Original Article

# Serum Gamma-glutamyl Transferase Concentration Within the Reference Range is Related to the Coronary Heart Disease Risk Prediction in Korean Men: Analysis of the Korea National Health and Nutrition Examination Survey (V-1, 2010 and V-2, 2011)

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## Abstract

**Background:** Limited data exist on the association of serum gamma-glutamyl transferase (GGT) level within the reference range with the increased risk of coronary heart disease (CHD) prediction in men. The study examined the association between serum GGT concentration within the reference range and the CHD risk prediction in Korean men.
**Methods:** The study employed data from Korean National Health and Nutrition Examination Survey (V-1, 2010 and V-2, 2011) where a total of 1301 individuals were analyzed. A 10-year CHD risk prediction was computed using the Framingham Risk Score (FRS) modified by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III).
**Results:** Positive correlations were established between log-transformed GGT concentration and FRS ($r$ = 0.237, $P$ < 0.001). After adjustment of body mass index, the amount of alcohol intake and low-density lipoprotein-cholesterol, the odds ratio (95% confidence interval) for intermediate risk and beyond of 10-year CHD prediction (10-year risk ≥10%) with lowest quartile of participants was 1.21 (0.78–1.87) for second quartiles, 1.39 (0.88–2.21) for third quartiles and 2.03 (1.23–3.34) for highest quartiles.
**Conclusions:** Higher serum GGT within its reference range was significantly correlated with a 10-year CHD risk prediction estimation using NCEP ATP III in Korean men.

**Key words:** Framingham Risk Score; Gamma-glutamyl Transferase; Reference Range

## Introduction

There are various pathophysiologic reasons for coronary heart disease (CHD) including atheroma, also known as atherosclerosis, which is critical for CHD occurrence.[1] Of these, oxidative stress is one of the most significant aspects in the pathogenesis of CHD, which is thought to play an important role in the progression of atherosclerosis.[2,3] Several studies suggest that gamma-glutamyl transferase (GGT) is at the pathophysiological background in the precipitation and progression of atherosclerosis.[4,5]

The GGT is regarded as a biomarker of hepatobiliary disease and alcohol consumption or abuse.[6] However, it has been recently demonstrated that the activity of GGT in serum is a sensitive marker of oxidative stress associated with concomitant risk factors, such as obesity, fatty liver, hypertension, dyslipidemia, diabetes, and metabolic syndrome.[7-9] Serum GGT levels are also related positively to novel cardiovascular risk factors like C-reactive protein (CRP), and fibrinogen.[10] Many studies were executed in order to prove that the higher level of serum GGT within normal range is related to higher incidence of hypertension, diabetes mellitus, fatty liver, and metabolic syndrome, especially in men.[9-14] However, limited data exist on the significance of serum GGT level within the reference range with the increased risk of CHD prediction in men.

This study aimed at determining whether serum GGT within its reference range in Korean men is associated with the risk of CHD prediction. The Framingham Risk Score (FRS) modified by the National Cholesterol Education

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Program (NCEP) Adult Treatment Panel III (ATP III) guidelines from the Korea National Health and Nutrition Examination Surveys (KNHANES) from 2010 to 2011 was employed for computation.

## Methods

### Subjects

The KNHANES has been conducted periodically by the Korea Centers for Disease Control and Prevention since 1998 and provides comprehensive information on health status, health behavior, nutritional status, and sociodemographics in 600 national districts. The cross-sectional analysis used samples containing serum GGT taken from KNHANES data (KNHANES V-1, 2010 and V-2, 2011). About 5932 out of 8983 people were excluded due to missing data on FRS, smoking, or alcohol history. Moreover, approximately 1750 subjects with diabetes mellitus, CHD, hepatobiliary disease, positive tests for antibody to hepatitis B surface antigen, antibody to hepatitis B virus core antigen or anti-hepatitis C virus, and patients taking drugs influencing liver function and lipid-lowering drugs were excluded. Thus, the final sample comprises 1301 subjects. Subjects that had been smoking cigarettes regularly 1-year before the time of survey were considered as current smokers. The weekly alcohol intake was calculated and converted based on grams of ethanol consumed.[15]

### Reference sample

A reference sample constituted by healthy subjects was obtained according to the following inclusion criteria: No smoking, no heavy alcohol intake (<70 g of ethanol per week), and absence of cardiovascular disease, hypertension, diabetes, obesity, renal diseases, metabolic syndrome, and dyslipidemia. The final reference serum GGT was drawn from the population, and reference range between 6 and 65 IU/L, which was a statistical interval representing 95% or 2 standard deviations.

