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Serum Gamma-Glutamyl Transferase Level Is an Independent Predictor of Incident Hypertension in Korean Adults

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Abstract

The aim of our study was to assess the relationship between serum gamma-glutamyl transferase (GGT) level within the normal range and incident hypertension according to drinking and obesity status in nonhypertensive individuals. We followed up 4783 normotensive adults (mean age = 44 years) who had serum GGT levels within the normal range at baseline for 3 years. Subjects were divided into four GGT quartile groups according to their serum GGT level at baseline. The overall incidence of hypertension was 8.1%, and the incidence increased with increasing GGT quartile (3.8%, 6.9%, 9.0%, and 12.4% in the lowest, second, third, and highest GGT quartiles, respectively; $P < .001$). In the logistic regression analysis adjusted for age, sex, body mass index, lifestyle factors, glucose, uric acid, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, high-sensitivity C-reactive protein, and baseline systolic blood pressure, the odds ratio (ORs) for incident hypertension increased with increasing GGT quartile (P for trend = .030). In the above model, the highest quartile group showed increased ORs compared with those in the lowest quartile group (ORs [95% confidence interval], 2.638 [1.259–5.528]). Subgroup analyses revealed a significant association between GGT quartile and the incidence of hypertension in the drinker and non-overweight groups. Our results indicate that elevated serum GGT levels within the normal range are associated with a higher risk of incident hypertension in Korean adults, particularly, in drinkers and non-overweight individuals, suggesting possible different pathophysiologic mechanisms in the incidence of alcohol- and obesity-related hypertension.

Keywords: gamma-glutamyl transferase, hypertension, obesity, alcohol consumption, blood pressure

INTRODUCTION

Gamma-glutamyltransferase (GGT) is a sensitive indicator of hepatic cell inflammation and hepatic triglyceride (TG) accumulation, which are observed in obesity, diabetes mellitus, and excessive alcohol consumption (1,2). GGT has a pro-oxidative effect (3), as it is involved in the degradation of the antioxidant glutathione and has an indirect pro-oxidative effect by causing low-density lipoprotein (LDL) cholesterol oxidation in the presence of iron. GGT is also considered a proinflammatory marker (4), and enzyme activity of serum GGT found within atherosclerotic lesions directly contributes to atherosclerosis progression (5). It has been suggested that serum GGT is independently associated with several pathological conditions including cardiovascular disease (1), diabetes (6), and metabolic syndrome (7).

Several cross-sectionalstudies have reported a positive association between serum GGT level and prehypertension/hypertension (8–10). Recently, the relationship between serum GGT level and incident hypertension has been investigated in several longitudinal studies. However, the results from these studies are inconsistent (11–16), and most of these studies included subjects with abnormal serum GGT levels and did not exclude subjects with hepatic pathological conditions such as hepatitis B or C that could directly influence serum GGT level. A Western study reported an association between serum GGT level within the normal range and incident hypertension according to drinking status and obesity status (17). Their results showed that increasing GGT quintiles increased the incidence of hypertension in both drinker and nondrinker groups and only in the group with increased central fat distribution.

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However, the study populations were only Western people.

Therefore, our aims in this study were to evaluate whether serum GGT is an independent predictor for the development of hypertension in Korean normotensive adults and to assess the relationship between serum GGT level and incident hypertension according to drinking status and obesity status in this subject group.

MATERIALS AND METHODS

Subjects

A total of 7858 Korean adults who were inhabitants of either Seoul or Kyunggi Province visited Kangbuk Samsung Hospital for health examinations in 2002 and 2005. Among them, 3075 subjects were excluded from this study: 438 subjects had positive results for hepatitis B virus surface antigen or hepatitis C virus antibody, 1318 subjects showed GGT concentrations higher than the upper limit of the reference range (>51 U/L), 1244 subjects were hypertensive at baseline (systolic blood pressure [SBP] $\geq$ 140 mm Hg or diastolic blood pressure [DBP] $\geq$ 90 mm Hg, or current use of antihypertensive agents), and 75 subjects did not provide information about their alcohol consumption habits. Ultimately, 4783 subjects (mean age = 44 $\pm$ 5.8 years, 3246 men) were enrolled in this study and were followed up for an average of 3 years. Nine (0.2%) subjects had taken antidiabetic medication at baseline.

