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Serum Gamma-Glutamyltransferase Levels are Associated With Concomitant Cardiovascular Risk Factors in Korean Hypertensive Patients

A Nationwide Population-Based Study

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Abstract: Previous studies suggested that serum gamma-glutamyltransferase (GGT) levels were associated with the prevalence of cardiovascular disease (CVD) risk factors including hypertension, diabetes mellitus (DM), and metabolic syndrome (MetS) in the general population. We aimed to investigate the relationship between serum GGT levels and CVD risk factors in Korean hypertensive patients.

This cross-sectional study was based on data from the Korea National Health and Nutrition Examination Survey (KNHANES) 2011 to 2012. The analysis included 1541 hypertensive participants. Study participants were divided into groups according to tertiles of serum GGT with cutoff points of 20 and 35 U/L.

Serum GGT levels were positively associated with the components of MetS (P value < 0.05 , except for systolic blood pressure and high-density lipoprotein cholesterol). After adjusting for possible confounders, serum GGT levels were associated with an increased risk of MetS, high waist circumference, high triglyceride level, fasting plasma glucose, DM, and the urinary albumin-to-creatinine ratio ($P = 0.001$).

In hypertensive patients, serum GGT levels are positively associated with major cardiovascular risk factors such as MetS, DM, and urinary albumin excretion.

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Abbreviations: BMI = body mass index, CHD = coronary heart disease, CHF = congestive heart failure, CVD = cardiovascular disease, DBP = diastolic blood pressure, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, GGT = serum gamma-glutamyltransferase, HDL-C = high-density lipoprotein cholesterol, MetS = metabolic syndrome, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides, UACR = urinary albumin-to-creatinine ratio, WBC = white blood cell, WC = waist circumference.

INTRODUCTION

Hypertensive patients have a 2-fold risk of cardiovascular disease (CVD) including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease. Appropriate antihypertensive therapy reduces cardiovascular and renal disease risk, but significant portions of the hypertensive population are either untreated or inadequately treated.¹

Serum gamma-glutamyltransferase (GGT) levels may be elevated in hepatobiliary disease with or without the elevation of other liver enzymes. Thus, GGT may be an indicator of alcohol abuse or alcoholic liver disease. Serum GGT levels can also elevate due to the ingestion of certain medications such as barbiturates or phenytoin. Recently, several studies demonstrated associations between serum GGT levels and CVD including hypertension, diabetes, and metabolic syndrome (MetS).²⁻⁷ In addition, previous studies of Korean adults showed that serum GGT levels were independently associated with incident hypertension.² This is potentially explained by the oxidative stress mechanism demonstrated in the series of Coronary Artery Risk Development in Young Adults (CARDIA) studies.^{3,4,8} Although the relationship between serum GGT and cellular GGT is unknown, cellular GGT has been known to play an important role in antioxidant defense systems.⁹ Moreover, serum GGT was revealed as an early and sensitive marker of oxidative stress in a recent study.¹⁰ However, previous investigations of the association between serum GGT levels and cardiovascular risk factors were based on the general population. We therefore aimed to evaluate this relationship in Korean hypertensive patients. We considered diabetes mellitus (DM), MetS, and the urinary albumin-to-creatinine ratio (UACR) as additional cardiovascular risk factors in hypertensive individuals.

METHODS

Survey and Subject

This cross-sectional study was based on data from the Korea National Health and Nutrition Examination Survey

(KNHANES) 2011 to 2012. The KNHANES was designed to evaluate national health and nutritional status and was conducted by the Division of Chronic Disease Surveillance under the Korea Centers for Disease Control and Prevention (KCDC). The survey consists of an interview on health status, a nutritional assessment, and a health examination.

Of the 8518 KNHANES 2011 to 2012 participants, 6977 were excluded from the present analysis. Reasons for exclusion were an age <19 years ($n=1952$), absence of hypertension ($n=4634$), cancer ($n=5$), pulmonary tuberculosis ($n=103$), chronic hepatitis B or C ($n=7$), missing data ($n=212$), and not fasting for at least 8 h ($n=29$). Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mm Hg, diastolic blood pressure (DBP) ≥ 90 mm Hg, or antihypertensive medication use. Finally, a total of 1541 subjects were included in the analysis. All participants provided written informed consent and the Institutional Review Board of the KCDC approved the study protocol.

