Original Article

Serum Gamma-Glutamyl Transferase Levels are Associated with Metabolic Syndrome in Community-Dwelling Individuals

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Aim: Serum gamma-glutamyl transferase (GGT) activity changes in response to oxidative stress. Metabolic syndrome (MetS) is associated with an increased risk of major cardiovascular events. Few data are available on the association between serum GGT and the prevalence of MetS among community-dwelling individuals in Japan.

Methods: We recruited 793 men (mean age, 60 ± 14 years), and 1,073 women (62 ± 12 years), free from any history relating to cardiovascular disease during their annual health examination, from a single community. We performed a cross-sectional study to examine whether serum GGT was associated with MetS.

Results: The levels of most confounding characteristics varied with increasing GGT activity. After adjustment for age, smoking status, drinking status, low-density lipoprotein cholesterol, uric acid, estimated glomerular filtration rate and alanine aminotransferase, the odds ratios (95% confidence interval) for MetS increased across serum GGT tertiles (1, 2.23 (1.22–4.07), and 2.32 (1.18–4.56) in men; and 1, 1.43 (0.81–2.51), and 2.64 (1.50–4.64) in women). After additional adjustment for insulin resistance markers (immuno-reactive insulin or homoeostasis model assessment of insulin resistance index), the association was attenuated and the linear relation no longer significant in both genders. Furthermore, serum GGT was significantly associated with the presence of individual components of MetS in both genders, except for dyslipidemia in men and hypertension in women.

Conclusions: These results suggested that higher serum GGT was significantly associated with MetS and its components in the general population. This association was related with insulin resistance but was independent of other confounding factors.

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Key words; Gamma-glutamyl transferase, Metabolic syndrome, Risk factor, Insulin resistance

Introduction

Serum gamma-glutamyl transferase (GGT) is an enzyme that contributes to the extracellular catabolism of glutathione (GSH)¹⁾. The enzyme is present on cell surfaces and in serum, but most serum GGT is derived from the liver²⁾. Serum GGT is a clinical marker of several factors: alcohol consumption, body fat content, plasma lipid/lipoproteins and glucose lev-

els, and medications^{1, 2)}. Elevated serum GGT activity is also a sensitive marker of oxidative stress¹⁾ and is associated with cardiovascular disease (CVD)³⁻⁵⁾. Serum GGT can also reflect other concomitant risk factors, such as obesity⁶⁾, insulin resistance^{7, 8)}, diabetes⁷⁻¹⁰⁾, hypertension^{9, 11)}, and dyslipidemia and metabolic syndrome^{10, 12-14)}.

Metabolic syndrome (MetS), a clustering of cardiovascular risk factors such as insulin resistance, hypertension, glucose intolerance, hypertriglyceridemia, and low high-density lipoprotein cholesterol (HDL-C) levels, is a major worldwide public health problem. MetS affects 13.3% to 24.4% of Japanese men ≥ 30 years of age^{15, 16)}. With the continuous increase in obesity prevalence in Japan, MetS may become even more

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common. MetS increases the risk of atherosclerotic disease, diabetes^{17, 18)}, and CVD¹⁹⁾; however, there are few reports on the relationship between serum GGT and MetS in Japan.

The aim of this study was to determine whether serum GGT is associated with MetS risk, and we examined cross-sectional data from Japanese community-dwelling participants.

Materials and Methods

Subjects

Participants were recruited at the time of their annual health examination in a rural town with a total population of 11,136 (as of April 2002) located in Ehime prefecture, Japan, in 2002. Among 9,133 adults aged 19 to 90 years in this population, 3,164 (34.6%) were assessed for eligibility to participate in the study. Information on medical history, present conditions, and medications was obtained by interview. The final study sample included 1,866 eligible individuals free from any history or symptoms of CVD. The Ethics Committee of Ehime University School of Medicine approved all procedures.