Subjects were classified into one of four GGT quartile groups according to their baseline serum GGT concentrations: quartile 1 consisted of subjects with GGT levels between 0 and 12.9 U/L; quartile 2 included subjects with GGT levels between 13 and 18.9 U/L; quartile 3 was composed of subjects with GGT levels between 19 and 28.9 U/L; and quartile 4 included subjects with GGT levels between 29 and 51 U/L.

This research protocol was approved by the Institutional Review Board of Kangbuk Samsung Hospital (KBC10090). All participants provided written informed consent during health examinations.

Measurements

Medical and medication histories, smoking status (current smoker or nonsmoker), alcohol drinking frequency ($\geq$3 times per week), the amount of alcohol consumed (g/time), and physical activity ($\geq$3 times per week) were assessed using the same standard questionnaires in both 2002 and 2005.

The data for alcohol consumption history were collected primarily using self-reported questionnaires. Alcohol consumption history was assessed by asking the frequency of alcoholic beverage consumption and the amount of alcohol consumed per time, using the most popular alcoholic beverage (Soju) in Korea. One bottle of Soju contains 56.5 g of ethanol.

The SBP and DBP were measured by a trained registered nurse by placing a mercury sphygmomanometer on the right arm of the subject, who was in a seated position and had rested for 5 minutes or longer (18). When measured, SBP or DBP was $\geq$140/90 mm Hg; blood pressure was measured once more and the average value was used for this analysis.

Height and weight were measured with an automated scale while the participants were wearing a light hospital gown without shoes, and body mass index (BMI) was calculated as weight (kilograms) divided by height squared (meters squared).

Blood samples were obtained in the morning after an overnight fast. Concentrations of high-sensitivity C-reactive protein (hsCRP) were measured using particle-enhanced immunonephelometry, with a lower limit of detection of 0.02 mg/L (Behring Nephelometer II, Dade Behring, Marburg, Germany). Plasma glucose, total cholesterol, TG, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and uric acid levels were measured using an autoanalyzer (Advia 1650 Autoanalyzer, Bayer Diagnostics, Leverkusen, Germany). Serum concentrations of GGT were measured by kinetic spectrophotometric method, using L-γ-glutamyl-*p*-nitroanilide (Adiva 1800, Siemens Healthcare Diagnostics, Tokyo, Japan) with a normal range of 0–51 U/L. Serum GGT level was measured using the same reagent on the same autoanalyzer in both 2002 and 2005, and the within-run and total coefficients of variation for GGT determinations were not greater than 10% during the period. Baseline serum GGT levels were categorized by quartile (0–12.9, 13–18.9, 19–28.9, and 29–51 U/L).

Incident hypertension was defined as SBP of 140 mm Hg or greater, DBP of 90 mm Hg or greater, or current use of hypertensive medications at the follow-up visit.

STATISTICAL ANALYSIS

Data are expressed as mean $\pm$ standard deviation (SD) or median and interquartile ranges for continuous variables and percentages for categorical variables. Among the variables, TG and hsCRP levels were naturally logarithm-transformed to obtain a normal distribution for statistical analysis.

Differences in baseline characteristics according to GGT quartile were determined using analysis of variance and χ^2 test. Comparisons of characteristics according to the development of new hypertension were assessed using Student *t* test and χ^2 test.

Alcohol-adjusted correlation analyses were performed to assess the associations between baseline GGT level, SBP, and DBP, and changes in GGT, SBP, and DBP at baseline and at follow-up.

Multivariate adjusted logistic regression analyses were used to evaluate the association between serum GGT level and incident hypertension: model 1 was

adjusted for age, sex, lifestyle factors (amount of alcohol consumption, smoking status, and physical activity), and BMI; model 2 was adjusted for the variables in model 1 in addition to traditional risk factors (baseline glucose, uric acid, HDL cholesterol, LDL cholesterol, TG, and hsCRP) and baseline SBP.