Sociodemographic and Lifestyle Characteristics

Monthly household income and educational level, physical activity, and antihypertensive medication use were assessed via individual interviews by trained staff. Alcohol consumption and smoking status were assessed using a self-reported questionnaire. A lower income level was defined as the lowest 25th percentile of the total participants. A higher educational level was defined as high school graduate or more. Alcohol consumption was classified into 3 categories based on the mean amount of alcohol consumed per day up to 1 month before the interview: subjects who consumed ≥ 30 g/day of alcohol were classified as heavy drinkers and those who consumed ≤ 30 g/day were classified as mild to moderate drinkers.¹¹ Smoking status was classified as the current smoker or the nonsmoker at the time of the interview. As for physical activity, subjects who exercised moderately for >30 min per session >5 times per week or vigorously for >20 min per session >3 times per week were defined as regular physical exercisers.¹²

Anthropometric and Biochemical Measurements

Height and body weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. The body mass index (BMI) was calculated using the formula: body weight (kg)/height² (m²). Waist circumference (WC) was measured at the midpoint between the lower costal margin and the iliac crest during expiration. Blood pressure was measured from the right arm in the sitting position using a standard mercury sphygmomanometer (Baumanometer, WA Baum Co.) after 5 min of rest. Systolic blood pressure and DBP were measured 3 times in 5-min intervals and the average of the second and third measurements was used in the analysis.

Blood samples were obtained after a fasting period of at least 8 h and single spot midstream urine samples were collected from the first morning voiding. Serum GGT levels were measured enzymatically using a Hitachi Automatic Analyzer 7600. Levels of fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) were measured enzymatically with the same equipment. White blood cell (WBC) count was measured with using an XE-2100D (Sysmex) via laserflow cytometry. HbA1c levels were measured using an HLC-723G7 (Tosoh) via high-performance liquid chromatography. To calculate the UACR, serum and urine creatinine levels were measured by kinetic colorimetry using a Hitachi Automatic Analyzer 7600. Urine

albumin levels were measured with the same equipment by means of a turbidimetric assay. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease study Equation.¹³

Definitions of MetS

We used guidelines from the National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA) to define MetS. And it is defined as any 3 or more of the followings: (1) FPG ≥ 100 mg/dL (or receiving drug therapy for hyperglycemia); (2) blood pressure $\geq 130/85$ mm Hg (or receiving drug therapy for hypertension); (3) triglycerides ≥ 150 mg/dL (or receiving drug therapy for hypertriglyceridemia); (4) HDL-C < 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C); (5) WC ≥ 90 cm (35 in) in Asian men or ≥ 80 cm (32 in) in Asian women.¹⁴

Type 2 DM was defined according to the updated American Diabetes Association criteria. The diagnosis could be made when any of the 4 following criteria was satisfied: (1) HbA1c $\geq 6.5\%$; (2) FPG ≥ 126 mg/dL; (3) 2-h plasma glucose ≥ 200 mg/dL during a 75 g oral glucose tolerance test; (4) classic symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose measurement of ≥ 200 mg/dL. Impaired fasting glucose was defined as an FPG of 100 to 125 mg/dL. In this study, participants were defined as having DM when they were previously diagnosed with DM by physicians or were taking DM medications. Participants in the present study were defined as having newly diagnosed DM if they had an HbA1c $\geq 6.5\%$ or an FPG ≥ 126 mg/dL.

High WC (≥ 90 cm in men or ≥ 80 cm in women), high TG (≥ 150 mg/dL), high FPG (≥ 100 mg/dL), and low HDL-C (<40 mg/dL in men or <50 mg/dL in women) levels were defined using the same criteria used to define the MetS components. A high UACR was defined as the highest tertile of UACR.

Statistical Analysis

SAS 9.2 software (SAS Institute) was used for all statistical analyses. A *P* value of <0.05 was regarded as statistically significant.

