Relationship Between \(\gamma\)-Glutamyltransferase Levels and Left Ventricular Diastolic Dysfunction

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Background: The goal of this study was to examine the association of serum \(\gamma\)-glutamyltransferase (GGT) levels with left ventricular (LV) diastolic dysfunction and LV hypertrophy.

Methods and Results: A cross-sectional study of 79,459 Korean men and women who underwent an echocardiography as part of a comprehensive health examination between March 2011 and December 2014. The presence of LV diastolic dysfunction and LV hypertrophy was determined using echocardiography. Of the subjects, 5,447 had LV diastolic dysfunction and 2,070 had LV hypertrophy. Both LV diastolic dysfunction and LV hypertrophy were associated with higher levels of serum GGT. Multivariable-adjusted odds ratios (95% confidence interval) for LV diastolic dysfunction comparing serum GGT quartiles 2–4 with quartile 1 were 1.25 (1.08–1.44), 1.65 (1.43–1.91) and 2.23 (1.92–2.58), respectively (P for trend <0.001). Multivariable-adjusted odds ratios (95% CI) for LV hypertrophy comparing serum GGT quartiles 2–4 with quartile 1 were 1.13 (0.94–1.36), 1.14 (0.93–1.40) and 1.33 (1.07–1.65), respectively (P for trend 0.01). These associations of serum GGT levels with LV diastolic dysfunction and LV hypertrophy were modified by age (P for interaction <0.05).

Conclusions: This study demonstrated a positive association between serum GGT levels and LV diastolic dysfunction and LV hypertrophy in a large cohort of middle-aged men and women independent of potential confounders.

Key Words: Gamma-glutamyltransferase; Left ventricular diastolic dysfunction; Left ventricular hypertrophy

Heart failure (HF) is a major public health problem associated with high morbidity, mortality and healthcare expenditure. Previous studies have demonstrated that subclinical left ventricular (LV) diastolic dysfunction and LV hypertrophy (LVH) predict the development of clinical HF. Furthermore, LV diastolic dysfunction is associated with increased risk of sudden death, and the presence of LVH is a strong independent risk factor for future cardiac events and all-cause mortality. Because of the serious consequences of overt HF, there is substantial interest in developing strategies and identifying potential risk factors to prevent or reduce the progression of LV dysfunction and hypertrophy.

Serum \(\gamma\)-glutamyltransferase (GGT) has been widely used as an index of alcohol intake and liver dysfunction. Recently, serum GGT was proposed as a sensitive marker of oxidative stress because it has dose-response associations with many cardiovascular disease (CVD) risk factors, as well as future risks of diabetes, chronic kidney disease, coronary artery disease (CAD), HF, stroke, and CVD mortality. Therefore, it can be hypothesized that high levels of serum GGT may play a potential role in the development of subclinical LV diastolic dysfunction and LVH. Studies of subclinical HF can provide valuable information on clinical HF outcomes, particularly regarding the early stages of HF free from confounding secondary processes such as chronic liver damage. Only one study found that serum GGT predicted LV dilation and dysfunction in 40 patients with acute myocardial infarction. To date, the relationship between serum GGT levels and LV function has not been studied using large cohorts of healthy adults.

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Therefore, the goal of this study was to examine the association of serum GGT levels with LV diastolic dysfunction and LVH in a large sample of Korean men and women.

Methods

Study Population
The Kangbuk Samsung Health Study used data from a cohort of Korean men and women who underwent comprehensive annual or biennial examinations at Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon, South Korea. The cohort used in this study consisted of 85,691 men and women, aged 18 years or older, who were evaluated with echocardiography as part of a comprehensive health examination between March 2011 and December 2012. We excluded 6,232 participants for the following reasons: missing data on GGT levels (n=10); a history of a malignancy (n=2,175); a history of CVD (n=1,085), based on standardized, self-administered questionnaires; and evidence of systolic HF (ejection fraction <50%), hypertrophic or dilated cardiomyopathy, ischemic heart disease, any cardiac surgery including valvular replacement, mitral or atrial stenosis, mitral or atrial regurgitation, atrial fibrillation or congenital heart disease on echocardiography (n=3,208). As some individuals met more than 1 exclusion criterion, the total number of patients eligible for the study was 79,459. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, and the requirement for informed consent was waived because we used de-identified retrospective data routinely collected during the health screening process.

