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Gamma-glutamyltransferase and cardiovascular mortality in Korean adults: A cohort study

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ABSTRACT

Background and aims: Insufficient evidence has been reported on the associations between gamma-glutamyltransferase (GGT) and cardiovascular disease (CVD) mortality from studies with an adequate number of participants.

Methods: 512,990 Korean adults who participated in routine health examinations during the period 2002–2003 were followed up until 2013. Hazard ratios (HRs) were calculated after adjusting for potential confounders.

Results: Each 1-unit higher natural-log-transformed GGT (Log_eGGT) level was associated with approximately 30–50% higher mortality risk of CVD (HR = 1.31): hypertensive diseases (HR = 1.31), ischemic heart diseases (IHD, HR = 1.29), total stroke (HR = 1.29), acute myocardial infarction (HR = 1.30), chronic IHD (HR = 1.27), heart failure (HR = 1.48), hemorrhagic stroke (HR = 1.42), and ischemic stroke (HR = 1.27). The associations with CVD mortality did not vary by sex, or alcohol use, whereas they were stronger in younger (<60 years), non-hypertensive (systolic blood pressure [SBP] <140 mmHg), physically more active, normal-weight (body mass index<25 kg/m^2), and normocholesterolemic (total cholesterol <200 mg/dL) adults than in their respective counterparts. Adding Log_eGGT to prediction models for CVD mortality increased AUC value (0.0020, $p < 0.001$), especially in persons aged <60 years (0.0055), with SBP <140 mmHg (0.0030), and with both age <60 years and SBP <140 mmHg (0.0086).

Conclusions: Higher GGT significantly increased the risk of mortality due to CVD and its subtypes. The relative risks were greater in subjects with younger age, no hypertension, more physical activity, normal weight, and normocholesterolemia than in their respective counterparts. In the general population, adding GGT to conventional CVD risk factors may improve the prediction of CVD mortality, especially in subjects younger than 60 years and in those without hypertension.

1. Introduction

Cardiovascular disease (CVD), including ischemic heart disease (IHD) and stroke, is currently the major cause of premature mortality and disability worldwide [1,2]. Several studies have shown that elevated gamma-glutamyltransferase (GGT) activity is associated with higher risk of CVD [3–5], although blood GGT levels have been mainly used as a liver function test and a marker of alcohol ingestion. Blood GGT is suggested to have the potential to be an indicator, or a risk factor, for cardiovascular risk prediction and evaluation [6–8].

The available evidence, however, is not consistent regarding the association of elevated GGT activity with the risk of the leading cause of premature mortality: IHD, particularly acute myocardial infarction (MI) [5,7,9]. Information from prospective studies on the associations between GGT and subcategories of CVD, such as heart failure and hemorrhagic stroke, is lacking [10,11]. It is unclear whether the associations between GGT and CVD differ by risk factors such as age [5,12], sex [13], alcohol intake [4,12], and metabolic

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risk factors. Furthermore, despite some evidence linking GGT and CVD, it remains unclear whether GGT provides additional information on top of known conventional risk factors for the prediction of CVD, considering the existence of strong correlations between GGT and conventional risk factors [12,14].

Through a prospective cohort study that included approximately 513,000 participants, we aimed to examine whether blood GGT levels were associated with the risk of CVD mortality, and whether any such associations varied by individually specific factors such as sex, age, alcohol use, and blood pressure. Additionally, whether blood GGT provides an incremental benefit on top of known risk factors for the prediction of CVD mortality was examined.

2. Materials and methods

2.1. Study population and follow-up

The National Health Insurance Service (NHIS) provides compulsory health insurance that covers 97% of the Korean population [15]. The study cohort (n = 514,795) comprised a 10% random sample of 5.15 million NHIS beneficiaries aged 40–79 years in 2002 who participated in health examinations during the period 2002–2003. A total of 1805 people were excluded due to missing information (n = 1753) on GGT, serum glucose, systolic blood pressure, total cholesterol, and body mass index (BMI) or because they had an extremely high BMI (≥50 kg/m^2, n = 52). For the remaining 512,990 people, follow-up on underlying causes of death until December 31, 2013 was carried out using national death records. The International Classification of Diseases-10th Revision (ICD-10) was used to define death from CVD (I00-I99), and instances of CVD mortality were classified into hypertensive diseases (I10-I13), IHD (I20-I25), acute MI (I21), chronic IHD (I25), other heart diseases (I26-I51), heart failure (I50), total stroke (I60-I69), hemorrhagic stroke (I60-I62), and ischemic stroke (I63). For research in accordance with the conditions documented in Korean laws, health examination data can be provided without specific informed consent from the participants [16]. This study was approved by the Institutional Review Board of Catholic Kwandong University, Republic of Korea. Anonymized data were provided to the authors by the NHIS.

