

The Relationship Between Gamma-Glutamyl Transferase Levels and Coronary Plaque Burdens and Plaque Structures in Young Adults With Coronary Atherosclerosis

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ABSTRACT

Background: Elevated gamma-glutamyl transferase (GGT) levels have been demonstrated to be associated with poor prognoses in patients with coronary artery disease. Coronary computed tomography angiography (CCTA) is a noninvasive imaging modality that may differentiate the structure of coronary plaques. Elevated plaque burdens and noncalcified plaques, detected by CCTA, are important predictors of atherosclerosis in young adults.

Hypothesis: The present study investigated the possible relationship between GGT levels and coronary plaque burdens/structures in young adults with coronary atherosclerosis.

Methods: CCTA images of 259 subjects were retrospectively examined, and GGT levels were compared between patients with coronary plaques and individuals with normal coronary arteries. Coronary plaques, detected by CCTA, were categorized as noncalcified, calcified, and mixed, according to their structures. The significant independent predictors of coronary atherosclerosis were also analyzed using multivariate logistic regression analysis.

Results: GGT levels were significantly higher in patients with coronary plaque formation than in controls (35.7 ± 14.7 vs 19.6 ± 10.0 U/L; $P < 0.001$). GGT levels were also positively correlated with the number of plaques; presence of noncalcified plaques; and levels of high-sensitivity C-reactive protein (hs-CRP), hemoglobin A_{1c}, uric acid, and triglycerides. Moreover, smoking and levels of GGT, hs-CRP, uric acid, and low high-density lipoprotein cholesterol were independent predictors of coronary atherosclerosis.

Conclusions: GGT is an inexpensive and readily available marker that provides additional risk stratification beyond that provided by conventional risk factors for predicting coronary plaque burdens and plaque structures in young adults.

Introduction

Globally, cardiovascular diseases are among the leading causes of morbidity and mortality. The incidence of symptomatic coronary artery disease (CAD) at a young age is low, involving approximately 3% of all CAD cases.¹ Although CAD is rarely seen in adults younger than 45 years of age, identification of risk factors and early diagnoses

are important, as symptoms may indicate unexpected and serious consequences. Atherosclerotic changes are well-known to begin early in life, and the presence of additional risk factors, such as a genetic predisposition, obesity, dyslipidemia, high blood pressure, and smoking may accelerate the disease progress, resulting in acute coronary syndromes.²

Noninvasive imaging modalities, such as carotid intima-media thickness measurements and coronary artery calcium (CAC) score calculations, have gained attention in the

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diagnosis of subclinical atherosclerosis and risk predictions for future adverse cardiovascular events.^{3,4} Coronary computed tomography (CT) angiography (CCTA), which is a noninvasive imaging technique with a high sensitivity and specificity for the diagnosis of CAD, may provide valuable information about an individual's plaque burden and plaque structure.^{5–8}

Gamma-glutamyl transferase (GGT) measurement is a second-generation hepatic function test that is used as an indicator of alcohol ingestion, hepatic inflammation/infection, and fatty liver disease. GGT levels are also associated with the presence and severity of atherosclerosis, and also may be a risk factor for future cardiovascular events.^{9–12} However, the exact pathophysiological relationship between coronary atherosclerosis and GGT remains unclear, especially in young adults.

To our knowledge, there are no studies regarding the association between GGT levels and coronary plaque burdens/structures in young adults with coronary atherosclerosis. This study investigated this relationship using CCTA in patients under 45 years old.