For subgroup analyses, the study population was divided into two pairs of groups: a nondrinker group versus a drinker group, according to the presence/absence of alcohol consumption, and a nonobese group (BMI < 25 kg/m^2) versus an overweight group (BMI ≥ 25 kg/m^2), according to the proposed classification of weight by BMI in adults.

Data were analyzed using PASW version 18.0 (SPSS Inc., Chicago, IL, USA), and P values $<.05$ were considered statistically significant.

RESULTS

Among 4783 adults without hypertension at baseline, the overall incidence of new hypertension was 8.1% (389 of 4783). The incidence of new hypertension increased with increasing serum GGT quartile (3.8%, 6.9%, 9.0%, and 12.4% in the lowest, second, third, and highest GGT quartiles, respectively; $P < .001$).

Baseline subject characteristics according to serum GGT quartile are presented in Table 1. As the serum GGT quartile increased, age, the proportion of men, prehypertension at baseline, prevalence of DM at baseline, baseline SBP and DBP, BMI, body weight, current smoking status, and alcohol consumption increased; in other words, subjects in higher serum GGT quartiles had more unfavorable metabolic and lipid profiles than did those in lower serum GGT quartiles (Table 1).

Comparisons of subject characteristics according to the development of new hypertension revealed that subjects in the incident hypertension group were older and more likely to be male. Moreover, subjects in the incident hypertension group consumed alcohol more frequently and had higher baseline SBP and DBP, BMI, and body weight, and more unfavorable metabolic and lipid profiles compared with those in the nonincident hypertension group. Furthermore, the incident hypertension group had higher GGT levels at baseline and higher magnitude changes in GGT level between baseline and follow-up than did the nonincident hypertension group (3.4 ± 13.7 in nonincident hypertension group vs. 5.2 ± 12.8 in incident hypertension group; $P = .006$; Table 2).

Alcohol-adjusted correlation analyses revealed that baseline GGT level was significantly positively correlated with baseline SBP and DBP ($r = 0.182$ and $r = 0.197$, respectively; $P < .001$). Furthermore, the change in GGT level between baseline and follow-up was positively correlated with changes in SBP and DBP ($r = 0.05$, $P = .001$ and $r = 0.039$, $P = .007$, respectively).

In the multivariate regression analyses of all models, the incidence of new hypertension was significantly associated with increasing quartile of GGT level (all P for trend $<.05$). Furthermore, the odds ratios (Ors) for incident hypertension in the highest quartile group in the multivariate regression models were significantly increased compared with that of the lowest quartile group (ORs [95% confidence interval] = 2.408 [1.212–4.785] in model 1; 2.638 [1.259–2.528] in model 2; Table 3). Meanwhile, when substituting GGT quartile with serum GGT (as a continuous variable), the association between serum GGT level and incident hypertension was not significant in any of the models (all P values $>.05$; data not shown).

Sex-specific analyses showed that baseline serum GGT level was higher in men (25.8 ± 10.7 U/L) than in women (13.3 ± 7.1 U/L) and that the incidence of hypertension was about twofold higher in men than in women (men vs. women: 9.8% vs. 4.6%). Furthermore, the incidence of hypertension increased according to increasing GGT quartiles in both sexes (8.0%, 7.8%, 11.2%, and 12.1% in the lowest, second, third, and highest GGT quartiles in men, $P = .003$; 2.8%, 2.9%, 4.0%, and 7.8% in the lowest, second, third, and highest GGT quartiles in women, $P = .002$). However, sex-specific regression analyses revealed that both the baseline serum GGT quartiles and the absolute values of serum GGT were not significantly associated with incident hypertension in either sex (data not shown).

In the subgroup analyses in the alcohol/nonalcohol consumption groups, the incidence of new hypertension in the drinker group was higher than that in the nondrinker group (9.3% vs. 6.1%, respectively; $P < .001$). In the multivariate regression analyses, the incidence of new hypertension was significantly associated with increasing GGT quartile in the drinker group, although no significant association was found between incident hypertension and GGT quartile in any of the models in the nondrinker group (Table 4).

