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Association between gamma-glutamyltransferase and coronary artery calcification ☆

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ABSTRACT

Background: The exact mechanisms behind the association between atherosclerosis and gamma-glutamyltransferase (GGT) are unclear. Coronary artery calcification (CAC) detected by computerized tomography is an important marker of atherosclerosis and its severity correlates with coronary plaque burden. The aim of this study was to investigate if serum GGT levels are associated with CAC in patients without known coronary heart disease (CHD) who had low-intermediate risk for CHD.

Methods: Two hundred and seventy two patients who had low-intermediate risk for coronary artery disease were included in the study. Serum GGT levels were measured spectrophotometrically. CACS (Agatston method) were performed using a 64-slice computerized tomography scanner. The patients were grouped according to their GGT values in four quartiles.

Results: Patients in higher GGT quartiles had elevated CAC score ($P<0.001$). Patients in higher GGT quartiles were predominantly males ($P<0.001$) and were more likely to be smoking ($P=0.004$), and have elevated uric acid ($P<0.001$), fasting blood glucose ($P<0.001$), CRP levels ($P=0.003$) and 10-year total cardiovascular risk ($P=0.007$) and low HDL levels ($P<0.001$). Positive correlations were found between log GGT and CAC ($r=0.233$, $P<0.001$). In the multivariate analysis GGT, age, smoking and serum uric acid levels appeared as independent factors predictive of presence of CAC.

Conclusions: We demonstrated a significant correlation between serum GGT levels and CAC and CHD risk factors. Serum GGT level was an independent marker of CAC.

1. Introduction

Serum gamma-glutamyltransferase (GGT) is a marker of hepatobiliary disease and alcohol consumption. It is well known that serum GGT activity represents a true marker of atherosclerotic cardiovascular disease and has prognostic importance. Previously studies showed that serum GGT levels even within normal range are associated with atherosclerotic risk factors and are predictors of future heart disease, hypertension, stroke, metabolic syndrome and type 2 diabetes mellitus [1–4]. A meta-analysis showed a relation between GGT and the incidence of cardiovascular events independent of alcohol intake [5]. One U/L higher GGT (on a log scale) was associated with a 20% increase in the risk of coronary heart disease (CHD), a 54% increase in the risk of stroke, and a 34% increase in the risk of CHD and stroke combined.

The exact mechanisms behind the association between atherosclerosis and GGT are unknown. Coronary artery calcification (CAC) detected by computerized tomography is an important marker of atherosclerosis and its severity correlates with coronary plaque burden [6,7]. CAC is also an independent marker of CHD risk [8,9]. The relation between GGT and CAC has not been evaluated before. The aim of this study was to investigate if serum GGT levels are associated with CAC in patients without known CHD who had low-intermediate risk for CHD.

2. Methods

2.1. Study sample

Two hundred and seventy two consecutive patients who had low-intermediate risk for coronary artery disease according to current guidelines and who did not have any exclusion criteria were included in the study. Mean age of patients was 53 ± 10 years and 210 of them were male.

Patients with a history of heart failure or cardiomyopathies, coronary artery disease, renal dysfunction, hepatitis B or C infection or other known liver diseases, liver enzymes exceeding three times the upper reference range, hemolytic disorders, concomitant inflammatory diseases, neoplastic diseases, thyroid disease, acute infectious/inflammatory conditions, and use of hepatotoxic drugs were excluded from the study. The Framingham risk score for CHD has been computed according to the version described by Wilson et al. for all patients [10]. The study was conducted in compliance with the Declaration of Helsinki. All participants gave informed consent and the study protocol was approved by the local ethics committee.

2.2. Laboratory data

Standard techniques were used to measure creatinine, blood glucose, total cholesterol, high density lipoprotein (HDL), low-density lipoprotein (LDL), and calcium and C-reactive protein (CRP) levels at 12 hour fasting state. Serum GGT levels were measured

☆ Grants: None

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Table 1
Crude and unadjusted risk factor levels according to serum GGT concentration quartiles.