### Methods

Before collection of blood samples, each subject fasted for more than 10 h. After overnight fasting, a venous blood sample was obtained between 08:00 and 10:00 a.m. to measure GGT and fasting blood glucose (FBG), liver enzymes, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol. Serum GGT was assayed by the standard method recommended by the International Federation for Clinical Chemistry using L-F-glutamyl-3-carboxy-4-nitroanilide as substrate with a Toshiba 200FR autoanalyzer. In addition, the FBG, liver enzymes, and lipid levels were assayed using a Toshiba-200FR automatic analyzer (Toshiba Medical Systems, Tokyo, Japan). Blood pressure (BP) was measured using a standard mercury manometer with the participant in a sitting position for 5 min prior to measurement, where the average measurement was recorded. Hypertension was defined as a systolic BP (SBP) ≥140 mmHg or a diastolic BP ≥90 mmHg or by the use of antihypertensive medication. Body mass index (BMI) was calculated as weight (kg) divided by height squared ($m^2$).

### Statistical analyses

Complex sample analysis was employed for KNHANES data for weighting assessment values. The distribution of GGT values and weekly alcohol consumption were right-skewed; therefore, a natural log-transformation was applied. After assessment, the general characteristics were presented, and the study subjects were grouped into quartiles according to levels of serum GGT. Analysis of variance (ANOVA) trend analysis using polynomial contrasts was adapted to perform tests for trends. In order to evaluate the relationship between serum GGT activity within reference range and the individual components of the FRS, Spearman's correlation analysis was employed. The FRS was calculated from the NCEP ATP III algorithm based on six coronary risk factors: Age gender, total cholesterol, HDL-cholesterol, SBP, and smoking habit. Among these factors, age, BP, and cholesterol levels were categorized according to their values. Framingham risk equations were used to predict the risk of developing coronary disease events (myocardial infarction or CHD death) over the next 10-year for adults aged 20 and older without heart disease or diabetes. Participants were divided into three groups: Low risk (<10% risk of developing a CHD event over the next 10-year), intermediate risk (10–20% risk), and high risk (>20% risk). However, the number of high-risk group was so small that it included the high-risk group into intermediate-risk group and beyond. Smoking status was classified as either current smoker or nonsmoker. For analysis relating to serum GGT within reference interval to the intermediate-risk group and beyond, we constructed adjusted logistic regression analyses that considered BMI, weekly alcohol intake, and LDL cholesterol.

The results of group data were expressed as mean ± standard error (SE). The $P < 0.05$ was considered statistically significant. Data were analyzed using PASW SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

## Results

The study subjects were divided into four groups according to the GGT levels. The range of the first-to-fourth quartiles of serum GGT values was 6–13, 14–18, 19–28, and 29–65 IU/L, respectively. The general characteristics of the study participants are shown in Table 1. This study included a total of 1301 subjects. Participants in higher GGT quartiles were older and had more general CHD risk factors such as hypertension, dyslipidemia, more alcohol consumption, and current smoking history. In addition, higher quartiles of serum GGT concentration were significantly associated with increasing trends in Framingham point scores and the risk of 10-year CHD prediction ($P$ for trend <0.05).

The correlation between log-transformed GGT and 10-year CHD risk was $r = 0.237$ ($P < 0.001$) [Table 2]. Log-transformed GGT was also well-correlated with individual risk factor scores including age, smoking, total cholesterol, HDL-cholesterol, and SBP ($P < 0.05$ for all).

