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Longitudinal increase in γ-glutamyltransferase within the reference interval predicts metabolic syndrome in middle-aged Korean men

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Abstract

In the absence of existing research, we examined the association between longitudinal changes in serum γ-glutamyltransferase (GGT) levels and the risk for metabolic syndrome (MetS). A MetS-free cohort of 9148 healthy male workers, who had participated in a health checkup program in 2002, was followed until September 2007. *Metabolic syndrome* was defined according to the modified National Cholesterol Education Program, using body mass index instead of waist circumference. Standard Cox proportional hazards and time-dependent Cox models were performed. During 37 663.4 person-years of follow-up, 1056 men developed MetS. The risk of incident MetS increased across the baseline GGT quartiles, even after further updating GGT values during the follow-up. A longitudinal increase in GGT as a time-dependent variable as well as a non–time-dependent variable was significantly related to MetS after adjusting for age plus the elapsed time from visit 1 to visit 2, baseline MetS traits, uric acid, regular exercise, alcohol consumption, and smoking. Even within the GGT reference interval (<40 U/L), the fourth quartile of GGT change predicted the development of MetS (adjusted hazard risk, 1.61; 95% confidence interval, 1.26-2.07). Furthermore, these associations were consistently observed within the subgroups—those with body mass index less than 23 kg/m^2, C-reactive protein less than 3.0 mg/L, homeostasis model assessment of insulin resistance less than 2.04, alcohol intake not exceeding 20 g/d, alanine aminotransferase less than 35 U/L, an absence of ultrasonographically detected fatty liver, and an absence of any MetS traits. A longitudinal increase in the GGT level, even within the GGT reference interval, may be an independent predictor for MetS, regardless of the baseline GGT.

1. Introduction

Metabolic syndrome (MetS), which is a clustering of disturbed glucose and insulin metabolism, overweight and abdominal fat distribution, hypertension, and dyslipidemia, has become a major public health issue worldwide [1,2]. Individuals with MetS are at increased risk for diabetes and cardiovascular disease [3], as well as cardiovascular-associated and all-cause mortality [4,5]. Although MetS is not fully understood, inflammation and oxidative stress have been suggested to play key roles in its pathogenesis [6].

γ-Glutamyltransferase (GGT) is an enzyme contributing to the extracellular catabolism of the antioxidant glutathione [7]. It is produced in many tissues [7], but most GGT in serum is derived from the liver [7]. Traditionally, GGT is used as a reliable index of hepatobiliary dysfunction

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and alcohol overconsumption [7]. Recently, GGT has been suggested to have a direct involvement in atherosclerotic plaque formation [8,9]. Epidemiologic studies have shown that high levels of serum GGT, even within the GGT reference interval, can predict a spectrum of a disease process from the established cardiovascular risk factors (type 2 diabetes mellitus, hypertension) to outcomes (renal dysfunction, stroke, cardiovascular mortality), irrespective of alcohol intake [10-15]. A few prospective studies have shown that high-normal GGT levels were independently associated with an increased risk for incident MetS in a dose-response manner [12,16,17]. However, although levels of GGT may vary over time [18], virtually no study has examined the time-dependent association between the level of GGT and incident MetS. Therefore, it has not been determined whether high-normal GGT levels, even within the reference interval, are independently associated with an increased risk for incident MetS.

Furthermore, considering that measuring serum GGT levels may assist in predicting the development of MetS, new strategies are needed to identify individuals who are at risk for this disorder, especially those whose serum GGT levels are within the reference interval. Our hypothesis is that sequential changes in GGT levels still within the reference interval may be a predictor for MetS, but there are currently little data on this perspective.

To clarify the relationship between GGT levels and the risk for MetS, we assessed the independent effects of GGT on the risk of incident MetS in middle-aged Korean men, even with changes in the level of GGT over time. In particular, we examined whether a change in GGT per se, especially within the GGT reference interval, provides additional information as an independent predictor for MetS, regardless of the baseline GGT.