Participants were classified into 3 groups according to tertiles of serum GGT and the cutoff values were 20 and 35 U/L. Baseline clinical and metabolic characteristics are expressed as the mean \pm standard error or percentage (standard error). Differences in clinical characteristics according to GGT categories were assessed using an analysis of variance (ANOVA) or chi square test. Logistic regression models were used to calculate multivariable adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Covariates in the minimally adjusted model (Model 1) were age and gender. The second model (Model 2) was additionally adjusted for BMI. The third model (Model 3) was adjusted for alcohol consumption, smoking status, physical activity, and antihypertensive medication use in addition to the Model 2 variables. The fourth model (Model 4) was adjusted for total energy intake and fat intake percentage per day in addition to the Model 3 variables.

RESULTS

Baseline Characteristics According to the GGT Level

Table 1 presents participants' baseline clinical and metabolic characteristics according to serum GGT tertile. Age and

TABLE 1. Subject Baseline Characteristics by GGT Category

Characteristics	T1 (GGT < 20 U/L)	T2 (20 ≤ GGT < 35 U/L)	T3 (GGT ≥ 35 U/L)	P Value [†]
N	497	534	510	
Sex (female), %	76.2(2.7)	45.6(2.5)	17.7(1.8)	<0.001
Age, years	62.2 ± 1	57.4 ± 0.8	50.7 ± 0.9	<0.001
BMI, kg/m ²	24.2 ± 0.2	25.3 ± 0.2	25.7 ± 0.2	<0.001
WC, cm	82.9 ± 0.7	86.7 ± 0.6	89.3 ± 0.5	<0.001
SBP, mm Hg	134.8 ± 1.1	134.4 ± 0.9	135.5 ± 0.9	0.733
DPB, mm Hg	80.1 ± 0.7	83.6 ± 0.7	88.5 ± 0.6	<0.001
FPG, mg/dL	99 ± 1.2	105.2 ± 1.3	106.7 ± 1.4	<0.001
HbA1c, %	5.9 ± 0	6 ± 0	5.9 ± 0	0.036
TG, mg/dL*	109.1(102.9,115.6)	133.9(125.4,143)	167.1(156,179)	<0.001
TC, mg/dL	194.1 ± 1.8	194.1 ± 2.1	196.8 ± 2.1	0.604
WBC count*	5.7(5.5,5.9)	6.3(6.1,6.5)	6.6(6.4,6.8)	<0.001
eGFR, mL/min/1.73m ²	86.1 ± 1.2	86.7 ± 1.0	89.8 ± 0.9	0.012
UACR*	7.5(6.3,8.8)	7.1(6.1,8.3)	7(6,8.3)	0.847
Monthly income (lowest quartile), %	36.4(2.5)	22.7(2)	19.2(2.3)	<0.001
Education (high school), %	31.4(3.2)	44(2.7)	65.1(3.1)	<0.001
Alcohol consumption				<0.001
Nondrinker, %	48.3(3.1)	31.2(2.2)	11.7(1.7)	
Mild to moderate drinker, %	49(2.9)	60.1(2.4)	53.1(2.6)	
Heavy drinker, %	2.7(1.6)	8.7(1.6)	35.3(2.8)	
Current smoker, %	7.1(1.6)	19.8(2.4)	43.1(2.8)	<0.001
Regular exercise, %	18.3(2.7)	21.1(2.3)	19.4(2.1)	0.739
Use of antihypertensive medications, %	65.9(3.1)	62.9(2.8)	41.3(2.9)	<0.001
Energy intake, kcal	1686 ± 48.8	2050.5 ± 67.6	2344.8 ± 67.3	<0.001
Fat intake, %	13.3 ± 0.5	15.4 ± 0.5	18.4 ± 0.7	<0.001
Protein intake, %	13.4 ± 0.3	13.9 ± 0.2	15.5 ± 0.3	<0.001
Carbohydrate intake, %	73.3 ± 0.6	70.8 ± 0.6	66 ± 0.8	<0.001

Data are presented as the mean ± standard error (SE) or as percentages (SE). BMI = body mass index, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, GGT = gamma-glutamyltransferase, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides, UACR = urinary albumin-to-creatinine ratio, WBC = white blood cell, WC = waist circumference.

* TG, WBC count, and UACR were tested after logarithmic transformation.