Measurements
Serum glucose, hemoglobin A1c, insulin, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels were measured as previously described. Serum GGT levels were measured enzymatically using an automatic analyzer (Modular D2400; Roche Diagnostics, Tokyo, Japan). Both low- and high-level quality control (QC) materials were used, with coefficients of variation (CV) of 1.57–5.45% and 0.76–4.45%, respectively. Insulin resistance was assessed with the homeostatic model assessment-insulin resistance (HOMA-IR) equation: fasting blood insulin (uIU/mL)×fasting blood glucose (mmol/L)/22.5. Serum high-sensitivity C-reactive protein (hsCRP) levels were determined using a particle-enhanced immunoturbidimetric assay on a Modular Analytics P800 apparatus (Roche Diagnostics). Both low- and high-level QC materials were used, with CVs of 3.36–9.86% and 0.79–9.33%, respectively. The Laboratory Medicine Department at Kangbuk Samsung Hospital in Seoul, Korea is accredited by the Korean Society of Laboratory Medicine and the Korean Association of Quality Assurance for Clinical Laboratories. The laboratory participates in College of American Pathologists Survey Proficiency Testing.

Blood pressure (BP) was measured using an automated oscillometric device (53000, Welch Allyn, NY, USA) while subjects were seated with the arm supported at heart level. Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or the current use of antihypertensive medication. Diabetes was defined as fasting serum glucose ≥126 mg/dL, hemoglobin A1c ≥6.5%, or the current use of insulin or antidiabetic medications. Abdominal ultrasound was performed using a Logic Q700 MR 3.5-MHz transducer (GE, Milwaukee, WI, USA) by experienced radiologists, all of whom were unaware of the aims of the study. Ultrasonographic diagnosis of fatty liver was defined as the presence of a diffuse increase of fine echoes in liver parenchyma compared with kidney or spleen parenchyma. Data on demographic characteristics, medication use, medical history, education level, smoking and alcohol intake were also collected by standardized, self-administered questionnaires as previously described. Physical activity levels and sitting time were assessed using the validated Korean version of the International Physical Activity Questionnaire Short Form (IPAQ-SF). Physical activity levels were classified into 3 categories: inactive, minimally active (600 MET-minutes per week), and health-enhancing physically active (HEPA; 3,000 MET-minutes per week) as previously described. Usual dietary intake was assessed using a 103-item, self-administered food frequency questionnaire (FFQ) designed and validated for use in Korea. The validity and reproducibility of our FFQ were evaluated previously by comparing nutrient and food intake derived from 12 24-h dietary recalls during 4 seasons and with a second FFQ administered 1 year later. Total energy and nutrient intake were calculated by using a food composition table developed by the Korean Nutrition Society. Height and weight were measured by trained nurses with the participants wearing a lightweight hospital gown and no shoes. Body mass index (BMI) was calculated as height (m) divided by weight (kg) squared (m/kg²). We classified BMI according to the criteria proposed for Asian populations.

Echocardiography
Conventional echocardiography was performed with ultrasound scanners (Vivid 7 and E9, General Electric) by trained sonographers and measurements were done using a standardized guideline. Linear measurements of the left posterior wall thickness (PWT), intraventricular septum thicknesses (IVST) and diameter of the LV cavity at the end of diastole and systole were obtained in M-mode in the parasternal long-axis view. LV mass (LVM) was calculated with measurements obtained in M-mode using the following equation: LVM=0.8×[(IVST+PWT+LVEDD)–LVEDS]+0.6. The LVM index (LVMi) was calculated as LV mass/height² and LVH was defined as LVMi ≥45 g/m² for women and LVMI ≥49 g/m² for men. The anteroposterior diameter of the left atrium (LA) was measured in all subjects.