Serum GGT Level (U/L)	All patients	Quartile 1 1–19	Quartile 2 20–25	Quartile 3 26–37	Quartile 4 38–62	*P* value
	N: 272	N: 69	N: 68	N: 69	N: 66	
Age (year)	53 ± 10	51 ± 11	55 ± 11	54 ± 8	52 ± 9	0.051
Sex, male, n (%)	210 (77.2)	35 (50.7)	55 (80.9)	57 (82.6)	63 (95.5)	<**0.001**
Diabetes mellitus, n (%)	71 (26.1)	22 (31.9)	15 (22.1)	17 (24.6)	17 (25.8)	0.603
Hypertension, n (%)	162 (59.6)	43 (62.3)	35 (51.5)	43 (62.3)	41 (62.1)	0.482
Smoking, n (%)	59 (21.7)	6 (8.7)	15 (22.1)	15 (21.7)	23 (34.8)	**0.004**
Mean LVEF, %	63 ± 6	62 ± 6	62 ± 5	62 ± 6	65 ± 7	0.463
Creatinine (mg/dL)	0.8 ± 0.2	0.9 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	0.358
FBG (mg/dL)	100 ± 29	93 ± 18	94 ± 14	113 ± 44	101 ± 27	<**0.001**
CRP (mg/dL)	3.5 ± 2.4	3.1 ± 2.5	2.9 ± 1.6	3.6 ± 2.0	4.5 ± 3.1	**0.003**
Calcium (mg/dL)	9.4 ± 0.7	9.4 ± 0.5	9.3 ± 0.5	9.5 ± 0.5	9.3 ± 1.2	0.417
Uric acid (mg/dL)	5.8 ± 1.3	5.0 ± 1.2	5.8 ± 1.2	5.9 ± 1.3	6.4 ± 1.3	<**0.001**
Total cholesterol (mg/dL)	197 ± 32	191 ± 32	194 ± 32	198 ± 30	205 ± 34	0.987
LDL (mg/dL)	121 ± 30	116 ± 28	120 ± 30	120 ± 33	127 ± 29	0.231
HDL (mg/dL)	46 ± 12	52 ± 14	46 ± 11	45 ± 11	42 ± 10	<**0.001**
10-year total risk, %	11.7 ± 7.7	9.2 ± 6.6	12.6 ± 8.8	11.7 ± 6.6	13.5 ± 8.2	**0.007**

LVEF: left ventricular ejection fraction; FBG: Fasting blood glucose; GGT: Gama-Glutamyltransferase, CRP: C-reactive protein, LDL: low-density lipoprotein, HDL: high-density lipoprotein.

spectrophotometrically with the Roche/Hitachi 912 (Roche Diagnostics Co., Mannheim, Germany). The intra-assay and interassay coefficient of variation was <5%. Reference ranges for GGT was 11–50 U/L. The patients were classified into 4 quartiles according to their serum GGT level: Quartile 1 included patients with serum GGT between 1 to 19 U/L, Quartile 2: 20–25 U/L, Quartile 3: 26–37 U/L, Quartile 4: 38–62 U/L.

2.3. Measurement of CAC score

All computerized tomography scans were performed on a 64-slice scanner (Philips Brilliance 64, Philips Medical Systems, Eindhoven, The Netherlands) with a 0.42-second rotation time with a pitch of 0.2, tube voltage of 120 kV, and tube current of 600–1050 mAs. Patients with heart rates >70 beats/min received, unless they had known any contraindication for beta-blocker usage, intravenous metoprolol 5 to 15 mg or orally metoprolol 100 mg 1 h before the scan. All data sets were reconstructed using retrospective electrocardiographic-gating at 40%, 75%, and 80% of the RR interval. Data sets were used to a dedicated workstation (EBW, Philips Medical Systems). The calcium score for each artery was the sum of calcium scores of the left main, left anterior descending, left circumflex and right coronary arteries according to the Agatston method as previously described [11].