**Table 1: The general characteristics of the study subjects according to serum GGT grading**

| Characteristics | GGT grading (*n*) | | | | |
|---|---|---|---|---|---|
| | Q1 (*n* = 350) | Q2 (*n* = 289) | Q3 (*n* = 336) | Q4 (*n* = 326) | *P* for trend |
| Age (years) | 35.22 ± 0.50 | 37.05 ± 0.64 | 41.22 ± 0.61 | 41.26 ± 0.56 | <0.001 |
| BW (kg) | 56.53 ± 0.47 | 61.86 ± 0.57 | 66.00 ± 0.59 | 71.39 ± 0.64 | <0.001 |
| BMI (kg/m$^2$) | 21.55 ± 0.12 | 22.84 ± 0.17 | 23.78 ± 0.16 | 24.93 ± 0.16 | <0.001 |
| WC (cm) | 73.05 ± 0.42 | 77.33 ± 0.45 | 81.19 ± 0.44 | 85.68 ± 0.47 | <0.001 |
| SBP (mmHg) | 109.57 ± 14.60 | 113.12 ± 0.60 | 117.00 ± 0.61 | 121.22 ± 0.72 | <0.001 |
| DBP (mmHg) | 70.95 ± 0.40 | 73.82 ± 0.43 | 77.13 ± 0.48 | 81.03 ± 0.60 | <0.001 |
| Glucose (mg/dl) | 87.18 ± 0.35 | 89.50 ± 0.46 | 92.91 ± 1.05 | 95.99 ± 0.68 | <0.001 |
| Current smoker (%) | 4.57 ± 0.008 | 12.76 ± 0.01 | 24.57 ± 0.01 | 37.72 ± 0.01 | <0.001 |
| Alcohol (g/week) | 14.74 ± 1.49 | 32.22 ± 3.45 | 52.01 ± 3.47 | 83.04 ± 4.90 | <0.001 |
| Total cholesterol (mg/dl) | 173.30 ± 1.61 | 178.30 ± 1.62 | 188.99 ± 1.60 | 196.14 ± 1.66 | <0.001 |
| HDL-C (mg/dl) | 55.36 ± 0.74 | 51.46 ± 0.73 | 47.44 ± 0.87 | 42.75 ± 0.92 | <0.001 |
| LDL-C (mg/dl) | 101.28 ± 1.41 | 108.30 ± 1.46 | 117.14 ± 1.44 | 121.73 ± 1.51 | <0.001 |
| TG (mg/dl) | 83.25 ± 2.02 | 92.94 ± 2.12 | 123.94 ± 3.78 | 165.01 ± 5.82 | <0.001 |
| AST (IU/L) | 16.67 ± 0.29 | 18.33 ± 0.32 | 20.41 ± 0.24 | 23.93 ± 0.43 | <0.001 |
| ALT (IU/L) | 12.05 ± 0.29 | 15.39 ± 0.38 | 19.71 ± 0.39 | 28.80 ± 0.81 | <0.001 |
| Total Framingham point scores | 0.89 ± 0.29 | 2.42 ± 0.36 | 5.78 ± 0.33 | 7.35 ± 0.25 | <0.001 |
| 10-year CHD risk | 0.66 ± 0.08 | 1.47 ± 0.15 | 3.53 ± 0.24 | 5.11 ± 0.22 | <0.001 |

Data are expressed as mean ± SE after data weighting in complex sample analysis. GGT: Gamma-glutamyl transferase; BW: Body weight; BMI: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TG: Total glycerides; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CHD: Coronary heart disease; SE: Standard error; Q1: 1st quartile; Q2: 2nd quartile; Q3: 3rd quartile; Q4: 4th quartile. The amount alcohol consumption calculation formula: 10 g × shots × frequency/week.

**Table 2: The Spearman's rank correlation coefficients relating individual components and total Framingham risk score to log-transformed GGT**

| Variables | Correlation coefficient | *P* |
|---|---|---|
| Age score | 0.124 | <0.001 |
| Total cholesterol score | 0.186 | <0.001 |
| Smoking score | 0.091 | 0.001 |
| HDL-C score | 0.111 | <0.001 |
| SBP score | 0.184 | <0.001 |
| Total Framingham point scores | 0.241 | <0.001 |
| 10-year CHD risk | 0.237 | <0.001 |

GGT: Gamma-glutamyl transferase; HDL-C: High-density lipoprotein cholesterol; SBP: Systolic blood pressure; CHD: Coronary heart disease.

Table 3 shows the odds ratio (*OR*) for intermediate-risk and beyond for CHD in relation to quartiles of serum GGT. The 10-year CHD risk was significantly associated with increasing quartiles of serum GGT (*P* for trend <0.05). Compared with individuals with lowest quartile of serum GGT, the nonadjusted *OR* (95% confidence interval [*CI*]) was 1.18 (0.78–1.78) for the second quartile, 1.42 (0.94 – 2.16) for the third quartile, and 2.77 (1.74 – 4.40) for the highest quartile. After adjustment of BMI, the amount of alcohol intake and LDL cholesterol, the *OR* (95% *CI*) for intermediate risk and beyond of 10-year CHD prediction with lowest quartile of participants was 1.21 (0.78 − 1.87) for second quartiles, 1.39 (0.88 – 2.21) for third quartiles, and 2.03 (1.23 – 3.34) for highest quartiles. In addition, the *OR* for intermediate risk and beyond of 10-year CHD prediction showed an increased tendency as the serum GGT quartile gets greater (*P* for trend <0.05).