To assess diastolic function, pulse-wave Doppler of transmural LV inflow was obtained in the apical 4-chamber view. Early diastolic mitral inflow peak velocity (E), late diastolic peak velocity (A) during atrial contraction and deceleration time of the E velocity were measured. The early (E') and late (A') tissue velocities were measured from tissue Doppler imaging of the septal mitral anulus. We assessed LV diastolic function using E' at the septal mitral annulus only and E'/E' measurements, which were available in all subjects. LV diastolic function was categorized based on the following criteria: normal LV diastolic function was defined as when both E' (≥7 cm/s) and E' (≤15) were met; LV diastolic dysfunction was defined as when both decreased E' (<7 cm/s) and increased E'/E' (>15) were met; and otherwise participants were categorized into the indeterminate group. Because only 152 participants...
BMI. Finally, analysis was further adjusted for family history (unknown), total energy intake (in quintile or missing) and university graduate, graduate school or higher, and (high-school graduate or less, community college or ≥ university graduate). Additional adjustments were then made for smoking history (never, past, current, or unknown), alcohol intake (<20 g/day, or unknown), educational level (high-school graduate or less, community college or university graduate, graduate school or higher, and unknown), total energy intake (in quintile or missing) and BMI. The basic model was adjusted for confounding variables. The association of LV diastolic dysfunction and LVH across GGT quartiles, we used a logistic regression model to estimate odds ratios (ORs) with 95% CI. We used 3 models with progressively increased adjustment for confounding variables. The basic model was adjusted for family history of heart disease, history of diabetes, history of hypertension, evidence of fatty liver, hsCRP level, HOMA-IR score and systolic BP. To test for linear trends, quartile values were used as continuous variables in each regression model.

We performed stratified analyses in prespecified subgroups defined by sex (female vs. male), age (<50 vs. ≥ 50 years), history (never or ex-smoker vs. current smoker), alcohol intake (<20 g/day of alcohol), HEPA (no vs. yes), BMI (<25 vs. ≥25 kg/m2) and evidence of fatty liver (no vs. yes). Interactions between subgroups were tested using likelihood ratio tests comparing models with and without multiplicative interaction terms. All P-values were two-tailed, and values of P<0.05 were considered statistically significant. We used STATA version 14.0 (Stata Corp., College Station, TX, USA) for data analysis.

**Results**

Baseline characteristics of study participants in relation to the serum GGT levels are presented in Table 1. The study cohort included 56,519 men (71.1%) and 22,940 women (28.9%). The mean age and BMI of the 79,459 participants was 40.3 years (SD, 8.0, range 18.7–89.1) and 23.9 kg/m2. The mean age and BMI of the study participants were examined by GGT quartile. Estimated mean values (95% confidence interval [CI]) of echocardiographic findings after adjusting for age and sex were also examined by GGT quartile. To test for linear trends, quartile values were used as continuous variables in each regression model.

**Statistical Analysis**

Characteristics of the study participants were examined by GGT quartile. Estimated mean values (95% confidence interval [CI]) of echocardiographic findings after adjusting for age and sex were also examined by GGT quartile. To test for linear trends, quartile values were used as continuous variables in each regression model.

To determine the association of LV diastolic dysfunction and LVH across GGT quartiles, we used a logistic regression model to estimate odds ratios (ORs) with 95% CI. We used 3 models with progressively increased adjustment for confounding variables. The basic model was adjusted for family history of heart disease, history of diabetes, history of hypertension, evidence of fatty liver, hsCRP level, HOMA-IR score and systolic BP. To test for linear trends, quartile values were used as continuous variables in each regression model.