2. Methods

2.1. Subjects

The study population was composed of Korean male workers and has been described in detail previously [13,19]. It included workers at least 40 years of age who underwent annual comprehensive health examinations and workers 30 to 39 years of age who underwent biennial comprehensive health examinations. In 2002, 15 347 workers, 30 to 59 years of age, participated in comprehensive health examinations at a university hospital in Seoul, Korea. A total of 2622 men were excluded based on the following exclusion criteria because of potential influence on MetS or liver enzyme activities: history of malignancy (n = 27), history of liver cirrhosis (n = 9), history of cardiovascular disease (n = 16), taking medications for dyslipidemia (n = 125), undergoing medical treatment of hepatitis (n = 11), a positive serologic test for hepatitis C virus (n = 8), missing data regarding past medical histories (n = 337), and MetS at baseline (n = 2,182). Because some individuals met more than one criterion for exclusion, the total number of eligible subjects for the study was 12 725, of whom 11 352 were reexamined at the same hospital annually or biennially until December 2007. Finally, 9148 participants who had 2 or more GGT measurements recorded before the assumed time of MetS development were included in the analysis, with a mean (SD) follow-up of 4.12 (0.87) years. This study was approved by the Institutional Review Board at Kangbuk Samsung Hospital.

2.2. Measurements

The baseline health examinations performed in 2002 included physical measurements, serum biochemical measurements, medical history, medication use, and a questionnaire addressing health-related behaviors [13,19]. Questions regarding alcohol intake included the frequency of alcohol consumption on a weekly basis and the usual amount that was consumed on a daily basis. Current smokers were identified based on self-report. In addition, participants were asked about their weekly frequency of moderate- or vigorous-intensity physical activity. These variables were assessed at each visit [13,19].

Blood specimens were sampled from the antecubital vein after more than 12 hours of fasting and measured within 4 hours of blood collection. Serum levels of glucose, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and GGT were measured using Bayer Reagent Packs (Bayer HealthCare, Tarrytown, NY) on an automated chemistry analyzer (ADVIA 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). Serum GGT levels were consistently measured between 2002 and 2007 using the same reagent on the same autoanalyzer, and the within-run and total coefficients of variation for GGT determinations were no greater than 10% during the period. Methods of the determinations were the hexokinase method for fasting blood glucose (FBG); enzymatic colorimetric assays for LDL-C, HDL-C, TC, and TG; and an immunoradiometric assay (Biosource, Nivelles, Belgium) for insulin. Insulin resistance was estimated by the homeostasis model assessment (HOMA-IR), as described by Matthews et al [20]. C-reactive protein (CRP) was analyzed by particle-enhanced immunonephelometry with the BN II System (Dade Behring, Malburg, Germany). Our clinical laboratory participates in inspections and surveys annually by the Korean Association of Quality Assurance for Clinical Laboratories and is certified for its quality control and performance of various measurements.

Trained nurses measured sitting blood pressure (BP) levels with a standard mercury sphygmomanometer. Body weight was measured with light clothing/no shoes to the nearest 0.1 kg using a digital weight scale. Height was measured to the nearest 0.1 cm. Body mass index (BMI) was

calculated as the weight in kilograms divided by the height in meters squared.

Diagnosis of fatty liver was based on abdominal ultrasonographic findings [19], and participants were required to have hepatorenal contrast and liver brightness for the diagnosis of fatty liver [21].

Metabolic syndrome was defined by the presence of the National Cholesterol Education Program–Adult Treatment Panel III diagnostic criteria, as follows [1]: (1) abdominal obesity, (2) FBG of at least 6.1 mmol/L, (3) TG of at least 1.69 mmol/L, (4) HDL-C less than 1.04 mmol/L, and (5) BP of at least 130/85 mm Hg. Because waist circumference measurements were not available for all subjects, we substituted abdominal obesity with overall adiposity (ie, a BMI $\geq$25 kg/m^2, which has been proposed as a cutoff for the diagnosis of obesity in Asians) [22]. Individuals with 3 or more of these 5 abnormalities were considered to have MetS.

2.3. Statistical analysis

The χ^2 test and 1-way analysis of variance were used to analyze the statistical differences among the characteristics of the study participants in relation to GGT changes. The distribution of continuous variables was evaluated; and transformations were used in the analysis, as required.