Evaluation of Risk Factors

Information on demographic characteristics and risk factors was collected using clinical files. Body mass index was calculated by dividing weight (in kilograms) by the square of the height (in meters). We measured blood pressure with an appropriately sized cuff on the right upper arm of the subjects using an automatic oscillometric blood pressure recorder (BP-103i; Colin, Aichi, Japan) while seated after resting for at least 5 min. Cigarette smoking was quantified based on daily consumption and a history of smoking for subjects who reported smoking. Total cholesterol (T-C), triglycerides (TG), HDL-C, fasting blood glucose (FBG), creatinine (enzymatic method), uric acid, immuno-reactive insulin (IRI), alanine aminotransferase (ALT), and GGT were measured during fasting. Serum GGT concentration was assayed with an automatic analyzer (TBA-c6000, TOSHIBA, Tokyo) and the intraassay coefficient of variation was 0.87 to 2.11%. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald formula²⁰⁾. Participants with TG ≥ 400 mg/dL were excluded (34 cases). Estimated GFR was calculated using the following equation: $eGFR = 194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female)²¹⁾. Participants with an $eGFR < 30$ mL/min/ 1.73 m² were excluded (8 cases). Homeostasis of minimal assessment of insulin resistance (HOMA-IR) was calculated from FBG and IRI levels using the follow-

ing formula; $FBG \{[(mg/dL) \times IRI (mU/mL)]/405\}$ ²²⁾.

Metabolic Syndrome

We applied condition-specific cutoff points for MetS based on the modified guidelines for the diagnosis of MetS in Japan²³⁾. Metabolic syndrome was defined as obesity with at least two of the following three conditions: hypertension, dyslipidemia, and impaired fasting glucose (IFG). Obesity was defined as a BMI ≥ 25.0 kg/m²^{24, 25)}. Hypertension was defined as systolic blood pressure (SBP) ≥ 130 mmHg, diastolic blood pressure (DBP) ≥ 85 mmHg, or current treatment for hypertension. Dyslipidemia was defined as TG concentrations ≥ 150 mg/dL, low HDL cholesterol (HDL-C < 40 mg/dL), or current treatment for dyslipidemia. IFG was defined as a FBG level ≥ 110 mg/dL or current treatment for diabetes mellitus.

Statistical Analysis

Statistical analyses were performed using SPSS 10.0J (Statistical Package for Social Science, Inc., Chicago, IL, USA). Data are presented as the mean $\pm$ standard deviation (SD) unless otherwise specified, and parameters with non-normal distributions (TG, ALT, IRI, HOMA-IR, and GGT), the data are the median (interquartile range). In all analyses, parameters with non-normal distributions were used after log transformation. Differences among 3 groups divided based on tertiles of serum GGT (12–27 IU/L, 28–54 IU/L and ≥ 55 IU/L in men; and 9–17 IU/L, 18–24 IU/L and ≥ 25 IU/L in women) were analyzed by the Mann-Whitney *U* test, Kruskal-Wallis test or chi-square (χ^2) test. Multiple logistic regression analysis was used to evaluate the contribution of confounding factors for MetS and each component of MetS. A *p*-value < 0.05 was considered significant.

Results

Subject Background Characteristics

The characteristics of the study participants in relation to sex are illustrated in **Table 1**. The study included 793 men, aged 60 ± 14 (range, 20–89) years, and 1,073 women, aged 62 ± 12 (range, 21–88) years. Body mass index, smoking status, drinking status, SBP, DBP, TG, uric acid, ALT, FBG, and GGT were higher in men than in women, but age, HDL-C, LDL-C, antilipidemic medication, IRI, and HOMA-IR were higher in women. There was no inter-group difference in antihypertensive medication, eGFR, and diabetic medication.