We performed stratified analyses in prespecified subgroups defined by sex (female vs. male), age (<50 vs. ≥ 50 years), history (never or ex-smoker vs. current smoker), alcohol intake (<20 g/day of alcohol), HEPA (no vs. yes), BMI (<25 vs. ≥25 kg/m2) and evidence of fatty liver (no vs. yes). Interactions between subgroups were tested using likelihood ratio tests comparing models with and without multiplicative interaction terms. All P-values were two-tailed, and values of P<0.05 were considered statistically significant. We used STATA version 14.0 (Stata Corp., College Station, TX, USA) for data analysis.
GGT levels were positively associated with age, male sex, current smoking and high educational level as well as with comorbidities of obesity, hypertension, diabetes and fatty liver. Serum GGT levels were also positively associated with BMI, systolic and diastolic BPs, glucose, total cholesterol, LDL-C, triglycerides, ALT, AST, hsCRP, insulin and HOMA-IR. HEPA, family history of CVD and HDL-C were inversely associated with serum GGT levels, whereas E, A, E/A ratio, septal E' and septal A were negatively associated. The respective ORs (95% CI) for LV diastolic dysfunction comparing serum GGT quartiles 2–4 with quartile 1 were 1.66 (1.47–1.87), 1.37 (1.20–1.56), 1.25 (1.08–1.44), and 1.23 (1.02–1.50). Increasing levels of serum GGT were associated with an increasing prevalence of LV diastolic dysfunction. In an age- and sex-adjusted model, the ORs (95% CI) for LV diastolic dysfunction comparing serum GGT quartiles 2–4 with quartile 1 were 1.66 (1.47–1.87), 1.37 (1.20–1.56), 1.25 (1.08–1.44), and 1.23 (1.02–1.50). Increasing levels of serum GGT were associated with an increasing prevalence of LV diastolic dysfunction (P for trend <0.001). In addition, this association persisted after further adjustment for family history of heart disease, history of diabetes, history of hypertension and presence of fatty liver; model 3: model 2 plus adjustment for high-sensitivity C-reactive protein, homeostasis model assessment of insulin resistance and systolic BP. Abbreviations as in Tables 1, 2.

Table 2. Estimated Mean Values (95% CI) of Echocardiographic Findings With Adjustment for Age and Sex of the Korean Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GGT quartile (u/L)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1 (&lt;16)</td>
<td>Q2 (16–24)</td>
</tr>
<tr>
<td>No. of participants</td>
<td>20,566</td>
<td>20,133</td>
</tr>
<tr>
<td>Heart rate (cm/s)</td>
<td>62.8 (62.6–62.9)</td>
<td>63.8 (63.7–63.9)</td>
</tr>
<tr>
<td>Ejection fraction (cm/s)</td>
<td>66.4 (66.3–66.5)</td>
<td>66.5 (66.5–66.6)</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>128.1 (127.6–128.5)</td>
<td>131.9 (131.5–132.3)</td>
</tr>
<tr>
<td>LVMI (g/ht^2, g/m^2)</td>
<td>30.5 (30.4–30.6)</td>
<td>31.6 (31.5–31.7)</td>
</tr>
<tr>
<td>LA size (mm)</td>
<td>32.8 (32.5–33.1)</td>
<td>33.4 (33.1–33.7)</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;16)</td>
<td>20,552</td>
<td>459</td>
</tr>
<tr>
<td>Q2 (16–24)</td>
<td>20,122</td>
<td>1,019</td>
</tr>
<tr>
<td>Q3 (25–41)</td>
<td>19,458</td>
<td>1,538</td>
</tr>
<tr>
<td>Q4 (≥42)</td>
<td>19,302</td>
<td>2,348</td>
</tr>
<tr>
<td>LV diastolic dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;16)</td>
<td>20,552</td>
<td>459</td>
</tr>
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</tr>
<tr>
<td>Q4 (≥42)</td>
<td>19,302</td>
<td>2,348</td>
</tr>
</tbody>
</table>

*Estimated from logistic regression models. Multivariable model 1 was adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, physical activity, educational level, total calorie intake and BMI; model 2: model 1 plus adjustment for family history of heart disease, history of diabetes, history of hypertension and presence of fatty liver; model 3: model 2 plus adjustment for high-sensitivity C-reactive protein, homeostasis model assessment of insulin resistance and systolic BP. Abbreviations as in Tables 1, 2.

