated in men who subsequently developed an event compared with

Table 3
Relative risks for incident coronary events according to quartiles of GGT among men aged 25–64 years at baseline

Men	GGT				
	<13 units/l	13 to <20 units/l	20 to <35 units/l	≥35 units/l	*p*-value for trend
Total number *n* = 1878	*n* = 395	*n* = 511	*n* = 494	*n* = 478	
Number of incident cases	13	38	43	56	
Person-years (PY)	6529	8052	7654	7257	
Crude rate per 10000 PY	19.9	47.2	56.2	77.2	
HR (95% CI)					
Model 1[a]	1.0	1.84 (0.98–3.46)	2.02 (1.08–3.75)	3.08 (1.68–5.63)	0.0001
Model 2[b]	1.0	1.88 (1.00–3.56)	1.63 (0.86–3.10)	2.34 (1.23–4.44)	0.0219

[a] Model 1: adjusted for age.
[b] Model 2: adjusted for age, education, history of diabetes, hypertension, TC/HDL ratio, regular smoking, physical activity, alcohol intake, and BMI.

those who did not. Furthermore, there was a strong correlation between serum GGT and the known cardiovascular risk factors. Although a part of the association between serum GGT and the risk of an acute coronary event was mediated through these risk factors, GGT was strongly and independently associated with incident coronary events even after multivariable adjustment.

It has been shown that serum GGT is an independent prognostic marker for reinfarction and cardiac death, both in patients with coronary artery disease and in unselected populations [2–4]. Few population studies [3,13–15] have examined the association between serum GGT and all cause mortality, but these studies focused on GGT as an indicator of alcohol consumption. Wannamethee et al. [3] investigated GGT as a prognostic marker for cardiovascular and overall mortality in a large population of middle-aged men. The study found that GGT levels in the top quintile were independently associated with both outcomes. A Swedish study reported that 10-year mortality was twice as high amongst patients in the two highest quartiles as compared with those in the lowest one [2]. Recently, a prospective study showed that GGT is an independent cardiac risk factor in ischaemic patients with established coronary atherosclerosis and previous myocardial infarction [4], using mortality and mortality plus non-fatal myocardial infarction as end-points. GGT showed an independent prognostic value beyond known established risk factors in 262 patients with previous MI, whereas it did not show significant prognostic value in 207 patients without previous MI.

The results of our study have important implications. We showed that serum GGT concentration discriminated men who subsequently developed an acute coronary event from those who remained event-free, even after adjustment for major CHD risk factors and alcohol consumption. A number of epidemiologic studies have examined the association between alcohol consumption and heart disease. Most of these studies have shown a U- or J-shaped relationship of alcohol intake to cardiovascular [16,17] and all-cause mortality [18] suggesting that a mild to moderate alcohol consumption may have a beneficial effect on cardiovascular disease risk [17]. One explanation for this relationship could be that light-to-moderate alcohol consumption is associated with a lower level of coagulatory factors, while higher alcohol intake is associated with impaired fibrinolytic potential [19]. Furthermore, it has been found that moderate alcohol consumption results in dose-dependent increases in plasma concentrations of HDL cholesterol, a well-established major protective factor against CHD [20]. In the present study, there was an increasing trend of incident coronary events with increasing levels of GGT. The dose-response relationship of serum GGT to first-ever coronary events was present in the subgroup with low alcohol intake as well as in the group with high alcohol intake. Thus the hypothesis that GGT may contribute to the clinical manifestation of CHD independently from alcohol consumption is supported. Moreover, the role of GGT in the atherosclerotic process seems to be more complex than it is currently thought. Recent findings suggested a possible role for GGT in the cellular process of LDL oxidation and atherogenesis [6]. Evidence from in vitro studies indicates that atherosclerosis represents a state of heightened oxidative stress characterized by lipid and protein oxidation in the vascular wall. Low-density lipoprotein oxidation is an early event in atherosclerosis and contributes to atherogenesis because oxLDL supports foam cell formation and has a number of potentially proatherogenic activities [21–24]. GGT is found in serum and in the plasma membranes of virtually all cell types. Its physiological role is to initiate the hydrolysis of extracellular GSH, a tripeptide in which cysteine lies between alpha-glycine and gamma-glutamate residues [5]. Cysteine and other thiol components are known to promote LDL oxidation by reducing Fe(III) to redox Fe(II) [6]. Moreover, it was shown that cysteinyl–glycine, a product of GGT/GSH reaction, but not GSH was responsible for reactive oxygen species (ROS) formation initiated by the reductive release of iron from transferring indicating that GGT is directly involved in ROS generation leading to free radical damage of nucleic acids and oxidative modifications of lipids and proteins [25]. Experimental studies have found that active GGT is present within coronary plaques underlining the hypothesis of a direct participation of GGT in LDL oxidation within the plaque and in atherogenesis [26].

The MONICA/KORA Augsburg Study has several limitations that need to be considered. GGT levels were measured only once at baseline, we were therefore unable to account for within-individual variability in the present study. Although we adjusted for a variety of confounders, additional factors that are known to be associated with acute coronary events, such as fasting blood glucose and triglycerides were not available in this study. Thus, confounding by unmeasured variables cannot be entirely excluded. Other reasons for a GGT elevation, for example acute/chronic cholecystitis, pancreatitis and hepatitis were not ascertained and could therefore have biased the present findings. Finally, because the study was limited to men of German nationality between 25 and 64 years of age, caution should be used in generalizing these results to women, other populations and other age groups. The strengths of the MONICA/KORA Augsburg Cohort Study are primarily its prospective design, the representativeness of the cohort, based on a random sample of the general population and the availability of data on lifestyle and multiple cardiovascular risk factors. Because the MONICA/KORA myocardial infarction registry in Augsburg is well established, we should have recovered all incident coronary events that occurred in the cohort.

In conclusion, the present results provide that serum GGT is a strong and independent predictor of acute coronary events in apparently healthy men from the general population. So far, the underlying pathophysiological mechanisms are not entirely clear. It seems that oxidative stress may be involved [27]. Further studies are needed to confirm the present findings and to investigate the biological mechanisms underlying this association.

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