Table 1. Characteristics of subjects categorized according to sex

Characteristics	Men (<i>n</i> = 793)	Women (<i>n</i> = 1,073)	<i>p</i> -value*
Age (years)	60 ± 14	62 ± 12	0.001
Body mass index (kg/m ²)	23.6 ± 3.0	23.3 ± 3.4	0.044
Smoking status, N (%)	456 (57.5)	27 (2.5)	<0.001
Drinking status, N (%)	691 (87.1)	384 (35.8)	<0.001
Systolic blood pressure (mmHg)	140 ± 21	138 ± 24	0.043
Diastolic blood pressure (mmHg)	84 ± 11	80 ± 12	<0.001
Antihypertensive medication, N (%)	183 (23.1)	260 (24.2)	0.582
Triglycerides (mg/dL)	98 (72–140)	90 (67–125)	<0.001
HDL cholesterol (mg/dL)	59 ± 15	65 ± 15	<0.001
LDL cholesterol (mg/dL)	111 ± 32	126 ± 30	<0.001
Antilipidemic medication, N (%)	27 (3.4)	66 (6.2)	0.007
Serum uric acid (mg/dL)	5.9 ± 1.4	4.5 ± 1.1	<0.001
Estimated GFR (mL/min/1.73 m ²)	81.8 ± 17.0	80.3 ± 17.3	0.077
Alanine aminotransferase (IU/L)	21 (16–28)	15 (12–20)	<0.001
Immuno-reactive insulin (mU/mL)	4.6 (3.0–7.3)	6.0 (4.1–8.6)	<0.001
HOMA-IR [‡]	1.1 (0.9–1.8)	1.4 (0.9–2.0)	<0.001
Fasting blood glucose (mg/dL)	101 ± 23	96 ± 19	<0.001
Diabetic medication, N (%)	27 (3.4)	34 (3.2)	0.793
Gamma-glutamyl transferase (IU/L)	38 (25–69)	20 (16–28)	<0.001

Data presented are the mean ± standard deviation. Data for triglycerides, alanine aminotransferase, insulin, HOMA-IR, and gamma-glutamyl transferase were skewed and are presented as the median (interquartile range). [‡]Homeostasis of minimal assessment of insulin resistance (HOMA-IR) was calculated using the following formula: fasting blood glucose {(mg/dL) × IRI (mU/mL)} / 405. HDL, high-density lipoprotein; LDL, low-density lipoprotein; GFR, glomerular filtration rate. Estimated GFR = $194 \times \text{Cr}^{-1.094} \times \text{Age}^{-0.287} \times 0.739$ (if female). **p*-value for comparison between men and women: Mann-Whitney *U* test or χ^2 test.

Relationship between Clinical Characteristics and Tertiles of Serum GGT

As shown in **Table 2**, tests for differences in characteristics across the three serum GGT levels were significant, except for the prevalence of antihypertensive and diabetic medications in both genders, and for age, smoking status, drinking status, and eGFR in women. In both genders, LDL-C, uric acid, ALT, IRI, HOMA-IR, BMI, DBP, TG, and FBG showed a linear trend in relation to serum GGT. Men in higher GGT tertiles were younger, smokers, drinkers, and had elevated eGFR. HDL-C showed a U-shaped association with serum GGT in men and a downward trend in women. Women in higher GGT tertiles had elevated SBP, and a prevalence toward antilipidemic medication.

Relationship between HOMA-IR and Serum GGT

HOMA-IR significantly increased in correlation with an increase in serum GGT in both men ($r = 0.275$) and women ($r = 0.337$) (**Fig. 1**).

Odds Ratio for MetS According to Tertiles of Serum GGT

Table 3 shows the risk of MetS in relation to serum GGT among 793 men and 1,073 women. Of these, 125 men (15.8%) and 137 women (12.8%) had MetS. In both genders, the prevalence of MetS significantly increased in relation to serum GGT. After adjustment for age, smoking status, drinking status, LDL-C, uric acid, eGFR, and ALT, the odds ratio for MetS was 1.00, 2.23 (95% CI, 1.22–4.07), and 2.32 (95% CI, 1.18–4.56) in men, and 1.00, 1.43 (95% CI, 0.81–2.51), and 2.64 (95% CI, 1.50–4.64) in women, respectively. After additional adjustment for insulin resistance markers (IRI or HOMA-IR), the association was attenuated and the linear relation no longer significant in either gender.