Methods

Patient Selection

This single-center, retrospective, case-control study was conducted at a tertiary heart center. The CCTA examinations performed between January 2011 and November 2013 were screened, and 410 patients under 45 years of age were identified. The indications for CCTA in the study population were patients with atypical chest pain, but at intermediate risk for CAD; inconclusive or uninterpretable stress test results; evaluation of suspected coronary anomalies; and exclusion of significant CAD before noncoronary cardiac surgery. The exclusion criteria were prior diagnosis of CAD, coronary revascularization procedures, heart failure, valvular heart disease, aortic aneurysms, renal dysfunction, hepatitis B or C infection, other known liver diseases, hemolytic disorders, acute/chronic inflammatory conditions, neoplastic diseases, use of alcohol (all alcohol drinkers) and hepatotoxic drugs, and missing laboratory parameters. In addition, abdominal ultrasonography was performed to exclude the presence of any underlying liver disease, including hepatosteatois. After the initial evaluation, 151 subjects were excluded from further analysis. Finally, a total of 259 patients were included in the study (Figure 1). Demographic information, cardiovascular risk factors (age, family history, smoking habit, hyperlipidemia, body mass index, hypertension, and diabetes mellitus) were recorded following a systematic review of the hospital records. Missing variables were obtained by telephone interviews with the patient and/or relatives. Informed consent was obtained from each subject, and the study protocol was approved by the local ethics committee.

Definitions

The data regarding the daily smoking habits of current smokers were obtained. Past smokers, included in the smoker category, were defined as those who had abstained from smoking for >3 months at the time of the examination.

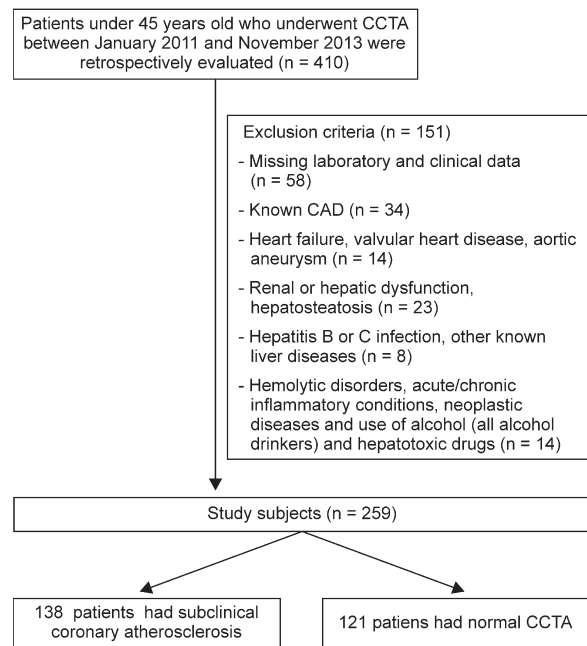


Figure 1. Selection of study participants. Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography.

Hypertension was diagnosed if systolic arterial pressure exceeded 140 mm Hg and/or diastolic arterial pressure exceeded 90 mm Hg, or if the patient was using antihypertensive drugs.¹³ Diabetes mellitus was diagnosed if fasting glucose levels exceeded 126 mg/dL or if the patient used prescribed glucose-lowering agents.¹⁴ Hyperlipidemia was defined as total serum cholesterol levels >240 mg/dL, low-density lipoprotein (LDL)-cholesterol >130 mg/dL, or serum triglycerides >180 mg/dL, or if the patient used lipid-lowering drugs.¹⁵

CCTA Examination

CCTA images were obtained using a dual-source CT system (Definition Flash; Siemens Medical Solutions, Forchheim, Germany) with 280 ms of rotation time, 2 × 128 slices, a pitch of 3.4, and triggering at 60% of the R-R interval. The tube current was set at 180–300 mAs, and a 0.6-mm slice collimation was achieved. Nonionic contrast material (Iomeron® 400 mg/mL; Bracco, Milan, Italy) at a dose of 80 to 100 mL was administered at a rate of 5 mL/s, with a dual-head power injector attached to an 18-gauge needle positioned in an antecubital vein. The bolus tracking technique was used and images were obtained during a single, 6-second breath-hold.

Image Analysis

Two experienced radiologists, blinded to the clinical properties of the subjects, analyzed the scans on a 3-dimensional workstation (Syngo; Siemens Healthcare, Erlangen, Germany). A final diagnosis using multidetector CT was achieved by consensus. The radiologists analyzed the characteristics of the stenosis and the number of plaques/segment based on the modified American

Heart Association classification.^{16,17} Stenosis >50% was considered significant and >75% was defined as severe.