The incidence of new hypertension in the nonobese group was lower than that in the overweight group (6.3% vs. 13.5%, respectively; $P < .001$). In the nonobese group, higher serum GGT quartile groups significantly had higher ORs for incident hypertension than did the lowest quartile group in all models. However, the overweight group showed no association between incident hypertension and GGT quartile group in any of the models (Table 5).

When subjects were subdivided into four groups according to drinking status (nondrinker vs. drinker) and BMI status (nonobese vs. overweight), the incidence of hypertension in the drinker and overweight group was highest (4.8% in the nondrinker and nonobese group, 11.5% in the nondrinker and overweight group, 7.3% in the drinker and nonobese group, and 14.3% in the drinker and overweight group). However, the association between serum GGT quartile and incident hypertension was more obvious in the drinker and nonobese group than it was in the remaining three groups (data not shown).

Table 1. Baseline characteristics of the subjects according to GGT quartile

	Serum GGT quartiles				
	Q1 ($n = 1182$)	Q2 ($n = 1087$)	Q3 ($n = 1276$)	Q4 ($n = 1238$)	P value
Age (y)	43 ± 6.2	44 ± 5.9	45 ± 5.7	45 ± 5.3	<.001
Men, *n* (%)	252 (21.3)	710 (65.3)	1115 (87.4)	1169 (94.4)	<.001
SBP (mm Hg)	106 ± 11.3	109 ± 10.0	111 ± 9.4	112 ± 8.9	<.001
DBP (mm Hg)	68 ± 8.3	71 ± 8.0	73 ± 7.3	73 ± 7.1	<.001
BMI (kg/m^2)	21.8 ± 2.3	22.6 ± 2.6	23.7 ± 2.5	24.7 ± 2.5	<.001
Body weight (kg)	57.4 ± 7.9	63.5 ± 9.4	68.2 ± 8.9	71.5 ± 8.8	<.001
Glucose (mmol/L)	4.83 ± 0.49	5.00 ± 0.63	5.05 ± 0.63	5.22 ± 0.94	<.001
TC (mmol/L)	4.87 ± 0.82	5.05 ± 0.82	5.28 ± 0.86	5.44 ± 0.89	<.001
TG[a] (mmol/L)	0.90 [0.71, 1.22]	1.11 [0.82, 1.49]	1.37 [1.01, 1.84]	1.67 [1.23, 2.26]	<.001
LDL-C (mmol/L)	2.80 ± 0.67	2.98 ± 0.71	3.13 ± 0.76	3.21 ± 0.81	<.001
HDL-C (mmol/L)	1.55 ± 0.35	1.48 ± 0.33	1.37 ± 0.31	1.32 ± 0.30	<.001
hsCRP[a] (mg/L)	0.02 [0.02, 0.02]	0.02 [0.02, 0.02]	0.02 [0.02, 0.02]	0.02 [0.02, 0.02]	.005
Uric acid (μmol/L)	255.8 ± 59.5	303.3 ± 77.3	339.0 ± 71.4	362.8 ± 71.4	<.001
Insulin (pmol/L)	47.23 ± 15.97	48.62 ± 16.67	51.39 ± 18.75	56.25 ± 18.06	<.001
GGT (U/L; baseline)	9.6 ± 2.1	15.4 ± 1.7	23.0 ± 2.9	37.8 ± 6.5	<.001
GGT (U/L; follow-up)	10.9 ± 4.9	17.9 ± 8.2	27.1 ± 11.4	43.7 ± 23.4	<.001
Net GGT (U/L)	1.34 ± 4.66	2.50 ± 7.90	4.11 ± 11.08	5.86 ± 22.60	<.001
Alcohol frequency (≥3 times/wk), *n* (%)	14 (1.2)	46 (4.2)	102 (8.0)	172 (13.9)	<.001
Alcohol amount (g/time)					<.001
<56.5	627 (95.1)	739 (87.7)	917 (81.8)	880 (76.3)	
56.5–113	27 (4.1)	86 (10.2)	157 (14.0)	208 (18.0)	
>113	5 (0.8)	18 (2.1)	47 (4.2)	66 (5.7)	
Smoking (current), *n* (%)	108 (9.4)	260 (24.3)	469 (37.2)	550 (44.5)	<.001
Physical activity (≥3 times/wk), *n* (%)	220 (19.3)	227 (21.3)	220 (17.5)	191 (15.6)	.003
Diabetes mellitus, *n* (%)	4 (0.3)	16 (1.5)	22 (1.7)	32 (2.6)	<.001
BP category, *n* (%)					<.001
Normal	865 (73.2)	670 (61.6)	667 (52.3)	583 (47.1)	
Prehypertension	317 (26.8)	417 (38.4)	609 (47.7)	655 (52.9)	