Odds Ratio for Individual Components of MetS According to Tertiles of Serum GGT

The prevalence of individual components of MetS was significantly and linearly associated with increasing tertiles of serum GGT in both genders (**Table 4**). After adjustment for age, smoking status, drinking status, LDL-C, uric acid, eGFR, and ALT,

Table 2. Characteristics of various risk factors and metabolic syndrome components of subjects categorized by sex and serum gamma-glutamyl transferase

Characteristics	Men, <i>n</i> = 793				Women, <i>n</i> = 1,073			
	GGT-1	GGT-2	GGT-3	<i>p</i> for trend*	GGT-1	GGT-2	GGT-3	<i>p</i> for trend*
	12–27 IU/L	28–54 IU/L	≥ 55 IU/L		9–17 IU/L	18–24 IU/L	≥ 25 IU/L	
	<i>n</i> = 257	<i>n</i> = 275	<i>n</i> = 261		<i>n</i> = 379	<i>n</i> = 352	<i>n</i> = 342	
	N (%)	N (%)	N (%)		N (%)	N (%)	N (%)	
Other confounding factors								
Age (years)	64 ± 15	60 ± 13	55 ± 12	<0.001	61 ± 13	63 ± 11	63 ± 10	0.534
Smoking status, N (%)	122 (47.5)	157 (57.1)	177 (67.8)	0.001	5 (1.3)	8 (2.3)	14 (4.1)	0.056
Drinking status, N (%)	205 (79.8)	235 (85.5)	251 (96.2)	<0.001	140 (36.9)	114 (32.4)	130 (38.0)	0.256
LDL cholesterolemia (mg/dL)	114 ± 28	113 ± 30	105 ± 36	0.003	119 ± 27	128 ± 28	132 ± 32	<0.001
Uric acid (mg/dL)	5.4 ± 1.3	5.9 ± 1.3	6.4 ± 1.4	<0.001	4.2 ± 1.0	4.5 ± 1.0	4.8 ± 1.1	<0.001
eGFR (mL/min/1.73 m²)	79.8 ± 17.5	81.0 ± 15.0	84.6 ± 18.2	0.001	80.7 ± 17.1	79.5 ± 17.3	80.7 ± 17.5	0.784
Alanine aminotransferase (IU/L)	16 (13–21)	20 (16–25)	29 (21–38)	<0.001	13 (11–16)	15 (13–18)	21 (16–28)	<0.001
Immuno-reactive insulin (mU/mL)	3.7 (2.3–5.8)	4.8 (3.2–7.3)	5.5 (3.8–8.5)	<0.001	5.0 (3.6–6.6)	6.0 (4.2–8.6)	7.7 (5.1–10.7)	<0.001
HOMA-IR	0.8 (0.5–1.4)	1.2 (0.8–1.9)	1.5 (0.9–2.2)	<0.001	1.1 (0.8–1.5)	1.4 (1.0–2.0)	1.8 (1.2–2.7)	<0.001
Metabolic syndrome component								
Body mass index (kg/m²)	22.5 ± 2.6	23.8 ± 2.9	24.4 ± 3.1	<0.001	22.4 ± 2.8	23.4 ± 3.4	24.4 ± 3.5	<0.001
Systolic blood pressure (mmHg)	138 ± 22	140 ± 21	141 ± 19	0.084	135 ± 24	138 ± 23	140 ± 24	0.030
Diastolic blood pressure (mmHg)	81 ± 11	84 ± 11	87 ± 11	<0.001	78 ± 12	80 ± 12	82 ± 12	0.001
Antihypertensive medication, N (%)	58 (22.6)	65 (23.6)	60 (23.0)	0.957	70 (18.5)	98 (27.8)	92 (26.9)	0.814
Triglycerides (mg/dL)	82 (63–110)	100 (75–136)	118 (83–180)	<0.001	83 (62–109)	88 (66–120)	103 (77–150)	<0.001
HDL cholesterol (mg/dL)	58 ± 14	57 ± 14	61 ± 17	0.023	65 ± 15	66 ± 15	63 ± 16	0.027
Antilipidemic medication, N (%)	6 (2.3)	14 (5.1)	7 (2.7)	0.158	11 (2.9)	19 (5.4)	36 (10.5)	<0.001
Fasting blood glucose (mg/dL)	95 ± 16	100 ± 19	106 ± 30	<0.001	91 ± 11	97 ± 19	101 ± 24	<0.001
Diabetic medication, N (%)	11 (4.3)	7 (2.5)	9 (3.4)	0.544	8 (2.1)	10 (2.8)	16 (4.7)	0.132