For the incident MetS cases, the time of MetS onset was assumed to be the midpoint between the assessment at which MetS was diagnosed and the previous assessment. We confirmed that the proportional hazards assumption was not violated for other covariates as well as GGT change categories and the risk for MetS by using a graph of estimated Ln(−Ln) survival, stratified by category [23].

Categories of baseline GGT comprised the following quartiles: less than 17, 17 to 23, 24 to 35, and at least 36. The GGT levels at follow-up were categorized for each subject by the same quartiles as that of baseline GGT. These cutoff points were chosen to ensure an adequate number of subjects in each group. We used the baseline GGT as time-dependent categorical variable to compare the risk for MetS across the quartiles of GGT over time since the baseline of the study. Exposure categories are represented in the model by dummy variables.

The association between GGT change and the risk of MetS was assessed using Cox proportional hazards modeling with GGT change as a time-dependent categorical variable. The GGT changes were calculated for each subject as the differences in GGT value from visit 2 to baseline (visit 1), from visit 3 to visit 2, from visit 4 to visit 3, from visit 5 to visit 4, and from visit 6 to visit 5. The GGT change was categorized into the following quartiles: less than −3, −3 to 1, 2 to 7, and at least 8 U/L in the MetS-free cohort. Person-years were calculated as the sum of the follow-up duration from visit 2 until the assumed time of MetS development or until the final examination of each individual. We first estimated hazard ratios with 95% confidence interval (CI) for the association of GGT change from visit 1 to visit 2 with the risk of MetS by using standard Cox proportional hazards models, adjusted for baseline potential covariates, including age, baseline MetS traits (BMI, FBG, TG, HDL-C, systolic blood pressure [SBP], and diastolic blood pressure [DBP]), uric acid, HOMA-IR, CRP, smoking, alcohol consumption, and regular exercise. To incorporate repeated measurements, we recalculated all hazard ratios using extended Cox proportional hazards models simultaneously adjusting for the covariates as time-dependent variables. For the linear trends of risk, we treated the categories of GGT change as a continuous variable in the Cox proportional hazards regression models.

Statistical data analysis was performed using SAS version 9.1 (SAS Institute, Cary, NC). All reported P values were 2-tailed, and statistical significance was set at $P < .05$.

3. Results

During 37 663.4 person-years of follow-up, 1056 participants developed MetS. At baseline, the mean age of the 9148 participants in the analytic cohort was 37.0 years (SD, 4.9; range, 30-59 years). Compared with participants in the analytic cohort, 3577 participants not included in the analytic cohort were, on average, 0.6 years older and had a less favorable metabolic profile at baseline (data not shown).

The baseline characteristics of the study participants in relation to the GGT change categories are illustrated in Table 1. The GGT loss category group (GGT change of <−3 U/L) had higher average values of BMI, SBP, DBP, FBG, TC, LDL-C, TG, insulin, HOMA-IR, uric acid, and hepatic enzymes than the reference category group (GGT change categories of −3 to 1 U/L). The proportions of fatty liver and hypertension were inversely associated with GGT change.

Table 2 shows the incidence of MetS according to the baseline GGT categories. In standard Cox models adjusted for age, baseline MetS traits (BMI, FBG, HDL-C, TG, SBP, and DBP), uric acid, regular exercise, alcohol consumption, and smoking, the adjusted hazard risks (aHRs) for MetS across baseline GGT quartiles were 1.00, 1.06, 1.36, and 1.32, respectively (P for trend = .006). After further updating GGT values as well as covariates (uric acid, regular exercise, alcohol consumption, and smoking) on follow-up, the risk for MetS significantly increased across baseline GGT quartiles; and this association was more evident than that before updating.