Abbreviations: SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; TC – total cholesterol; TG – triglyceride; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; hsCRP – high-sensitivity C-reactive protein; BP – blood pressure; GGT – gamma-glutamyl transferase.

Notes: Data are means ± SD or medians [interquartiles] for continuous variables and percentages for categorical variables. GGT quartile groups were defined as follows: Q1 (0–12.9 U/L), Q2 (13–18.9 U/L), Q3 (19–28.9 U/L), and Q4 (29–51 U/L).

[a]TG and hsCRP are expressed as raw data but were naturally log-transformed prior to statistical analyses.

DISCUSSION

This longitudinal study showed that the overall incidences of new hypertension in Korean middle- and old-aged individuals with baseline serum GGT level within the normal reference range were 8.1% (9.8% in men and 4.6% in women, respectively) after a 3-year follow-up. Higher GGT levels were significantly associated with the development of new hypertension, irrespective of drinking or obesity status. However, in subgroup analyses, serum GGT level was significantly associated with incident hypertension only in the drinker and nonobese groups.

The mechanisms that lead to increased BP in subjects with increased GGT within the normal range are not completely understood. GGT is present in the serum and on the surfaces of most cell types and plays a direct role in the generation of reactive oxygen species (3,4). GGT has the primary function of maintaining the intracellular concentration of glutathione in response to oxidative stress and is recognized as a marker of oxidative stress (19). GGT has also been used as a proinflammatory marker because of its indirect involvement in the generation of cysteinyl-glycine, which results in LDL oxidation (4). Recently, a study reported that enzyme activity of serum GGT found within atherosclerotic lesions directly contributes to atherosclerosis progression (5). For the reasons outlined above, it has been hypothesized that serum GGT level may be associated with prehypertension/hypertension, which are pathologic conditions associated with increased production of reactive oxygen species and proinflammatory substances.

Several cross-sectional observational studies have reported that serum GGT level is positively associated with prehypertension/hypertension (8–10). However, these studies included individuals with GGT levels above the normal range; other confounding conditions such as hepatic parenchymal disease that could directly increase serum GGT level were not excluded. Moreover, these studies were not able to

Table 2. Baseline characteristics according to the development of new hypertension