Plaques were defined as 1-mm² structures, within or adjacent to a vessel lumen, which could be clearly distinguished from the lumen and the surrounding pericardial tissue. Coronary plaques were classified as noncalcified, calcified, and mixed according to their structure. Plaques without any calcification were defined as noncalcified, plaques with >50% of the plaque area occupied by calcified tissue (density ≥ 130 Hounsfield in native scans) were defined as calcified, and plaques with <50% calcium were defined as a mixed type.¹⁶ The plaque burden was calculated as the sum of the atherosclerotic segments (1 point for each) in the coronary arteries, which were divided into 15 segments.¹⁷

Laboratory Analyses

Venous blood samples were drawn for the analysis of hemoglobin A1c (HbA1c), high-sensitivity C-reactive protein (hs-CRP), total cholesterol, triglycerides, uric acid, and serum creatinine levels after a minimum 12-hour fasting period (Cobas C501 Autoanalyzer; Roche Diagnostics, Mannheim, Germany). Serum creatinine levels were measured using the alkaline picrate (Jaffe) method, and hs-CRP was analyzed turbidimetrically. Serum GGT levels were measured using an enzymatic colorimetric test with a Roche/Cobas analyser at 37°C and L-gamma-glutamyl-3-carboxy-4-nitroanilide was used as a substrate (Cobas C501 Autoanalyzer; Roche Diagnostics). The normal GGT reference value for a healthy individual was 7 to 49 U/L in our laboratory.

Statistical Analysis

Descriptive statistics were expressed as numbers (%) for categorical variables and as mean, median, standard deviation, minimum, and maximum for numerical variables. The normal distribution of continuous variables was checked using the Kolmogorov-Smirnov test. Differences between patients and controls were evaluated using 2-sample *t* tests, analysis of variance, and the Mann-Whitney *U* test, as appropriate. A χ^2 test was used to compare independent categorical variables. Relationships between numerical variables were identified using Pearson or Spearman correlation tests, and a receiver operator characteristic (ROC) curve analysis was used to determine GGT cutoff values for the diagnosis of coronary atherosclerosis. In addition, backward, stepwise, multivariate logistic regression analyses, which included variables with *P* values <0.10 in the univariate analysis, were performed to identify the independent predictors of coronary atherosclerosis; a *P* value <0.05 was considered statistically significant. Data were analyzed using the Statistical Package for the Social Sciences version 16.0 (SPSS, Inc., Chicago, IL).

Results

The present study included 138 patients with coronary atherosclerosis (mean age, 41.6 ± 3.0 years; 72.5% male) and 121 control subjects (mean age, 41.9 ± 3.3 years; 64.5% male). Baseline demographic, clinical, and laboratory

characteristics of the study groups are summarized in Table 1. Age, gender, body mass index, and family histories of CAD were not statistically different between the 2 groups. However, the frequencies of smoking, diabetes mellitus, and hypertension were higher in the CAD group than in the controls. In the CAD patients, the mean number of diseased vessels per patient was 1.7 ± 0.8, and the total number of plaques was 2.1 ± 1.4. Although the number of noncalcified plaques was highest (1.2 ± 1.0), the numbers of calcified and mixed types were similar (0.8 ± 0.5 and 0.7 ± 0.4, respectively).