2.2. Data collection

GGT was measured using the method recommended by the International Federation of Clinical Chemistry (IFCC), or using the Szasz method. Fasting serum glucose and total cholesterol were assayed using enzymatic methods [17]. Blood pressure was measured in a seated position using a standard mercury sphygmomanometer. Weight and height were measured to the nearest kilogram and centimeter, respectively [15]. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters (kg/m^2). Smoking history, alcohol use, and known CVD were self-reported via a questionnaire. The health examinations and data collection followed a standard protocol officially documented by the Ministry of Health and Welfare. External quality assessments for clinical chemistry, such as GGT measurements, in hospitals was supervised by the Korean Association of Quality Assurance for Clinical Laboratory, and the quality of assays was regularly assessed [18].

2.3. Statistical analysis

GGT values were categorized into six groups using the 20th (reference), 40th, 60th, 80th, and 90th percentiles as sex-specific cut-points (quintiles, with the top quintile split). The cut-points corresponded to 20, 28, 40, 64, and 98 U/L in men, and 11, 15, 19, 26, and 35 U/L in women. The participants were also categorized into four groups based on quartiles for comparison with other research [19,20]. Natural-log transformed GGT (Log_eGGT) values were also analyzed as a continuous variable.

HRs for CVD mortality were calculated using Cox proportional hazards models stratified by age (years) at baseline (40–44, 45–54, 55–64, 65–74, 75–80) after adjustment for age at baseline (continuous variable within each age group), sex (when applicable), a history of heart disease or stroke (yes or no), smoking status (current smoker, former smoker, never-smoker, or missing information [n = 21,660]), alcohol use (frequency; rarely, 2 days/month to 2 days/week, 3–7 days/week, and missing information [n = 9657]), physical activity (at least once a week; yes or no), beneficiary income status (deciles; below 4 [low income], 4–7, 8–10 [high income]), systolic blood pressure (SBP; mmHg), serum total cholesterol (mg/dL), fasting serum glucose (mg/dL), and BMI (kg/m^2). Dose-response analysis using a restricted cubic spline transformation of Log_eGGT with 4 knots (5th, 35th, 65th, and 95th percentiles) with CVD mortality was done to evaluate the non-linearity of association.

The area under the curve (AUC) values were estimated using Proc Logistic (ROC statement). A prediction model with an AUC value of 1.0 or 0.5 represents a perfect or an uninformative model, respectively. When investigating changes in the AUC upon addition of GGT, a CVD mortality prediction model that included all variables in the fully adjusted analysis was used.

Subgroup analyses were done to examine evidence of differences in HRs according to individually specific characteristics, such as age, sex, and alcohol consumption. An inverse-variance weighted average method was used for the interaction test between subgroups [21]. Subgroup analyses were also used as a sensitivity test.

All *p*-values were 2-sided. All analyses used SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. General characteristics

During 5.3 million person-years of follow-up of 512,990 people (45.8% women), 4647 men and 3114 women died from CVD. At baseline, the mean (standard deviation) age was 53.1 (9.7) years and the mean Log_eGGT level was 3.26 (0.76) U/L (Table 1), with values of 3.59 (0.75) U/L for men and 2.87 (0.56) U/L for women. Subjects with higher GGT values tended to be more likely to be current smokers and to exhibit more frequent alcohol use, and less likely to be elderly (70 or above), than those with lower GGT levels. Higher GGT levels were generally associated with higher SBP, fasting glucose, total cholesterol, and BMI values (Table 1).

3.2. GGT and CVD mortality

Clear dose-response relationships between GGT and CVD mortality were observed in all participants (Fig. 1) and in both sexes (Supplementary Fig. 1 and 2). Compared with the lowest baseline GGT group, the sex-age adjusted HRs for CVD mortality were 1.06, 1.20, 1.32, 1.58, and 1.86 across the other five GGT categories (Fig. 1). After adjustment for age and sex, each 1-unit increase in Log_eGGT was associated with an approximately 35% higher risk of CVD mortality (HR per 1-unit increase in Log_eGGT = 1.35 [95% CI = 1.31–1.39]); and elevations of 33%–42% for deaths from hypertensive diseases, IHD, other heart diseases, and stroke (HRs of 1.42 [1.26–1.59], 1.33 [1.26–1.41], 1.35 [1.25–1.47], and 1.34