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Association between serum gamma-glutamyltransferase and the progression of coronary artery calcification

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ABSTRACT

Background: Elevated serum gamma-glutamyltransferase (GGT) has been demonstrated to be associated with coronary artery calcification (CAC). CAC progression is an important marker of atherosclerosis and correlates with future cardiovascular risk. However, there is a lack of research that directly examines the association between serum GGT and CAC progression. The aim of this study was to elucidate the association between serum GGT activity and CAC progression.
Methods: We enrolled 1246 asymptomatic participants who underwent repeated CAC score measurement during routine health examinations. To eliminate the dependence of the inter scan variability on the baseline CAC scores, square root-transformed CAC scores were used to analyze CAC progression. In addition, the annualized rate of change in CAC scores was computed.
Results: Serum GGT activities were significantly higher in "progressors" than "nonprogressors". The prevalence of progression increased with the GGT tertile (11.9%, 20.1% and 27.9% in the 1st, 2nd, and 3rd GGT tertiles, respectively; $p < 0.001$). In the multivariate logistic regression analysis, the odds ratio (95% confidence interval) for CAC score progression was 1.85 (1.14–3.00) in the highest GGT tertile group. By multivariate linear regression analysis, baseline serum GGT activity demonstrated a positive association with the annualized change in CAC score ($\beta = 0.002$; $p = 0.006$) after adjusting for cardiovascular risk factors.
Conclusion: Elevated serum GGT levels are independently associated with CAC progression. Serum GGT levels may be a potential biomarker of future coronary atherosclerosis and prognosis.

1. Introduction

Serum gamma-glutamyltransferase (GGT) is a commonly used indicator of liver or biliary tract disease and alcohol consumption [1]. GGT is also involved in the pathogenesis of cardiovascular diseases (CVD), especially coronary heart disease (CHD) [2]. Furthermore, the prognosis of CVD may be predicted by increasing GGT levels [3,4]. Although the role of GGT in CVD is partly explained by its correlation with conventional cardiovascular risk factors such as diabetes [5], dyslipidemia [6], and metabolic syndrome [7], irrespective of alcohol consumption, the exact mechanism linking GGT and CVD remains still unclear.

Noncontrast multi-detector computed tomography (MDCT) is a noninvasive, reproducible, and rapid imaging technique with a high sensitivity and specificity for diagnosing CHD [8,9]. The coronary artery calcification (CAC) score, as measured by MDCT, reflects the overall coronary plaque burden, and a high CAC score is independently and incrementally predictive of future coronary events and prognosis [10]. Moreover, recent studies show that CAC score progression is significantly related to an increased risk of future CVD events and all-cause mortality [8,11]. Because atherosclerosis is a dynamic process, CAC progression is a better mirror of the activity of atherosclerosis progression and makes it possible to predict the

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risk of CVD events and prognosis in comparison to baseline CAC [11,12].

Only a few studies to date have shown that serum GGT activity is independently and positively associated with CAC score [13,14]. However, these studies mostly included Western populations and were cross-sectionally designed [13,14], so the temporal relationship between exposure and outcomes could not be assessed [15]. In light of these findings, we designed our current study to investigate the association between serum GGT activity and CAC progression in an asymptomatic, middle-aged, Korean population.

2. Methods

2.1. Study population

The study population consisted of 7300 participants who underwent baseline coronary computed tomography angiography (CCTA) using the 64-slice MDCT scanner during routine health evaluations at Asan Medical Center (AMC, Seoul, Republic of Korea) between January 2007 and June 2011. Among these 7300 participants, repeated CCTA was performed on 1591 participants through December 2014. This analysis also used data obtained using in-person follow-up examinations after the baseline examinations. Each participant completed a questionnaire that listed a history of previous medical and/or surgical diseases, medications, and drinking and smoking habits. Drinking habits were categorized in terms of frequency per week (i.e., ≤1 times/week or ≥2 times/week [moderate drinker]), smoking habits as noncurrent or current, and exercise habits as frequency per week (i.e., ≤2 times/week or ≥3 times/week [physically active]) [16].

CVD history was based on each participant's history of physician-diagnosed angina, myocardial infarction, and/or cerebrovascular accidents. Participants with diabetes were defined as those with a fasting plasma glucose (FPG) level of ≥7.0 mmol/L and/or HbA1c level ≥6.5% [17]. In addition, participants who reported the use of antidiabetic medications on a self-report questionnaire were considered to have diabetes [18]. Hypertension was defined as systolic and/or diastolic blood pressure (BP) ≥140/90 mmHg or receiving antihypertensive medications.