Data presented are the mean ± standard deviation. Data for triglycerides, alanine aminotransferase, immuno-reactive insulin, and HOMA-IR were skewed and are presented as median (interquartile range). Metabolic syndrome: component conditions of the metabolic syndrome defined as obesity and two of the following conditions: hypertension, dyslipidemia and impaired fasting blood glucose. LDL, low-density lipoprotein; HOMA-IR, homeostasis of minimal assessment of insulin resistance; GGT, gamma-glutamyl transferase. **p*: Kruskal-Wallis test or χ^2 test.

serum GGT was significantly associated with the presence of individual components of MetS in both genders, except for dyslipidemia in men and hypertension in women.

Discussion

In this cross-sectional, population-based study, we determined the prevalence of MetS, as defined by modified Japanese criteria²³⁾, and examined the association between serum GGT and MetS and its components. MetS was common, occurring in 15.8% of men and 12.8% of women. Serum GGT levels were significantly associated with a risk for MetS and its components, except for dyslipidemia in men and hypertension in women, even after adjusting for age, smoking status, drinking status, LDL-C, uric acid, eGFR, and ALT. The OR of MetS dose-dependently increased from the upper normal range with increasing tertiles

Fig. 1. Relationship between HOMA-IR and gamma-glutamyl transferase HOMA-IR, homeostasis of minimal assessment of insulin resistance.

Table 3. Odds ratio (95% CI) for metabolic syndrome according to tertiles of serum gamma-glutamyl transferase

	Men, <i>n</i> = 793				Women, <i>n</i> = 1,073			
	GGT-1 12–27 IU/L <i>n</i> = 257	GGT-2 28–54 IU/L <i>n</i> = 275	GGT-3 ≥55 IU/L <i>n</i> = 261	<i>p</i> for trend	GGT-1 9–17 IU/L <i>n</i> = 379	GGT-2 18–24 IU/L <i>n</i> = 352	GGT-3 ≥25 IU/L <i>n</i> = 342	<i>p</i> for trend
Cases, N (%)	18 (7.0)	47 (17.1)	60 (23.0)	<0.001	22 (5.8)	36 (10.2)	79 (23.1)	<0.001
Model 1								
Odds ratio	1.00	2.74	3.96	<0.001	1.00	1.85	4.87	<0.001
(95% CI)		(1.54–4.85)	(2.27–6.93)			(1.07–3.21)	(2.96–8.03)	
Model 2								
Odds ratio	1.00	2.67	3.70	<0.001	1.00	1.80	4.82	<0.001
(95% CI)		(1.50–4.73)	(2.09–6.55)			(1.04–3.13)	(2.93–7.95)	
Model 3								
Odds ratio	1.00	2.23	2.32	0.016	1.00	1.43	2.64	0.001
(95% CI)		(1.22–4.07)	(1.18–4.56)			(0.81–2.51)	(1.50–4.64)	
Model 4								
Odds ratio	1.00	1.78	1.93	0.127	1.00	1.01	1.75	0.067
(95% CI)		(0.95–3.34)	(0.96–3.88)			(0.55–1.86)	(0.95–3.22)	
Model 5								
Odds ratio	1.00	1.66	1.63	0.259	1.00	0.92	1.53	0.133
(95% CI)		(0.88–3.13)	(0.81–3.30)			(0.50–1.71)	(0.82–2.86)	

Metabolic syndrome: component conditions of the metabolic syndrome defined as obesity and two of the following conditions: hypertension, dyslipidemia and impaired fasting blood glucose. Model 1: non-adjusted; Model 2: adjusted for age; model 3: adjusted for age, smoking status, drinking status, low-density lipoprotein cholesterol, uric acid, estimated glomerular filtration rate, and log alanine aminotransferase; model 4: adjusted as described for model 2 plus log immuno-reactive insulin; model 5: adjusted as described for model 2 plus log homeostasis of minimal assessment of insulin resistance. GGT, gamma-glutamyl transferase.