† P-values were obtained by an ANOVA or chi square test.

the proportion of women differed significantly among the 3 GGT groups. Metabolic variables including BMI, WC, DBP, FPG, HbA1c, TG, WBC, and eGFR showed significant differences across GGT groups. With the exception of HbA1c, these values were significantly higher in the higher GGT groups. Meanwhile, the rate of antihypertensive medication use was highest in the lowest GGT group. Sociodemographic and lifestyle variables including household income and educational level, alcohol consumption, and smoking status also differed significantly among the 3 GGT groups.

Relationship Between Serum GGT level and CVD Risk Factors

Table 2 shows correlations between the serum GGT level and variables related to CVD risk. The serum GGT level correlated negatively with age and positively with BMI, WC, DBP, FPG, TG, WBC, and eGFR.

Figure 1 shows the associations between the serum GGT level and the number of satisfied MetS components (a), tertiles of UACR (T1 ≤ 2.42 mg/g, 2.42 < T2 < 9.43 mg/g, T3 ≥ 9.43 mg/g) (b), and glucose metabolism status (c). Serum GGT levels showed increasing trends with higher numbers of MetS components (P for trend < 0.001), higher UACRs (P for trend = 0.003), and higher glucose levels (P for trend < 0.001).

Subjects with newly diagnosed DM had higher serum GGT levels than those with previously diagnosed DM.

ORs and 95% CIs for Major CVD Risk Factors and Their Associated Traits According to Serum GGT

Table 3 presents ORs (95% CIs) for MetS, high WC, high TG, high FPG, low HDL-C, high UACR, and DM according to serum GGT. The ORs for MetS, high WC, high TG, high FPG, high UACR, and DM tended to increase in the higher GGT groups in all adjusted analyses. However, the ORs for low HDL-C were not significantly associated with serum GGT levels.

DISCUSSION

A number of previous studies suggested that serum GGT levels may play an important role in various CVDs including hypertension and DM. The present study showed a significant association between serum GGT levels and various CVD risk factors even among Korean hypertensive patients.

The pro-oxidant and pro-inflammatory activities¹⁵ of GGT and its direct involvement in atheromatous plaque formation have been suggested¹⁶ as possible mechanisms underlying the association between increased cardiovascular risk and elevated serum GGT levels. Gamma-glutamyltransferase was recently reported to be composed of 4 fractions with distinct molecular

TABLE 2. Pearson’s Correlations Between GGT and Cardiovascular Risk Factors

	γ	<i>P</i> Value [†]
Age, years	-0.3	<0.001
BMI, kg/m ²	0.17	<0.001
WC, cm	0.28	<0.001
SBP, mm Hg	0.05	0.162
DBP, mm Hg	0.3	<0.001
FPG, mg/dL	0.16	<0.001
HbA1c, %	0.001	0.969
TG, mg/dL*	0.37	<0.001
TC, mg/dL	0.03	0.475
WBC count*	0.18	<0.001
eGFR, mL/min/1.73m ²	0.12	<0.001
UACR*	-0.01	0.684

BMI = body mass index, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, GGT = gamma-glutamyltransferase, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides, UACR = urinary albumin-to-creatinine ratio, WBC = white blood cell, WC = waist circumference.

*TG, WBC count, and UACR were tested after logarithmic transformation.

[†] γ (Pearson correlation coefficient) and *P* values were obtained via Pearson’s correlation analysis.

weights and physiochemical properties, namely big-GGT (b-GGT), medium-GGT (m-GGT), small-GGT (s-GGT), and free-GGT (f-GGT).¹⁷ Of these fractions, the b-GGT fraction is known to correlate strongly with conventional cardiovascular and metabolic risk factors and is the only fraction found in atherosclerotic plaque.¹⁶

Several previous studies showed that the GGT level is positively associated with blood pressure change and hypertension.^{2,3,18–20} In our study, DBP tended to increase as the serum GGT level increased. However, the rate of antihypertensive medication use was the highest in the lowest GGT group. This may indicate an association between strict blood pressure control and low serum GGT levels.