Table 3. Odds Ratiosa (95% CI) of LV Diastolic Dysfunction and LV Hypertrophy According to GGT Quartile

<table>
<thead>
<tr>
<th>Serum GGT level (u/L)</th>
<th>n</th>
<th>Cases</th>
<th>Age-/sex-adjusted ORa (95% CI)</th>
<th>Multivariate-adjusted ORa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td>Model 3</td>
<td></td>
</tr>
<tr>
<td>LV diastolic dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;16)</td>
<td>20,566</td>
<td>542</td>
<td>1.00 (Refs.)</td>
<td>1.00 (Refs.)</td>
</tr>
<tr>
<td>Q2 (16–24)</td>
<td>20,133</td>
<td>1,019</td>
<td>1.66 (1.47–1.87)</td>
<td>1.37 (1.20–1.56)</td>
</tr>
<tr>
<td>Q3 (25–41)</td>
<td>19,458</td>
<td>1,538</td>
<td>2.85 (2.53–3.21)</td>
<td>1.97 (1.73–2.24)</td>
</tr>
<tr>
<td>Q4 (≥42)</td>
<td>19,302</td>
<td>2,348</td>
<td>5.23 (4.64–5.89)</td>
<td>3.00 (2.63–3.42)</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;16)</td>
<td>20,552</td>
<td>459</td>
<td>1.00 (Refs.)</td>
<td>1.00 (Refs.)</td>
</tr>
<tr>
<td>Q2 (16–24)</td>
<td>20,122</td>
<td>464</td>
<td>1.40 (1.22–1.62)</td>
<td>1.16 (0.98–1.38)</td>
</tr>
<tr>
<td>Q3 (25–41)</td>
<td>19,449</td>
<td>465</td>
<td>1.90 (1.63–2.20)</td>
<td>1.17 (0.97–1.40)</td>
</tr>
<tr>
<td>Q4 (≥42)</td>
<td>19,291</td>
<td>622</td>
<td>3.42 (2.94–3.96)</td>
<td>1.41 (1.16–1.70)</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Estimated from logistic regression models.
HEPA (P for interaction 0.02 for both, respectively). We also examined the association between serum GGT levels and LVH. Serum GGT levels were significantly associated with an increased prevalence of LVH. In an age- and sex-adjusted model, the ORs (95% CI) for LVH comparing serum GGT quartiles 2–4 with quartile 1 were 1.40 (1.22–1.62), 1.90 (1.63–2.20) and 3.42 (2.94–3.96), respectively (P for trend <0.001). In a multivariable model adjusting for potential confounders, serum GGT levels remained significantly correlated with an increased prevalence of LVH, with corresponding ORs of 1.19 (1.00–1.41), 1.22 (1.01–1.47), and 1.45 (1.19–1.77), respectively (P for trend <0.001) (Table 3). The associations of serum GGT levels with LV diastolic dysfunction and LVH persisted after further adjustments for HOMA-IR, hsCRP and systolic BP (Table 3). These results did not change after additional adjustment for ALT (data not shown). ORs for LV diastolic dysfunction with hypertrophy were also examined according to GGT quartiles. Serum GGT levels were significantly associated with an increased prevalence of LV diastolic dysfunction with hypertrophy (Table S1).

The interaction of serum GGT levels and age for both LV diastolic dysfunction and LVH was statistically significant (P for interaction <0.001 and 0.01, respectively). High serum GGT was more strongly associated with the prevalence of LV diastolic dysfunction in younger participants (<50 years) compared with older participants (≥50 years). In addition, the associations between serum GGT levels and LVH were significantly observed in younger participants (<50 years), but not in older participants (≥50 years) (Figures 1,2). And the association between serum GGT levels and LV diastolic dysfunction was also modified by alcohol intake and HEPA (P for interaction 0.02 for both, respectively). We found no significant difference between the serum GGT levels and LV diastolic dysfunction when considering additional variables of sex, current smoking, BMI, presence of fatty liver and ALT (Table S2). Interestingly, the association between serum GGT levels and LV diastolic dysfunction was still observed in subjects without fatty liver, with corresponding ORs of 1.14 (0.95–1.35), 1.51 (1.26–1.82), and 2.14 (1.76–2.60), respectively (P for trend <0.001) and even in subjects with ALT <36 U/L, with corresponding ORs of 1.24 (1.08–1.44), 1.65 (1.42–1.92), and 2.18 (1.86–2.56), respectively (P for trend <0.001).