Table 4. Adjusted odds ratio (95% CI) for each metabolic syndrome component according to tertiles of serum gamma-glutamyl transferase

Characteristics	Men, <i>n</i> = 793				Women, <i>n</i> = 1,073			
	GGT-1 12–27 IU/L <i>n</i> = 257	GGT-2 28–54 IU/L <i>n</i> = 275	GGT-3 ≥55 IU/L <i>n</i> = 261	<i>p</i> for trend	GGT-1 9–17 IU/L <i>n</i> = 379	GGT-2 18–24 IU/L <i>n</i> = 352	GGT-3 ≥25 IU/L <i>n</i> = 342	<i>p</i> for trend
Obesity								
Cases, N (%)	36 (14.0)	90 (32.7)	107 (41.0)	<0.001	63 (16.6)	102 (29.0)	144 (42.1)	<0.001
Adjusted odds ratio (95% CI)	1.00	2.29 (1.44–3.63)	2.00 (1.18–3.41)	0.002	1.00	1.62 (1.12–2.35)	1.94 (1.30–2.91)	0.003
Hypertension								
Cases, N (%)	161 (62.6)	202 (73.5)	192 (73.6)	0.008	226 (59.6)	235 (66.8)	228 (66.7)	0.069
Adjusted odds ratio (95% CI)	1.00	2.32 (1.49–3.59)	2.99 (1.77–5.07)	<0.001	1.00	1.10 (0.77–1.57)	0.82 (0.55–1.23)	0.327
Dyslipidemia								
Cases, N (%)	53 (20.6)	69 (25.1)	104 (39.8)	<0.001	64 (16.9)	80 (22.7)	134 (39.2)	<0.001
Adjusted odds ratio (95% CI)	1.00	1.03 (0.67–1.58)	1.50 (0.92–2.43)	0.155	1.00	1.16 (0.78–1.71)	2.24 (1.49–3.37)	<0.001
Impaired fasting blood glucose								
Cases, N (%)	45 (17.5)	56 (20.4)	76 (29.1)	0.004	27 (7.1)	45 (12.8)	66 (19.3)	<0.001
Adjusted odds ratio (95% CI)	1.00	1.49 (0.94–2.37)	2.95 (1.73–5.04)	<0.001	1.00	1.62 (0.96–2.71)	2.11 (1.22–3.65)	0.023

Adjusted for age, smoking status, drinking status, low density lipoprotein cholesterol, uric acid, and estimated glomerular filtration rate and log alanine aminotransferase.

of serum GGT. In addition, we demonstrated gender differences in MetS components with which serum GGT was independently associated.

In our study, higher GGT levels were positively associated with MetS, independent of other confounders. Similar results were found in a community-based cross-sectional study of 1,024 Caucasian adults, aged 40 to 59 years, in Finland¹². Elevated GGT may not always relate to alcohol consumption, but may also indicate the existence of MetS¹². In a pooled logistic analysis after adjustment for age, BMI, alcohol consumption, and gender, serum GGT (log-transformed GGT odds ratio 4.0, 95% CI 2.80–5.69) as well as BMI, uric acid, and T-C were independent contributors of MetS¹². Moreover, Nakanishi *et al.*¹⁰ also demonstrated that serum GGT may be an important predictor for developing MetS in 2,957 metabolic syndrome-free men and 3,260 nondiabetic men aged 35–59 years. After adjustment for age, family history of diabetes, BMI, alcohol intake, smoking status, regular physical activity, and white blood cell count, increased serum GGT was related to the risk of developing MetS, even among individuals with normal GGT concentrations, a finding consistent with previous prospective reports looking at GGT^{10, 14}.