2.4. Statistical analysis

The statistical package SPSS (Statistical Package for the Social Sciences, version 17.0, SSPS Inc, Chicago, Ill, USA) was used for statistical analyses. Continuous variables are expressed as means ± standard deviation and categorical variables are expressed as total number (percentage). All continuous variables were checked with Kolmogorov–Smirnov normality test to show their distributions. Continuous variables with normal distributions were compared using the unpaired Student *t* test and analysis of variance (ANOVA). Continuous variables with abnormal distributions were compared using the Mann–Whitney *U* test and analysis of variance (ANOVA). For categorical variables, the chi-square test was used. The patients were grouped according to their GGT values in four quartiles as in Framingham Heart study [12]. We compared the risk factors for CHD and CACS between the GGT quartiles. The relationship between GGT and CAC, age, male sex, diabetes mellitus, hypertension, smoking status, serum creatinine, fasting blood glucose, CRP, calcium, uric acid, total cholesterol, LDL cholesterol and HDL cholesterol levels and average 10-year total risk of Framingham risk score were examined by Pearson's correlation analyses.

A multivariable logistic regression model was used to examine the probability of CAC score ≥ 1. The alternative test hypothesis was built as two-sided for each statistical analysis. The tests were independent and so the experimentwise Type I error does not exceed 0.05 alpha levels. Significant univariate variables with $P<0.05$ were included in the multiple logistic regression analysis for odds ratios and 95% confidence intervals. Values for *P* less than 0.05 were considered statistically significant for all tests.

3. Results

Baseline clinical and laboratory characteristics of patients according to GGT quartiles were shown in Table 1. Participants in higher GGT quartiles had elevated CAC score ($P<0.001$) (Fig. 1). Patients in Quartile 1 (GGT 1–19 U/L) had a mean CAC score of 4.8 ± 12.6 (range: 0–48.3, median: 0). Patients in Quartile 2 (GGT 20–25 U/L) had a mean CAC score of 29.0 ± 51.7 (range: 0–202, median: 25.7). Patients in Quartile 3 (GGT 26–37 U/L) had a mean CAC score of 56.7 ± 119.3 (range: 3.1–674.0, median: 45.6). Patients in Quartile 4 (GGT 38–62 U/L) had a mean CAC score of 86.8 ± 192.8 (range: 20.6–1100, median: 93.7).

Participants in higher GGT quartiles were predominantly males and were more likely to be smoking, and have elevated total cholesterol, LDL, uric acid, fasting blood glucose, CRP levels and 10-year total risk and low HDL levels (Table 1; $P<0.05$ for quartile trend).

Positive correlations were found between log GGT and CAC ($r=0.233$, $P<0.001$), male gender ($r=0.350$, $P<0.001$), smoking status ($r=0.207$, $P=0.001$), CRP ($r=0.222$, $P=0.001$), uric acid ($r=0.387$, $P<0.001$), total cholesterol ($r=0.125$, $P=0.045$) and average 10-year total risk of Framingham risk score ($r=0.147$, $P=0.016$) (Table 2). Negative correlations were found between log GGT and HDL ($r=-0.307$, $P<0.001$) (Table 2). No correlations were found between log GGT and age, diabetes mellitus, hypertension, fasting blood glucose, LDL, creatinine and calcium.

Patients were stratified into 2 groups according to presence of CAC: CAC score = 0 and CAC score ≥ 1 to show if GGT is an independent predictor of CAC. In the univariate analysis, age, gender, hypertension, smoking, fasting blood glucose levels, GGT, serum uric acid levels and average 10-year total risk of Framingham risk score were significantly correlated with presence of CAC (Table 3). In the multivariate analysis

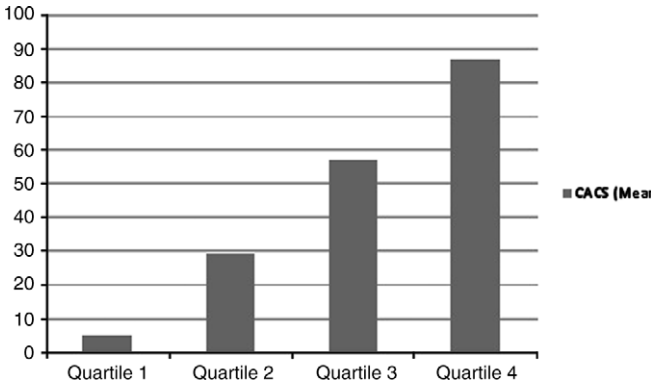

Fig. 1. Relation between Coronary Artery Calcium score and GGT quartiles.