Plasma creatinine, uric acid, HbA1c, hs-CRP, total cholesterol, LDL cholesterol, and triglyceride levels were significantly higher in the patient group than in the controls (*P* = 0.01, for each comparison). However, the high-density lipoprotein (HDL) cholesterol levels were significantly lower in the patient group (*P* = 0.01). The mean GGT level was significantly higher in the patient group than in the control group (35.7 ± 14.7 U/L vs 19.6 ± 10.0 U/L; *P* = 0.01). In the subgroup analysis, the GGT and hs-CRP levels were significantly higher in subjects with ≥ 3 plaques (*n* = 38) compared with those with <3 plaques (*n* = 100) (43.1 ± 13.1 vs 32.9 ± 14.4 U/L, *P* = 0.01; and 2.03 ± 0.76 vs 1.67 ± 0.67 mg/L, *P* = 0.01; respectively). When the relationship between the GGT levels and coronary plaque structure was investigated in subjects having only 1 coronary artery plaque (*n* = 61), the GGT level was not statistically different between the noncalcified (*n* = 36), calcified (*n* = 16), and mixed (*n* = 9) subgroups (31.5 ± 16.1 vs 30.9 ± 13.2 vs 34.7 ± 18.5 U/L, respectively; *P* = 0.82).

Twenty-three subjects (16.6%) from the CAD group and 14 subjects (11.6%) from the control group were administered statins (*P* = 0.26); 5 subjects (3.6%) from the CAD group and 2 subjects from the control group (1.7%) were using fenofibrate therapy (*P* = 0.45). In the subgroup analyses, when the subjects undergoing statin or fibrate treatment were excluded, GGT levels were still higher in the CAD group than in the control group (34.9 ± 14.5 U/L vs 20.1 ± 10.4 U/L, *P* = 0.01).

The discriminatory value of GGT levels for coronary atherosclerosis was assessed by ROC curve analysis and revealed a sensitivity (71.7%), specificity (80.2%), positive predictive value (71.3%), and negative predictive value (80.5%) of a cutoff value of >26 U/L (area under the curve, 0.823; 95% confidence interval [CI]: 0.773-0.874; *P* < 0.001).

In a univariate correlation analysis, the GGT level was positively correlated with the number of diseased vessels and the total number of plaques and levels of hs-CRP, HbA1c, uric acid, and triglycerides, and negatively correlated with HDL-cholesterol levels (Table 2). Moreover, the number of diseased vessels and the total number of coronary plaques were positively correlated with the hs-CRP and HbA1c levels (*P* = 0.01, for each correlation).

In a univariate regression analysis, diabetes mellitus; hypertension; smoking; and elevated levels of GGT, hs-CRP, uric acid, creatinine, total cholesterol, LDL-cholesterol, and triglycerides were significantly associated with coronary atherosclerosis, as were decreased HDL-cholesterol levels (Table 3). Smoking and levels of GGT, hs-CRP, uric acid, HDL-cholesterol, and triglycerides were independent

Table 1. Baseline Demographic, Clinical, and Laboratory Characteristics of the Study Groups

	Patients, n = 138	Controls, n = 121	P
Age, y	41.6 ± 3.0	41.9 ± 3.3	0.20
Gender			
Male, n (%)	100 (72.5)	78 (64.5)	0.17
Female, n (%)	38 (27.5)	43 (35.5)	
BMI, kg/m ²	30.03 ± 4.84	28.78 ± 3.95	0.10
Family history, n (%)	54 (39.1)	57 (47.1)	0.20
Smoking, n (%)	98 (71.4)	38 (31.4)	0.01
Diabetes mellitus, n (%)	32 (23.2)	15 (12.4)	0.02
Hypertension, n (%)	56 (40.6)	32 (26.4)	0.02
Hyperlipidemia, n (%)	58 (42)	30 (24.8)	0.01
CCTA findings			
No. of diseased vessels	1.7 ± 0.8	—	—
No. of plaques	2.1 ± 1.4	—	—
Distribution of plaques			
Calcified type	0.8 ± 0.5	—	—
Noncalcified type	1.2 ± 1.0	—	—
Mixed type	0.7 ± 0.4	—	—
Laboratory findings			
Creatinine, mg/dL	0.71 ± 0.13	0.68 ± 0.16	0.01
Total cholesterol, mg/dL	216.5 ± 43.5	200.2 ± 39.3	0.01
LDL-cholesterol, mg/dL	144.6 ± 40.6	129.8 ± 35.1	0.01
HDL-cholesterol, mg/dL	34.8 ± 6.6	44.2 ± 11.6	0.01
Triglyceride	187.6 ± 123.6	140.8 ± 90.1	0.01
Uric acid, mg/dL	5.8 ± 1.2	4.7 ± 1.07	0.01
HbA1c, %	6.2 ± 1.3	5.8 ± 0.6	0.01
hs-CRP, mg/dL	1.78 ± 0.72	1.04 ± 0.51	0.01
GGT, U/L	35.7 ± 14.7	19.6 ± 10.0	0.01