Serum GGT is a sensitive indicator of alcohol consumption and/or liver dysfunction, such as fatty liver¹, and is also high in patients with liver disease: chronic viral hepatitis, primary biliary cirrhosis (PBC), or drug induced liver injury. These liver diseases are present in community-dwelling individuals and are usually asymptomatic²⁶; hence, our study participants might include patients with subclinical liver diseases. Nevertheless, the influence of these liver diseases might be small because patients with PBC were rare²⁶, and those with viral hepatitis had already been identified during their annual health examination and treated. Further, the relationships between serum GGT and MetS persisted after adjusting for ALT. Of our enrolled patients, 87.1% of men and 35.8% of women drank alcohol, but MetS prevalence was similar in both genders, and the association between serum GGT and MetS persisted after adjusting for alcohol drinking; therefore, GGT may be an important biomarker for evaluating MetS risk.

In our study, serum GGT was significantly associated with the presence of individual components of MetS in both genders, excepting for dyslipidemia in men and hypertension in women, and was significantly lower in women than in men. It has been shown that the higher the baseline GGT level, the stronger the effect of age on the development of hypertension²⁷; thus, the well-described association between

serum GGT and blood pressure might not be significant in women. Furthermore, serum GGT has also been shown to be more associated with hypertriglyceridemia and abnormal glucose tolerance among components of MetS, suggesting that serum GGT has a closer relationship with hepatic insulin resistance^{13, 28}. In this study, serum GGT in men was not associated with dyslipidemia after adjustment; however serum GGT was significantly correlated with TG in multivariate analysis (data not shown).

The mechanisms by which GGT reflects the risk for MetS are not completely understood. Serum GGT was strongly associated with hypertension, dyslipidemia, and abnormal glucose tolerance, suggesting that elevated serum GGT accompanies hepatic insulin resistance, regardless of the presence of non-alcoholic fatty liver disease^{28–30}. In our study, serum GGT levels were strongly associated with HOMA-IR, which is a reliable marker of insulin resistance, and after additional adjustment for HOMA-IR, the association between serum GGT and MetS was attenuated. Elevated GGT may also reflect inflammation, which impairs insulin signaling in the liver, muscle, and adipose tissues³¹. Fat accumulation in the liver or adipose tissues can induce inflammatory cytokines, such as tumor necrosis factor- α , interleukin-6, and interleukin-8³². Higher C-reactive protein or white blood cells, which represent sub-clinical inflammatory processes, are associated with high GGT levels²⁴. GGT also plays a direct role in LDL oxidation by hydrolyzing glutathione into more potent iron reductants³³, and has an indirect role as a marker in antioxidant systems by maintaining the intracellular concentration of glutathione in response to oxidative stress³⁴.

Some limitations of this study must be considered. First, our cross-sectional study design does not eliminate potential causal relationships between GGT and MetS. There remain important questions about the cumulative effects of these CVD risk factors over several decades and the interactions with other risk factors. Second, the prevalence of MetS and GGT categories is based on a single assessment of blood, which may introduce a misclassification bias. Third, we used BMI ≥ 25 to classify individuals with visceral obesity because waist circumference measurements were not available, which might have underestimated the effect of visceral obesity on MetS³⁵. Fourth, the presence of viral hepatitis must be considered, but examinations of hepatitis B surface antigen and the antibody to hepatitis C were not performed; therefore, the demographics and referral source may limit generalizability.

In conclusion, the present study showed that serum GGT levels are strongly associated with MetS

or its components in the general population. The underlying mechanism behind this relationship is unclear, but seems to be independent of traditional cardiovascular risk factors, such as age, smoking status, drinking status, LDL-C, uric acid, or renal function. For community-dwelling healthy individuals, prospective population-based studies are needed to investigate the mechanisms underlying this association to determine whether intervention, such as effective lifestyle modifications that decrease GGT in adults, will decrease MetS risks.

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