	No development of HTN ($n = 4394$)	Development of HTN ($n = 389$)	P value
Age (y)	44 ± 5.7	46 ± 6.6	<.001
Men, n (%)	2927 (66.6)	319 (82.0)	<.001
SBP (mm Hg)	109 ± 10.1	116 ± 9.2	<.001
DBP (mm Hg)	71 ± 8.0	76 ± 6.1	<.001
BMI (kg/m^2)	23.1 ± 2.7	24.6 ± 2.7	<.001
Body weight (kg)	64.9 ± 10.2	70.1 ± 9.7	<.001
Glucose (mmol/L)	5.05 ± 0.68	5.16 ± 1.00	.027
TC (mmol/L)	5.15 ± 0.87	5.31 ± 0.92	<.001
TG[a] (mmol/L)	1.22 [0.87, 1.73]	1.42 [1.08, 2.02]	<.001
LDL-C (mmol/L)	3.03 ± 0.76	3.13 ± 0.78	.009
HDL-C (mmol/L)	1.42 ± 0.34	1.40 ± 0.33	.014
hsCRP[a] (mg/L)	0.02 [0.02, 0.02]	0.02 [0.02, 0.02]	.084
Uric acid (μmol/L)	315.2 ± 83.3	333.1 ± 77.3	<.001
Insulin (pmol/L)	50.70 ± 17.36	54.17 ± 18.75	.001
GGT (U/L; baseline)	21.4 ± 11.2	25.8 ± 11.3	<.001
GGT (U/L; follow-up)	24.8 ± 18.7	31.0 ± 17.7	<.001
Net GGT (U/L)	3.36 ± 13.75	5.23 ± 12.84	.006
Alcohol frequency (≥3 times/wk), n (%)	293 (6.7)	41 (10.5)	.004
Alcohol amount (g/time)			.557
<56.5	2891 (83.9)	272 (81.7)	
56.5–113	430 (12.5)	48 (14.4)	
>113	123 (3.6)	13 (3.9)	
Smoking (current), n (%)	1272 (29.3)	115 (29.9)	.794
Physical activity (≥3 times/wk), n (%)	770 (17.9)	88 (22.9)	.016
Diabetes mellitus, n (%)	64 (1.5)	10 (2.6)	.088
BP category, n (%)			<.001
Normal	2670 (60.8)	115 (29.6)	
Prehypertension	1724 (39.2)	274 (70.4)	

Abbreviations: SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; TC – total cholesterol; TG – triglyceride; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; hsCRP – high-sensitivity C-reactive protein; GGT – gamma-glutamyl transferase; BP – blood pressure; HTN – hypertension.
Notes: Data are means ± SD or medians [interquartiles] for continuous variables and percentages for categorical variables.
[a]TG and hsCRP are expressed as raw data but were naturally log-transformed prior to statistical analyses.

Table 3. Logistic regression analyses of the association between increased serum GGT quartile and incident hypertension

	Serum GGT quartiles				
	Quartile 1 ($n = 1182$)	Quartile 2 ($n = 1087$)	Quartile 3 ($n = 1276$)	Quartile 4 ($n = 1238$)	P for trend
Incident HTN, n (%)	45 (3.8)	75 (6.9)	115 (9.0)	154 (12.4)	
Age- and sex-adjusted	1	1.528 [1.019–2.291]	1.885 [1.256–2.830]	2.645 [1.763–3.968]	<.001
Model 1	1	2.189 [1.094–4.379]	1.937 [0.975–3.849]	2.408 [1.212–4.785]	.047
Model 2	1	2.256 [1.079–4.714]	2.000 [0.963–4.154]	2.638 [1.259–5.528]	.030

Abbreviations: HTN – hypertension; GGT – gamma-glutamyl transferase.
Notes: Values are odds ratio [95% confidence interval]. Model 1 was adjusted for age, sex, lifestyle factors (alcohol amount, smoking status, and physical activity), and body mass index. Model 2 was adjusted for model 1 and traditional risk factors (baseline glucose, uric acid, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, and high-sensitivity C-reactive protein) and baseline systolic blood pressure.

determine any cause-and-effect relationships between serum GGT level and incident hypertension due to their cross-sectional design.

Recently, several longitudinal studies have investigated the association between serum GGT level and incident hypertension; however, the results from these studies are not consistent (11–16). One longitudinal study showed a positive association between serum GGT level within the normal range and incident hypertension after a 15-year follow-up (12), consistent with

Table 4. Logistic regression analyses of the association between increased serum GGT quartile and incident hypertension in the presence/absence of alcohol consumption