Table 3 shows the association between incident MetS and GGT change from visit 1 to visit 2. The time of GGT change assessment between visit 1 and visit 2 differed among study subjects; and the average period between visit 1 and visit 2 was 1.7 years (SD 0.6), with a total of 22 214.3 person-years at risk. We first analyzed the relationships between GGT change and incident MetS adjusting for age only, then adjusted for age plus elapsed time from visit 1 to visit 2, baseline MetS traits, uric acid, regular exercise, alcohol consumption, and smoking. In multivariate-adjusted

Table 1
Baseline characteristics of study participants by change in GGT over time

	GGT change (kg) quartiles over 1.7 y from visit 1 to visit 2				*P* value for trend
	Q1	Q2	Q3	Q4	
n	2,007	2,189	2,542	2,410	
Range (U/L)	−736 to −4.0	−3 to 1.0	2∼7	8∼512	
Age (y)	38.8 (5.0)	37.5 (5.1)	36.2 (4.5)	35.8 (4.3)	<.001
BMI (kg/m^2)	24.3 (2.5)	23.1 (2.5)	23.0 (2.5)	23.7 (2.5)	<.001
FBG (mg/dL)	92.0 (11.7)	90.0 (11.7)	90.1 (10.7)	91.6 (11.6)	.525
SBP (mm Hg)	115.1 (12.2)	112.9 (11.2)	113.4 (11.4)	114.2 (11.6)	.076
DBP (mm Hg)	75.0 (9.8)	73.2 (9.1)	73.2 (9.2)	74.0 (9.4)	.001
Uric acid (mg/dL)	6.13 (1.19)	5.88 (1.11)	5.86 (1.08)	6.05 (1.14)	.058
TC (mg/dL)	209.6 (35.5)	197.6 (32.9)	194.8 (33.4)	200.8 (33.3)	<.001
HDL-C (mg/dL)	54.0 (11.3)	53.9 (11.3)	53.1 (11.0)	52.5 (11.0)	<.001
LDL-C (mg/dL)	125.8 (30.1)	119.0 (27.7)	116.6 (28.3)	120.0 (28.8)	<.001
TG (mg/dL)	133 (99-182)	111 (81-148)	108 (81-146)	124 (93-169)	<.001
GGT (U/L)	37 (26-57)	20 (16-27)	19 (14-26)	28 (20-42)	<.001
ALT (U/L)	33 (24-48)	22 (17-30)	21 (17-28)	26 (20-36)	<.001
AST (U/L)	26 (22-32)	22 (19-26)	22 (19-25)	23 (20-28)	<.001
CRP (mg/L)	0.60 (0.30-1.10)	0.40 (0.20-0.80)	0.40 (0.20-0.80)	0.50 (0.30-1.00)	.005
Insulin (μU/dL)	7.67 (5.84-9.78)	6.50 (5.16-8.56)	6.46 (5.18-8.56)	7.17 (5.52-9.45)	<.001
HOMA-IR	1.71 (1.27-2.23)	1.43 (1.11-1.92)	1.42 (1.12-1.91)	1.61 (1.22-2.09)	<.001
Current smoker (%)	41.1	41.1	43.3	53.8	<.001
Alcohol intake (%)[a]	20.3	10.1	10.8	17.6	.096
Regular exerciser (%)[b]	48.1	49.5	49.6	49.2	.512
Fatty liver on US (%)	35.6	20.1	17.8	27.8	<.001
No. of baseline MetS traits					
None	30.1	48.4	49.4	37.6	<.001
1	37.5	33.3	33.7	37.0	.966
2	32.4	18.3	17.0	25.4	<.001
Baseline MetS traits					
Obesity	35.7	22.6	19.9	27.9	<.001
Elevated BP	19.5	14.4	15.4	16.7	.059
Elevated glucose	2.3	1.4	1.0	1.5	.033
Elevated TG	39.5	24.5	23.5	33.7	<.001
Low HDL-C	5.3	7.1	7.7	8.0	.001
Diabetes mellitus (%)	0.8	0.6	0.4	0.6	.210
Hypertension (%)	14.3	9.2	9.6	10.5	.001

Data are means (SD), medians (interquartile range), or percentages. US indicates ultrasound.
[a] At least 20 g of ethanol per day.
[b] At least once a week.