Insulin resistance appears to be involved in the relationship between serum GGT levels and CVD risk factors. Although the mechanism underlying the relationship between elevated serum

GGT levels and insulin resistance is not well understood, several studies found that an elevated serum GGT level is a predictor of type 2 DM and MetS, both of which are closely related to insulin resistance.^{21–24} In our study, the FPG level was positively associated with serum GGT level both in newly diagnosed diabetic patients ($\gamma = 0.28022, P = 0.0080$) and in previously diagnosed diabetic patients ($\gamma = 0.28828, P = 0.0257$). Additionally, serum GGT level was slightly higher in newly diagnosed DM patients than in previously diagnosed patients, although there was no significant difference between these 2 subgroups. Newly diagnosed DM is thought to be an earlier stage of diabetes with shorter disease duration or less complication than previously diagnosed DM; therefore, the higher level of serum GGT in newly diagnosed diabetic patients than previously diagnosed diabetic patients might possibly be in accordance with the predictable role of GGT in type 2 DM that was shown in the previous studies. Whereas the no relationship was observed between HDL-C and serum GGT levels, higher serum GGT levels were observed in subjects with more MetS components.

It was reported that a significant proportion of Korean hypertensive patients has albuminuria and that those with albuminuria tend to be older, have a longer duration of hypertension, and have a higher prevalence of obesity, and an SBP ≥ 130 mm Hg and/or DBP ≥ 80 mm Hg compared with normoalbuminuric patients.²⁵ Our study showed that the UACR elevated as the serum GGT level increased. Taken together, these findings may explain the possible association between serum GGT levels and albuminuria in hypertensive patients.

Notably, the serum GGT level showed a significantly negative association with age in the present study. Most previous studies reported positive associations between the serum GGT level and age. Because our study focused on hypertensive patients, this could be explained by the greater likelihood of uncontrolled hypertension in younger participants, which may be associated with elevated serum GGT levels. Younger subjects may also have greater exposure to alcohol consumption and cigarette smoking than older subjects.

The limitations of this study are as follows. First, this was a cross-sectional study, and therefore, causal relationships could not be demonstrated. Second, subjects with fatty liver were not excluded either ultrasonographically or using invasive diagnostic tools. Third, the GGT level is a sensitive indicator of alcohol intake, but chronic heavy alcohol drinkers were not excluded. Fourth, serum GGT levels are known to increase during an

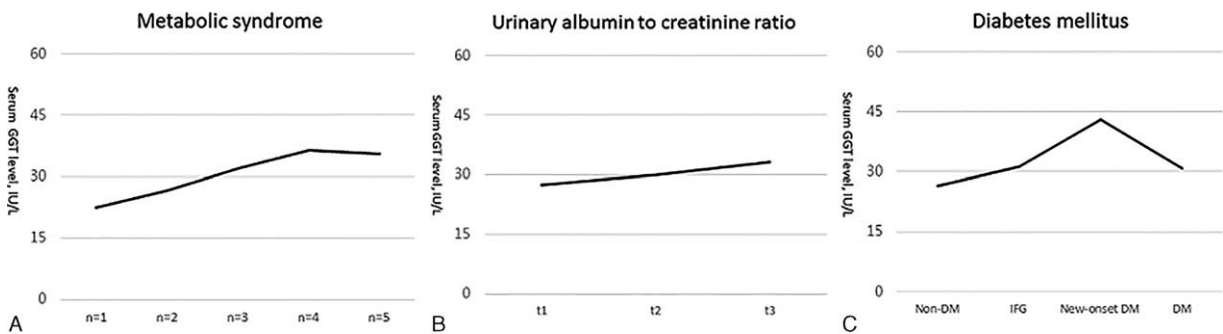


FIGURE 1. Figure shows the distribution of serum GGT levels for each component after adjustment for age and sex: (A) association between the serum GGT level and the total number of metabolic syndrome components ($P < 0.0001$), (B) association between the serum GGT level and the UACR level (T1 < 2.42 mg/g, 2.42 mg/g \leq T2 < 9.43 mg/g, T3 ≥ 9.43 mg/g) ($P = 0.0025$), (C) association between the serum GGT level and the diabetic status ($P < 0.0001$). GGT = gamma-glutamyltransferase, UACR = urinary albumin-to-creatinine ratio.