Discussion

In this large cross-sectional study, we observed a positive linear relationship between serum GGT levels and LV diastolic dysfunction and LVH, independent of potential confounders. The strength of these associations varied when subdividing patients by age. High levels of serum GGT were significantly more strongly associated with the prevalence of LV diastolic dysfunction in younger subjects than in older subjects. The associations between serum GGT levels and LVH were significantly observed in younger participants (<50 years), but not in older participants (≥50 years).

Previous prospective studies have evaluated the utility of serum GGT as a risk factor for the development of HF and subsequent adverse outcomes. Data from the Framingham Heart Study showed that higher serum GGT levels (within normal range) were associated with a greater risk of HF after a mean follow-up of 23.6 years. A prospective population-based cohort study in Finland reported a positive association between serum GGT and the risk of HF. Data from the British Regional Heart Study also
showed that elevated GGT was associated with a significant increase in risk of HF in men aged <70 years. Thus far, limited information is available on the association of serum GGT and the development of subclinical LV diastolic dysfunction and LVH. One prior study reported that serum GGT predicted LV dilation and dysfunction in 40 patients with acute myocardial infarction. To the best of our knowledge, our study is the first to demonstrate an association between serum GGT levels and the prevalence of LV diastolic dysfunction and LVH in a large cohort of adults without prior evidence of heart disease.

The mechanism by which serum GGT levels are associated with LV diastolic dysfunction and LVH has yet to be elucidated. An increase in serum GGT level is often clinically interpreted as evidence of alcohol abuse or liver disease. In this study, serum GGT correlated with LV diastolic dysfunction and LVH independent of alcohol consumption, ALT level and presence of fatty liver. Therefore, it is unlikely that the observed association between serum GGT and LV function was the result of excessive alcohol consumption or liver disease. Adiposity is a potential mechanism that would link serum GGT levels to LV diastolic dysfunction and LVH, as obesity is known to produce changes in cardiac structure and function, including LV diastolic dysfunction and LVH. However, adjusting for BMI did not change the association of serum GGT levels with LV diastolic dysfunction and LVH. Similarly, insulin resistance syndrome has been associated with serum GGT, and several studies have described a close link between insulin resistance and LV diastolic dysfunction.

However, the association of serum GGT levels with LV diastolic dysfunction and LVH persisted after adjusting for HOMA-IR. The positive association of serum GGT levels with LV diastolic dysfunction and LVH might be explained by high BP. The relationship of hypertension with LV diastolic dysfunction and LVH has been established. Recently, results from a meta-analysis showed that serum GGT level is associated with an increased risk of hypertension in the general population. These results did not change after adjustment for history of hypertension and systolic BP.

Recently, the serum GGT level was proposed to be a sensitive and reliable marker of oxidative stress. In the CARDIA study, serum GGT level inversely correlated with circulating dietary antioxidants, such as α-carotene, β-carotene, β-cryptoxanthin, zeaxanthin/lutein and α-tocopherol, and positively correlated with other biomarkers of oxidative stress, such as F-2 isoprostanes. Based on current experimental and human studies, serum GGT may be associated with LV diastolic dysfunction and LVH secondary to oxidative stress. In vitro studies suggest that myocyte contractile function may be impaired by increased reactive oxygen species (ROS) through several mechanisms, including disruption of calcium cycling, altered myofilament responsiveness to calcium, and interference with cellular metabolism and energetics. A recent study showed that ROS production by uncoupled nitric oxide synthase may contribute to the development of LVH during chronic pressure overload, and pressure overload LVH was attenuated by antioxidants in guinea pig and mouse models, suggesting a role for ROS. Several clinical studies have provided substantial evidence that increased oxidative stress might be associated with the process underlying LVH, adverse LV remodeling and HF. These experimental and clinical studies support the hypothesis that oxidative stress plays an important role in LV diastolic dysfunction and LVH.