analyses, the risk for MetS increased with increasing quartiles of GGT change (*P* for trend < .001). This association remained significant when GGT change was modeled as a time-dependent categorical variable with additional adjustments for all the above confounding factors except age, baseline MetS traits, and the period from visit 1 to visit 2 as time-dependent variables. Subjects in the fourth quartile (GGT change of ≥8 U/L) were at a significantly elevated risk for MetS (aHR, 1.43; 95% CI, 1.10-1.85). In multivariate-adjusted models and models using time-dependent variables, the aHR of the weight change categories did not change much. This may indicate that the increase in GGT

Table 2
Associations between development of MetS and baseline GGT

GGT quartiles	Person-y	Case	Age-adjusted HR (95% CI)	Multivariate HR[a] (95% CI)	HR (95% CI)[b] in the model using time-dependent variables
Q1 (<17)	8529.6	89	Reference	Reference	Reference
Q2 (17∼23)	10 045.5	181	1.64 (1.28-2.12)	1.06 (0.82-1.38)	1.76 (1.25-2.49)
Q3 (24∼35)	9433.8	300	2.85 (2.25-3.61)	1.36 (1.06-1.73)	2.05 (1.47-2.84)
Q4 (≥36)	9687.6	488	4.37 (3.48-5.48)	1.32 (1.04-1.69)	2.48 (1.79-3.43)
P for trend			<.001	.006	<.001

[a] Estimated from Cox proportional hazard models adjusted for age, MetS traits (BMI, BP, FBG, TG, and HDL-C), uric acid, regular exercise, and alcohol consumption at baseline.
[b] Estimated from extended Cox proportional hazard models with GGT as a time-dependent variable adjusted for age and baseline MetS traits, and uric acid, regular exercise, alcohol consumption, and smoking over time as time-dependent variables.

Table 3
Associations between development of MetS and change in GGT over time

Quartiles of GGT change (kg) over 1.7 y	Person-y	Incident case	Age-adjusted HR (95% CI)	Multivariate HR[a] (95% CI)	HR (95% CI)[b] in the model using time-dependent variables
Q1 (<−3)	5,218.1	323	1.67 (1.40-2.00)	1.04 (0.86-1.25)	1.05 (0.82-1.35)
Q2 (−3 to 1)	5,577.2	195	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q3 (2∼7)	6,028.4	217	1.13 (0.93-1.37)	1.13 (0.93-1.37)	1.26 (0.97-1.64)
Q4 (≥8)	5,390.6	321	1.92 (1.61-2.30)	1.36 (1.13-1.64)	1.43 (1.10-1.85)
P for trend			.070	<.001	.004

[a] Estimated from Cox proportional hazard models adjusted for period (years) from visit 1 to visit 2, age, MetS traits (BMI, BP, FBG, TG, and HDL-C), GGT, uric acid, regular exercise, alcohol consumption, and smoking at baseline.

[b] Estimated from extended Cox proportional hazard models with GGT change as a time-dependent categorical variable adjusted for age and baseline MetS traits, and baseline GGT and uric acid, regular exercise, alcohol consumption, and smoking over time as time-dependent variables.

levels, either "close to baseline" or "more recent," was equally associated with incident MetS. Furthermore, these associations were consistently observed among the following subgroups: GGT less than 40 U/L at baseline in the highest quartile of our study population, BMI less than 23 kg/m^2, alcohol intake not exceeding 20 g/d, ALT less than 35 U/L, CRP less than 3.0 mg/L, HOMA-IR less than the 75th percentile (2.04), those without fatty liver on ultrasound, and those without any MetS traits (Table 4).

To make direct comparisons of the effect of GGT change vs GGT at baseline on the risk of MetS, we performed analyses using a single reference group (a stable GGT change of −3 to 1 U/L over 1.7 years among men with GGT <17 U/L at baseline; Fig. 1). In the lowest GGT quartile at baseline, a linear association between GGT change categories and MetS development existed. Interestingly, the subsequent increase in GGT of at least 8 U/L over 1.7 years significantly predicted an increased risk of MetS, after adjusting for potential confounders (Fig. 1).