In the use of serum GGT as a test variable to predict the presence of intermediate risk beyond a 10-year CHD prediction, a receiver-operating characteristic (ROC) curve was prepared [Figure 1]. The area under the ROC curve was 0.58 (95% *CI*: 0.55–0.61). Based on the ROC curve, the best serum GGT cut-off obtained was ≥28.5 IU/L that predicted the intermediate risk, beyond a 10-year CHD prediction with sensitivity of 58%, specificity of 52%, positive predictive value of 54.7%, and negative predictive value of 55.3%.

## Discussion

We investigated the association between the GGT level in normal range and the possible prevalence of CHD in 10-year, using FRS calculated from the NCEP ATP III algorithm in Korean men. FRS is one of the numbers of scoring systems used to determine an individual's chances of developing CHD. Cardiovascular risk scoring systems presents an estimate of the probability that a person will develop CHD within a given time-frame, usually 10–30 years.

In this study, a higher quartile of serum GGT level, even within the reference range, was found to be significantly related to the elevated risk of CHD which resulted from the calculation of FRS in men. Moreover, this association persisted even after adjusting established cardiovascular risk factors such as LDL-cholesterol and BMI, which were not used in the NECP ATP III and confounding factors like the amount of alcohol intake. The *OR* of a 10-year CHD risk prediction increased in dose-dependent manner with increasing quartiles of serum GGT activity. The best serum GGT cut-off was ≥28.5 IU/L, which predicted

**Table 3: The *OR* of intermediate-risk and beyond for CHD (10-year risk ≥10%) by GGT**

| Model | GGT (*CI*) | | | | |
|---|---|---|---|---|---|
| | Q1 ($n$ = 350) | Q2 ($n$ = 289) | Q3 ($n$ = 336) | Q4 ($n$ = 326) | *P* for trend |
| Model 1 | 1.00 | 1.18 (0.78–1.78) | 1.42 (0.94–2.16) | 2.77 (1.74–4.40) | <0.001 |
| Model 2 | 1.00 | 1.21 (0.78–1.87) | 1.39 (0.88–2.21) | 2.03 (1.23–3.34) | <0.001 |

Multivariate logistic regression model was used after data weighting in complex sample analysis. Model 1: Unadjusted; Model 2: After adjustment for BMI, the amount of alcohol intake and LDL-C. GGT: Gamma-glutamyl transferase; CHD: Coronary heart disease; *OR*: Odds ratio; *CI*: Confidence interval; BMI: Body mass index; LDL-C: Low-density lipoprotein cholesterol; Q1: 1st quartile; Q2: 2nd quartile; Q3: 3rd quartile; Q4: 4th quartile.

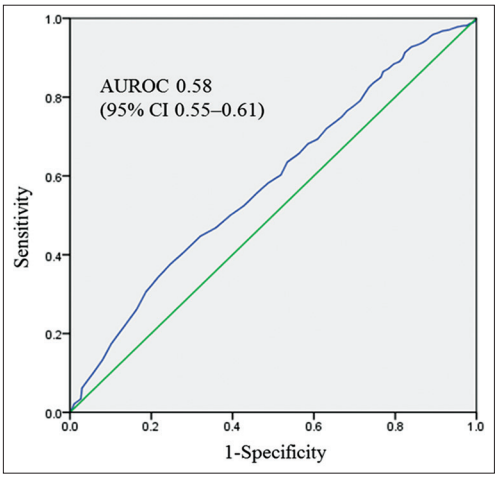


**Figure 1:** Receiver operating characteristic in serum gamma-glutamyl transferase.

FRS ≥10%. Kim *et al*.[16] previously demonstrated that multivariable-adjusted *ORs* for FRS >20% were significantly increased from the lowest to highest GGT quartiles, compared to the lowest baseline GGT category. However, it was a single center-based study and did not target reference value of serum GGT. In other words, the present study derives its significance in the aspect that the association between serum GGT activity within reference value and a 10-year CHD prediction risk was evaluated.