Nondrinker group	Quartile 1 ($n = 782$)	Quartile 2 ($n = 440$)	Quartile 3 ($n = 308$)	Quartile 4 ($n = 182$)
Incident HTN, n (%)	33 (4.2)	22 (5.0)	28 (9.1)	21 (11.5)
Age- and sex-adjusted	1	0.986 [0.552–1.761]	1.648 [0.910–2.985]	2.006 [1.027–3.917]
Model 1	1	0.836 [0.456–1.532]	1.171 [0.619–2.213]	1.297 [0.624–2.695]
Model 2	1	0.727 [0.378–1.396]	0.721 [0.350–1.483]	0.756 [0.317–1.802]
Drinker group	Quartile 1 ($n = 398$)	Quartile 2 ($n = 647$)	Quartile 3 ($n = 968$)	Quartile 4 ($n = 1056$)
Incident HTN, n (%)	12 (3.0)	53 (8.2)	87 (9.0)	133 (12.6)
Age- and sex-adjusted	1	2.485 [1.280–4.823]	2.654 [1.380–5.106]	3.841 [2.012–7.332]
Model 1	1	2.289 [1.149–4.559]	2.105 [1.065–4.160]	2.673 [1.355–5.270]
Model 2	1	2.312 [1.112–4.805]	2.124 [1.029–4.386]	2.847 [1.370–5.913]

Abbreviations: HTN – hypertension; GGT – gamma-glutamyl transferase.
Notes: Values are odds ratios [95% confidence interval]. Model 1 was adjusted for age, sex, lifestyle factors (smoking status and physical activity), and body mass index. Model 2 was adjusted for model 1 and traditional risk factors (baseline glucose, uric acid, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, and high-sensitivity C-reactive protein) and baseline systolic blood pressure.

Table 5. Logistic regression analyses of the association between increased serum GGT quartile and incident hypertension in the BMI subgroups

Nonobese group	Quartile 1 ($n = 844$)	Quartile 2 ($n = 615$)	Quartile 3 ($n = 470$)	Quartile 4 ($n = 272$)
Incident HTN, n (%)	28 (2.7)	58 (6.4)	73 (7.9)	67 (9.5)
Age- and sex-adjusted	1	2.023 [1.236–3.311]	2.323 [1.397–3.862]	2.714 [1.607–4.584]
Model 1	1	3.350 [1.352–8.302]	3.099 [1.246–7.708]	4.037 [1.615–10.089]
Model 2	1	2.956 [1.166–7.496]	2.579 [1.009–6.593]	3.332 [1.280–8.678]
Overweight group	Quartile 1 ($n = 326$)	Quartile 2 ($n = 451$)	Quartile 3 ($n = 790$)	Quartile 4 ($n = 947$)
Incident HTN, n (%)	17 (13.1)	17 (9.2)	42 (11.8)	87 (16.3)
Age- and sex-adjusted	1	0.624 [0.293–1.327]	0.797 [0.399–1.594]	1.174 [0.594–2.318]
Model 1	1	1.121 [0.362–3.476]	1.239 [0.431–3.563]	1.676 [0.597–4.704]
Model 2	1	1.323 [0.371–4.712]	1.421 [0.430–4.690]	2.081 [0.635–6.825]

Abbreviation: HTN – hypertension; GGT – gamma-glutamyl transferase; BMI – body mass index.
Notes: Values are odds ratio [95% confidence interval]. Model 1 was adjusted for age, sex, and lifestyle factors (alcohol amount, smoking status, and physical activity). Model 2 was adjusted for model 1 and traditional risk factors (baseline glucose, uric acid, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, and high-sensitivity C-reactive protein) and baseline systolic blood pressure.

our results. However, this previous study included only black and white American individuals, whereas we investigated only Asian subjects. Moreover, the previous longitudinal study did not exclude subjects with hepatic diseases that could affect serum GGT level. Another longitudinal study in Korean male workers reported that elevated GGT level was not significantly associated with new hypertension in the total study population after a 4-year follow-up; however, the authors of this study did report that a GGT level ≥30 U/L was a predictor for new hypertension compared with a GGT level <30 U/L, in contrast to our results (11). Although the same ethnic group was evaluated in both the previous study and our study, the earlier study did not exclude subjects with hepatic diseases such as hepatitis B or C, which are prevalent in Korea; furthermore, a different definition of hypertension was used in the earlier study, which may explain the conflicting findings. A study performed in Norway to investigate the association between concurrent changes in GGT level and SBP over a period of 7 years demonstrated a weak association, only in females (13). However, the design of the Norwegian study was very different from those of the other three longitudinal studies, including our study, and may not have had the power to assess the effects of GGT level on the development of new hypertension.