4. Discussion

The present prospective study is the first study to demonstrate that a longitudinal increase in the serum GGT level, even within the reference interval, predicts incident MetS irrespective of the baseline GGT value. In addition, this is the first prospective study to demonstrate a time-dependent association between GGT and incident MetS. As reported by previous studies [12,16,24,25], baseline GGT was an independent predictor for MetS. Even after further updating GGT levels during the follow-up period, the risk of MetS progressively increased across the baseline GGT quartiles; and this association was more evident in the analysis adjusted for updated values than in the analysis without adjustment, which could suggest that more recent GGT levels are more strongly associated with incident MetS than baseline values, after taking into account potential confounding factors. Interestingly, there was a linear association in the subgroup within the lowest quartile of GGT at baseline.

Although several studies have demonstrated an association between an elevated level of serum GGT and fatty liver [19,26], previous studies on the relationship between serum GGT and MetS did not assess the influence of the presence of fatty liver. This study showed that the relationship between serum GGT and the risk of incident MetS remained consistently significant in a dose-response manner, even after analyses were restricted to participants with an alcohol intake not exceeding 20 g/d, those having the reference

Table 4
Associations between development of MetS and change in GGT over time in subgroups

Subgroup	Quartiles of GGT change (kg) over 1.7 y				*P* for trend
	Q1	Q2	Q3	Q4	
GGT <40 U/L at baseline (n = 7176)	0.63 (0.49-0.81)	Reference	1.17 (0.91-1.50)	1.61 (1.26-2.07)	<.001
Ethanol intake per day <20 g (n = 7823)	0.82 (0.65-0.99)	Reference	1.20 (0.96-1.50)	1.74 (1.41-2.15)	<.001
No fatty liver on US (n = 6871)	0.95 (0.72-1.26)	Reference	1.56 (1.19-2.06)	1.71 (1.30-2.24)	<.001
Fatty liver on US (n = 2277)	0.95 (0.61-1.48)	Reference	1.30 (0.88-1.94)	1.96 (1.30-2.96)	<.001
No fatty liver on US and ethanol intake per day <20 g (n = 5838)	0.91 (0.67-1.25)	Reference	1.55 (1.13-2.13)	1.87 (1.37-2.55)	<.001
BMI <23 kg/m^2 (n = 3752)	0.79 (0.39-1.61)	Reference	2.36 (1.18-4.71)	3.06 (1.63-5.76)	<.001
ALT <35 U/L (n = 6788)	0.73 (0.57-0.93)	Reference	1.34 (1.04-1.73)	1.66 (1.31-2.12)	<.001
CRP <3.0 mg/L (n = 8082)	0.93 (0.75-1.14)	Reference	1.29 (1.05-1.59)	1.87 (1.54-2.26)	<.001
HOMA-IR <2.04[a] (n = 6862)	0.85 (0.66-1.10)	Reference	1.36 (1.05-1.76)	1.57 (1.22-2.02)	<.001
No MetS traits (n = 3825)	0.86 (0.33-2.24)	Reference	4.81 (2.00-11.6)	4.18 (1.71-10.2)	<.001

[‡]Data are adjusted hazard ratios (95% CI) for incident MetS by GGT change; estimated from extended Cox proportional hazard models with GGT change as a time-dependent categorical variable adjusted for age and baseline MetS traits, baseline GGT, and alcohol consumption over time as time-dependent variables.

[a] 75th percentile.