Abbreviations: BMI, body mass index; CCTA, coronary computed tomography angiography; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

Values are presented as means ± standard deviation or number (%), as appropriate.

predictors of coronary atherosclerosis, after adjusting for other risk factors (Table 4).

Discussion

The main findings of the present study were that (1) GGT levels were significantly higher in individuals with coronary atherosclerosis under 45-years-old; (2) GGT levels correlated with the total number of coronary plaques and

Table 2. The Correlation Analysis Between Gamma-Glutamyl Transferase Levels and Coronary Artery Disease Risk Factors

	r	P
No. of diseased vessels	0.324	0.01
No. of plaques	0.335	0.01
hs-CRP	0.572	0.01
HbA1c	0.199	0.02
Uric acid	0.321	0.01
Total cholesterol	0.069	0.42
LDL-cholesterol	0.025	0.77
HDL-cholesterol	-0.383	0.01
Triglyceride	0.271	0.01

Abbreviations: HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

Table 3. Univariate Analysis for Predictors of Coronary Atherosclerosis

	OR	CI	P
Gender	1.451	0.856-2.458	0.167
Age	1.092	0.995-1.200	0.065
Diabetes mellitus	2.13	1.092-4.168	0.027
Hypertension	1.899	1.120-3.220	0.017
Smoking	5.531	3.245-9.106	<0.001
GGT	1.110	1.080-1.140	<0.001
hs-CRP	9.076	4.904-16.797	<0.001
Creatinine	5.627	0.999-31.685	0.050
Uric acid	2.382	1.815-3.127	<0.001
Total cholesterol	1.010	1.003-1.016	0.002
LDL-cholesterol	1.011	1.004-1.018	0.003
HDL-cholesterol	0.885	0.857-0.919	<0.001
Triglyceride	1.005	1.002-1.008	0.001

Abbreviations: CI, confidence interval; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; OR, odds ratio.

were highest in subjects with ≥3 plaques; and (3) smoking and levels of GGT, hs-CRP, uric acid, HDL-cholesterol, and triglycerides were independent predictors of coronary atherosclerosis. These findings indicated that elevated GGT levels may implicate the presence of atherosclerotic changes and may suggest risk beyond that described by well-defined cardiovascular risk factors.

GGT measurements are low-cost, simple, and highly sensitive indicators that provide an index of hepatobiliary dysfunction. The relationship between high GGT levels with well-known cardiovascular risk factors, such as obesity, high blood pressure, unfavorable plasma lipid profiles, diabetes

Table 4. Multivariate Logistic Regression Analysis for Independent Predictors of Coronary Atherosclerosis

	OR	CI	P
Smoking	3.027	1.738-6.651	0.006
GGT	1.056	1.015-1.098	0.006
hs-CRP	4.843	2.004-11.705	<0.001
Uric acid	1.894	1.270-2.825	0.002
HDL-cholesterol	0.915	0.866-0.967	0.002

Abbreviations: CI, confidence interval; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio.

or insulin resistance, and decreased physical activity have been reported in previous studies.^{18–21} Additionally, the prognostic value of raised GGT levels has been presented in patients with cardiovascular disease.²² In this study, GGT levels were correlated with plaque burden and structure, as detected by CCTA, in patients without established CAD. Moreover, elevated GGT levels were significant independent predictors of coronary atherosclerosis in young adults.