In our current study, high levels of serum GGT were more strongly associated with the prevalence of LV diastolic dysfunction and LVH in younger subjects (<50 years) compared with older subjects, despite the fact that the absolute prevalence of LV diastolic dysfunction and LVH was over 3-fold and 5-fold higher in older subjects (>50 years), respectively. Several studies have reported a strong age interaction, with associations between GGT and incident CAD being strong in young individuals but relatively weak in the elderly. A previous cohort study of 163,944 Austrian adults also demonstrated a stronger relationship of serum GGT to CVD mortality in younger participants compared with the elderly. A recent nested case-control study showed that higher GGT values (within normal range) had a stronger association with the incidence of CVD death in younger vs. older subjects. Similar results were observed in data from the British Regional Heart Study. Although these studies clearly identified a strong association between serum GGT and CVD in young patients, further research is needed to help identify the mechanisms underlying these associations.

Study Limitations

Some limitations of our study should be considered when interpreting our findings. First, the cross-sectional design of our study limited our ability to establish temporal relationships and infer causality. Future prospective studies are needed to investigate potential causal relationships between serum GGT levels and the development of LV diastolic dysfunction and LVH. Second, we only measured peak mitral inflow velocity (E) during early diastole and peak tricuspid regurgitant velocity, among the measurements recommended by the American Society of Echocardiography to assess LV diastolic function. In the case of mitral annular velocity, the measurement was done only in the septal area. It is known than septal E’ is more useful than lateral E’, because septal E’ reflects LV longitudinal myocardial relaxation and diastolic function. Also, the AP dimension of the LA does not exactly reflect the actual size of the LA, but there is an epidemiologic study that showed a correlation between actual LA diameter and AP diameter measured by M-mode. Finally, subjects in this study were highly educated, young and middle-aged Korean men and women who regularly attended health screening exams, most often as part of work-related health check-up programs. Thus, our results may not represent the general Korean population or other populations with different demographics. Despite these potential limitations, a major strength of our study was the large sample size, which provided excellent statistical power to assess the entire cohort and subgroups. Our findings were strengthened by comprehensive exclusion of potential confounding variables, the availability of high-quality laboratory procedures with extensive QC, and the relative homogeneity of the participants, which reduces the confounding effect of variables such as socioeconomic status and access to health care.

In conclusion, this study demonstrated a positive linear relationship of serum GGT levels with LV diastolic dysfunction and LVH, independent of potential confounders, in a large sample of middle-aged Korean men and women in an age-dependent manner. The findings of this study extend the range of health outcomes associated with increased levels of serum GGT, and suggest that serum GGT, which
is usually considered a marker of alcohol consumption or liver dysfunction but also can be a marker of oxidative stress, may have important clinical implications as a biomarker of early-stage or preclinical heart dysfunction, overt HF, and other CVDs. From the clinical practice perspective, it is important that physicians and healthcare providers monitor those with increased serum GGT for the presence of preclinical heart dysfunction and cardiovascular risk. However, further prospective studies are needed to establish causal relationships between serum GGT levels and the development of LV diastolic dysfunction and LVH.

**Funding Sources**

None.

**Disclosures**

The authors have no conflicts of interest to disclose.

**References**


Supplementary Files

Supplementary File 1

Table S1. Odds ratios (95% CI) of LV diastolic dysfunction with LV hypertrophy according to GGT quartile

Table S2. Odds ratios (95% CI) of LV diastolic dysfunction according to GGT quartile in clinically relevant subgroups

Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-16-1084