The results of our subgroup analysis according to drinking status showed that GGT quartile and new

hypertension were significantly associated only in the drinker group, and that the drinker group had a higher incidence of hypertension development than did the nondrinker group. Previous results from studies that investigated the relationship between GGT level and drinking status are inconsistent. A cross-sectional Japanese study reported that the association between serum GGT level and the prevalence of hypertension was similar in drinkers and nondrinkers, which differs from our results; moreover, this previous study evaluated a different study population, including individuals with abnormal GGT level (9). In a longitudinal Japanese study with a 5-year follow-up, baseline GGT levels above 50 U/L were significantly associated with incidences of hypertension in drinkers only, which suggest that elevated serum GGT activity may identify drinkers at higher risk of developing alcohol-related hypertension (10). Another Japanese 10-year prospective study including only male drinkers suggested that increased serum GGT level (>20 U/L) may predict the further development of hypertension among drinkers, even though this previous study included a different subject population than our study (14). In addition, the other study reported that abnormal serum GGT values (≥50 U/L) were correlated with the development of hypertension in nondrinkers (15,16). Unlike these previous studies, we included only subjects with serum GGT level within the normal range.

Body mass index is known to be an important factor influencing the development of hypertension. Our subgroup analyses showed that the incidence of hypertension in the overweight group was 2.1-fold higher than that in the nonobese group. However, the association between increasing GGT quartile and incident hypertension was only significant in the nonobese group. This finding suggests that obesity itself is more strongly associated than GGT level with the development of hypertension, resulting in the attenuation of the relationship between serum GGT level and incident hypertension in the obese group. The incidence of hypertension in the highest GGT quartile in the nonobese group was lower than that in the lowest GGT quartile in the overweight group (9.5% vs. 13.1%, respectively). A previous study reported that serum GGT level showed a positive association with alcohol consumption and BMI (20), consistent with our results that serum GGT level is correlated with alcohol consumption and BMI. Another 6-year follow-up study investigated the association between GGT and hypertension within normotensive individuals according to drinking and BMI status and suggested that increasing GGT quintiles increased the incidence of hypertension in both drinker and nondrinker groups and only in groups with increased central fat distribution (17). However, this study included only Western subjects, and the results were inconsistent with our study.

Our study had several limitations. First, our definition of hypertension was based on a single estimate of blood pressure. Although high BPs were measured more than once, misclassification of BP cannot be excluded. Second, although most epidemiological studies have used a single GGT measurement, this single measurement might not be reliable, considering the previous report that 12% of adults in the American general population with initially elevated GGT levels had normal level on their second examination (21). Third, the reliability and the validity of self-reported alcohol consumption are questionable. Generally, individuals tend to conceal their alcohol consumption and report lower than actual consumption. Fourth, certain diet patterns are associated with increased GGT, including consumption of red meat and alcohol, whereas consumption of nonfried or canned vegetables, grains, beans, tree nuts, and coffee seems to be associated with lower levels of GGT (22). Furthermore, high sodium intake is generally associated with the development of hypertension. However, we have no data regarding dietary patterns. Finally, we have no data regarding hepatic ultrasonography to exclude parenchymal liver diseases, such as fatty liver, cirrhosis, and hepatocellular carcinoma. However, our study subjects were apparently healthy at baseline, and we excluded subjects who had viral hepatitis and abnormal baseline serum GGT level.

On the other hand, the strengths of our study are that we excluded individuals who had confounding conditions that could increase serum GGT level and demonstrated an epidemiologic association between serum GGT level and incident hypertension independent of drinking status, BMI status, and various coexisting factors.

In conclusion, we found that increasing serum GGT level within the normal range was independently associated with incident hypertension in Korean adults. This association was significant only in drinkers and nonobese individuals, respectively. Further prospective population-based studies are needed to assess a more accurate relationship between GGT level and the incidence of hypertension.

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