TABLE 3. ORs and 95% CIs for CVD Risk Factors and Their Associated Traits According to the Serum GGT Group

	MetS	High WC	High TG	High FPG	Low HDL-C	High UACR	DM
			Model 1				
T1	1	1	1	1	1	1	1
T2	2.31(1.60,3.33)	1.70(1.19,2.44)	2.05(1.54,2.74)	1.95(1.38,2.75)	1.06(0.75,1.50)	1.24(0.80,1.92)	2.30(1.57,3.35)
T3	3.23(2.04,5.09)	2.54(1.69,3.81)	3.23(2.17,4.79)	2.42(1.59,3.66)	0.82(0.55,1.21)	2.00(1.24,3.23)	2.23(1.43,3.49)
P for trend	<0.001	<0.001	<0.001	<0.001	0.283	0.004	0.001
			Model 2				
T1	1	1	1	1	1	1	1
T2	1.91(1.26,2.88)	1.03(0.66,1.61)	1.92(1.42,2.59)	1.83(1.28,2.60)	0.92(0.64,1.32)	1.21(0.77,1.91)	2.21(1.50,3.26)
T3	2.64(1.51,4.63)	1.80(1.10,2.93)	2.99(1.96,4.55)	2.20(1.42,3.39)	0.67(0.43,1.03)	1.92(1.15,3.21)	2.08(1.31,3.29)
P for trend	0.001	0.013	<0.001	0.001	0.062	0.012	0.004
			Model 3				
T1	1	1	1	1	1	1	1
T2	1.83(1.22,2.76)	0.98(0.63,1.54)	1.88(1.40,2.53)	1.76(1.24,2.50)	0.89(0.61,1.29)	1.21(0.77,1.90)	2.16(1.49,3.14)
T3	2.67(1.53,4.65)	1.72(1.03,2.87)	2.97(1.95,4.54)	2.25(1.44,3.51)	0.73(0.45,1.18)	2.00(1.17,3.41)	2.38(1.44,3.94)
P for trend	0.001	0.029	<0.001	0.001	0.201	0.011	0.001
			Model 4				
T1	1	1	1	1	1	1	1
T2	1.84(1.24,2.74)	1.27(0.79,2.06)	1.77(1.29,2.43)	2.00(1.40,2.84)	0.88(0.61,1.27)	1.68(1.00,2.84)	2.39(1.60,3.57)
T3	2.66(1.58,4.49)	2.15(1.29,3.58)	3.11(2.01,4.80)	2.44(1.61,3.68)	0.74(0.45,1.22)	2.54(1.44,4.50)	2.53(1.48,4.30)
P for trend	<0.001	0.003	<0.001	<0.001	0.244	0.001	0.001

Data are presented as ORs (95% CIs).

Data were analyzed using multiple logistic regression analysis after adjusting for age, sex, BMI, alcohol consumption, smoking status, physical activity, antihypertensive medication use, and nutritional status. (Model 1: adjusted for age and sex, Model 2: adjusted for BMI in addition to Model 1 variables, Model 3: adjusted for alcohol consumption, smoking status, physical activity, and antihypertensive medication use in addition to Model 2 variables, Model 4: adjusted for energy and fat intake in addition to Model 3 variables).

BMI = body mass index, CI = confidence interval, CVD = cardiovascular disease, DM = diabetes mellitus, FPG = fasting plasma glucose, GGT = gamma-glutamyltransferase, HDL-C = high-density lipoprotein cholesterol, MetS = metabolic syndrome, OR = odds ratio, TG = triglycerides, UACR = urinary albumin-to-creatinine ratio, WC = waist circumference.

inflammatory response.²⁶ However, subjects with inflammatory diseases or other such conditions were not excluded in advance, and the analysis was not corrected for this factor. Fifth, the potential influence of specific types of antihypertensive medications on urinary albumin excretion or renal function was not considered. Despite these limitations, to our knowledge, this study is the first to investigate the relationship between GGT levels and CVD risk factors specifically in hypertensive patients, whereas most previous studies investigated this relationship in the general population.

In conclusion, this study found that the level of serum GGT is associated with major CVD risk factor such as DM, MetS, and an increased UACR in Korean hypertensive patients. Although the mechanism remains to be fully clarified, the serum GGT level can be presumed to be associated with CVD risk factors.

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