GGT activity has been detected in the atheromatous plaques of the carotid and coronary arteries, where it colocalizes with oxidized LDL.²³ Serum GGT, within its high reference range, is an early and sensitive enzyme related to oxidative stress and plays a pivotal role in the pathogenesis of atherosclerosis.²⁴ The degradation of the extracellular antioxidant, glutathione, by GGT enhances the body's pro-oxidant status and the production of reactive oxygen species that result in atherosclerotic changes.²⁵ Additionally, GGT catalysis of LDL oxidation, in atherosclerotic plaques, may contribute to plaque evolution and instability.^{23–26} In support of these mechanisms, GGT levels were significantly correlated with inflammatory marker levels and the total plaque numbers in young adults with coronary atherosclerosis. The correlation between GGT levels and subclinical atherosclerosis has also been shown using imaging modalities, such as CAC and intima-media thickness measurements.^{27–29} Lee et al conducted a study in 14 439 adults without known CAD and reported an independent association between increased serum GGT levels and the frequency of CAC.²⁹ However, Bian et al found that GGT levels were only associated with the incidence of CAC scores (>100) in women.³⁰ Even though the exact relationship between GGT levels and atherosclerosis has not been fully elucidated, chronic inflammation, oxidative stress, and lipid metabolism abnormalities may contribute to the mechanism.

Nevertheless, a CAC score of 0 does not guarantee the absence of coronary atherosclerosis; CCTA imaging may show noncalcified plaques (NCPs) in patients without calcium deposition.^{31–33} In 12.4% of patients with a CAC score of 0, coronary plaques were detected, and in 1.6% of the cases the lesions were obstructive.³⁴ Jin et al reported the rate of subclinical atherosclerosis in asymptomatic young adults to be 9.4%.³⁵ Concordant with our findings, NCPs were the most frequent type of coronary plaque

and were independent risk factors for subclinical coronary atherosclerosis in young adults in their study. Thus, in patients <45 years old, especially those with multiple risk factors, coronary atherosclerosis develops as NCPs. However, in our study, as more than 1 type of plaque existed concomitantly in the same subject, we could not find a statistically significant difference between the different types of plaques. However, as NCPs were the most frequent type of plaque, and GGT levels were significantly correlated with the number of plaques, we may assume that GGT levels may be correlated with the presence of NCPs. Furthermore, the presence of NCPs, detected by CCTA, was associated with higher numbers of CAD risk factors (particularly smoking, obesity, and hypertension) in patients with 0 CACs.³³ Unstable NCPs cause positive arterial remodeling, which alters flow dynamics, heightens the surface tension on the plaque surface, and raises the vulnerability of coronary plaques, resulting in plaque rupture and acute coronary syndromes. Yoo et al highlighted the importance of NCPs, detected by CCTA, in asymptomatic patients with low CAC scores, and emphasized that CCTA was a beneficial technique for CAD risk stratification.³⁶ Thus, the establishment of new parameters associated with the presence of NCPs may have clinical importance in the prevention of cardiovascular events in young adults. In our study, the correlation of serum GGT levels with coronary atherosclerosis was demonstrated in terms of plaque burden/structure rather than only CAC scoring, which provides more accurate and reliable information about the severity of coronary artery atherosclerosis in young adults.

Study Limitations

There are some limitations associated with the present study. First, this study involved a single center and was retrospective in design. Second, the absence of follow-up data describing future cardiovascular events meant that the prognostic value of GGT levels was not evaluated. Third, the study participants were Turkish, so the results may not be applicable to other ethnic groups or populations.

Conclusion

We demonstrated a significant relationship between serum GGT levels and the total number of coronary plaques and the plaque structures, as detected by CCTA. In addition, GGT levels were found to be significant independent predictors of coronary atherosclerosis in young adults. GGT measurements are accurate, readily available, and cost-effective tests that may help identify young adults potentially at risk of coronary atherosclerosis who may require early CAD intervention.

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