Framingham risk score (FRS) was calculated to estimate the 10-year total CHD risk of an individual [19]. Subjects were categorized according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines updated in 2004 [20] as: 1) high-risk (CHD risk equivalents or CHD risk factors ≥2 and 10-year risk for CHD >20%) with a low-density lipoprotein-cholesterol (LDL-C) level of ≥2.6 mmol/L, 2) moderately high-risk (CHD risk factors ≥2 and 10-year risk for CHD 10–20%) with an LDL-C level of ≥3.4 mmol/L, 3) moderate-risk (CHD risk factors ≥2 and 10-year risk for CHD <10%) with an LDL-C level of ≥4.1 mmol/L, and 4) lower-risk (0–1 CHD risk factors) with an LDL-C level of ≥4.9 mmol/L. Diabetes was regarded as a CHD-risk equivalent [20]. CHD risk factors include smoking, hypertension, low high-density lipoprotein-cholesterol (HDL-C) (i.e., <1.0 mmol/L), family history of premature CHD (i.e., CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥45 years; women ≥55 years) [20].

We excluded participants with a history of CVD at baseline examinations (n = 95), as well as the participants receiving statins (n = 238). Participants who underwent percutaneous coronary intervention (n = 8) or coronary arterial bypass surgery (n = 3) after the initial examinations were also excluded. Finally, subjects that were not between the ages of 20 and 79 years were excluded (n = 3). Some participants met more than 2 criteria. After excluding ineligible subjects, 1246 subjects with a mean age of 54.2 years (range = 33–79 years) were enrolled in our final study population. All participants provided written informed consent. This study was approved by the institutional review board of AMC.

2.2. Clinical and laboratory measurements

Height and weight were obtained while the participants wore light clothing without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Waist circumference (WC) (in cm) was measured midway between the costal margin and the iliac crest at the end of a normal expiration. BP was measured on the right arm after resting ≥5 min using an automatic manometer with an appropriate cuff size. After overnight fasting, early-morning blood samples were drawn from the antecubital vein into vacuum tubes and subsequently analyzed by the central, certified laboratory at AMC. Measurements included the concentrations of fasting glucose, insulin, high-sensitivity C-reactive protein (hsCRP), several lipid parameters, and liver enzymes.

Fasting total cholesterol, HDL-C, LDL-C, triglycerides (TG), uric acid, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured using the enzymatic colorimetric method on the Toshiba 200FR Neo analyzer (Toshiba Medical System Co., Ltd., Tokyo, Japan). GGT was measured using the L-γ-glutamyl-p-nitroanilide method (Toshiba). HsCRP and FPG were measured using the immunoturbidimetric method (Toshiba) and the enzymatic colorimetric method on the Toshiba 200 FR autoanalyzer (Toshiba), respectively. Ion-exchange high-performance liquid chromatography (Bio-Rad Laboratories, Inc., Hercules, CA) was used to measure the HbA1c levels. The intra- and inter-assay coefficients of variation (CVs) of these analyses were consistently <3.5%. All enzyme activities were measured at 37 °C.

2.3. Using MDCT to assess the CAC score

MDCT examinations were performed by using either 64-slice, single-source, computed tomography (CT) (LightSpeed VCT; GE, Milwaukee, WI) or dual-source CT (Somatom Definition or Somatom Definition Flash; Siemens, Erlangen, Germany), as previously described [21]. The CAC score was calculated using an automated, computerized, software program using the Agatston scoring method [22], and participants were categorized according to the cut-off points used by Greenland et al. (i.e., none, 0; mild, 1–100; moderate to severe, 101–300; severe >300) [23].

2.4. Estimating changes in the CAC score

To eliminate the dependence of residual interscan variability on the baseline CAC score, square root transformation of the CAC score was performed prior to estimating CAC progression. Two measures of progression were used. In the first set of analyses, participants were classified as “progressors” or “nonprogressors”. Using the data published by Hokanson et al., progressors were defined as individuals with a difference of ≥2.5 units between the baseline and final square root of their CAC scores (i.e., the “SQRT method” [the square root-transformed difference]) [11,24,25]. To put it differently, a change of <2.5 units between the baseline and final square root the CAC score was considered within the margin of error for estimating the CAC score using MDCT, and, thus, attributed to interscan variability; such participants were classified as non-progressors [11,24,25]. In a second set of analyses, the annualized rate of change was computed [(final square root CAC score−baseline square root CAC score)/(follow-up interval in years)] and used as a continuous variable [25].