The present study also concluded that individuals with higher quartiles of serum GGT were well correlated with individual factors such as higher BMI, waist circumference, SBP, lipid levels, and FBG, which include FRS components.[10] These positive relationships are supported by previous studies. According to Ryu *et al*.,[12] the prevalence rate of metabolic syndrome increased significantly in relation to serum GGT level within normal range in Korean men. Moreover, Oh *et al*.[17] demonstrated that serum GGT level even within the reference interval was correlated with nonalcoholic fatty liver disease (NAFLD) and the *OR* of GGT activity for NAFLD was elevated according to elevation of the GGT grading. Liu *et al*.[11] also mentioned that GGT was strongly consistent with cardiovascular and metabolic variables in the cross-sectional study among 616 young healthy participants. This tendency has been proven not only in Asian studies but also in previous studies targeting Caucasians, Africans, and other countries. They indicated that individuals with metabolic syndrome, impaired fasting glucose, and NAFLD had considerably elevated levels of serum GGT regardless of any ethnicity.[18-22]

Increased serum GGT level has been traditionally understood as a marker of alcohol abuse and/or liver damage.[7] However, a large number of studies suggested that serum GGT is not only a marker for oxidative stress but also a relative factor of cardiovascular disease and metabolic syndrome.[8,10] Despite the fact that serum GGT activity which reflects the risk of CHD is not completely understood, there are several possible mechanisms that support the hypothesis. The first probable mechanism is that GGT is regarded as a biomarker for oxidative stress. The oxidative stress may contribute to the effect of GGT on atherosclerosis. In other words, the oxidative stress could be a crucial factor in the pathophysiology of cardiovascular disease and GGT has an important role in maintaining intracellular glutathione transport into most types of cells.[7] The second plausible mechanism is that GGT is related with subclinical chronic inflammation. Inflammation is an important mechanism of atherosclerotic cardiovascular disease. Elevated GGT could be the expression of subclinical inflammation because serum GGT is highly associated with white blood cell count and some features of low-grade inflammation.[23] Furthermore, excess reactive oxygen species and superoxide which is generated by oxidative stress and low-grade inflammation recapitulate not only endothelial dysfunction but also cardiovascular dysfunction.[24,25] The third acceptable mechanism could be a strong correlation of GGT with various atherosclerotic risk factors. Previous studies reported that serum GGT concentrations were related with hypertension, metabolic syndrome, and diabetes.[9,26-29] Serum GGT level was also found to increase insulin resistance and be positively correlated with risk factors of atherosclerotic CHD and inflammation such as male gender, CRP, total cholesterol and uric acid level.[28-31] Reversely, as also shown in this study, serum GGT was negatively correlated to HDL-cholesterol level which is a well-known negative risk factor of CHD.[30,31] Lastly, there is a hypothesis that GGT itself is directly atherogenic.[32] It has been reported that GGT is elevated in individuals with atherosclerotic plaques.[33] The origins of GGT in plaques could be through the influx of lipoproteins which carry it into lesions. One of the products of glutathione hydrolysis which were produced by GGT is cysteinyl-glycine. It can generate superoxide anion radicals through its interaction with free iron.[34] This effect could promote atherogenesis via LDL oxidation. It is also observed in the studies which

examined the enzymatic activity of GGT in the coronary and carotid atheroma.[33,35]

There are several strengths and limitations in this study. To start with, the study encompasses a broad range of individuals from the general population. Furthermore, the data may guarantee that it represent the whole population because it was derived from a random selection. Therefore, it is reasonable for the results to be generalized into the Korean population. In addition, a 10-year CHD risk prediction was computed using the NCEP ATP III. However, even though this study showed a positive relationship between serum GGT level within the reference range concentration and a 10-year CHD risk prediction, there are several limitations. This study was cross-sectional, and we did not measure oxidative stress directly. Additionally, the end point of this study is a mathematical substitute for the presence of CHD, even though FRS is a generalized tool. Furthermore, the statistical analysis to serum GGT concentration in women was not applied because the number of subjects with intermediate-risk and beyond for CHD (FRS ≥10%) in this gender group was too small. Therefore, further longitudinal cohort studies are needed to evaluate the predictive value of biomarkers for the increased risk of CHD in the Korean population.

In conclusion, this study suggests that serum GGT activity, within its reference range, is a useful predictor of a 10-year CHD risk using FRS calculated by NCEP ATP III. Therefore, serum GGT within the reference range could be a helpful tool and an additional marker in the prediction of CHD risk in Korean men. Further longitudinal cohort studies are needed to demonstrate the related pathways.

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