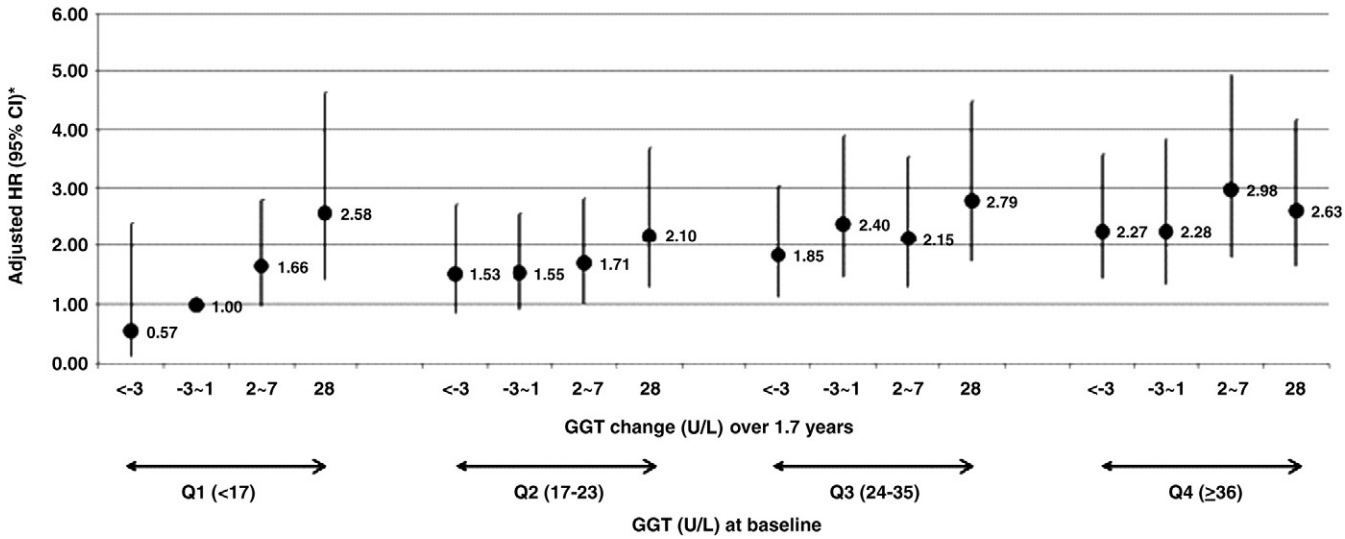

Fig. 1. Adjusted hazard ratios for the development of MetS by GGT changes over 1.7 years and GGT at baseline. The reference group is shown as a stable GGT change of −3 to 1 U/L over 1.7 years among men with GGT less than 17 U/L at baseline. Hazard ratios were adjusted for age, MetS components (BMI, BP, FBG, TG, and HDL-C), uric acid, regular exercise, alcohol consumption, and smoking at baseline.

interval (ALT <35 U/L), and those without fatty liver on ultrasonography. Therefore, biases, such as alcohol intake and fatty liver, did not account for the subsequent increases in GGT in an individual over time. Obesity could play a role in the association of serum GGT and incidence of MetS partly because obesity is one of the components of MetS and partly because an increase in GGT over time may be positively associated with an increase in BMI [18]. However, in the current study, increase in the GGT level was associated with an increased risk for MetS, even among lean subjects with BMI less than 23 kg/m^2 at baseline. In addition, our results did not change, even after further adjusting for CRP or HOMA-IR. Even in those without any MetS traits, a subsequent increase in the GGT level over time in an individual was consistently associated with an increased risk for MetS prospectively.

Given the epidemiologic nature of our findings, the exact mechanisms by which a longitudinal increase in serum GGT, as well as the baseline GGT value, are associated with the development of MetS cannot be elucidated based on the present investigation. Studies have shown that serum GGT is related to systemic inflammation as assessed by serum CRP [27,28]. Our findings may have been mediated by inflammation; however, even after analyses were restricted to participants with CRP less than 3.0 mg/L, serum GGT was independently associated with incident MetS. Serum GGT has been proposed to be a marker of oxidative stress [29,30]. The association of the serum GGT with the incidence of MetS has been attributed to a mechanism related to oxidative stress [31]. In our study, a subsequent increase in the GGT level over time in an individual might reflect an increasing burden of oxidative stress within that individual. However, this postulated mechanism was not directly addressed in the present study; and further study is needed for elucidation.

Our study had several limitations. First, we used a modified National Cholesterol Education Program definition of MetS with BMI instead of waist circumference. However, a number of studies have also shown that BMI is as effective as waist circumference for predicting the development of type 2 diabetes mellitus and other metabolic disturbances [32,33]. Indeed, BMI has recently been adopted instead of waist circumference for analyses of MetS [25]. Second, bias from loss to follow-up may have influenced our results. Participants who were not included in the analysis were on average 0.6 years older and had less favorable metabolic profiles at baseline than those in the analytic cohort. This loss to follow-up of high-risk people would likely lead to a conservative bias and subsequent underestimation of risk. Third, although dietary factors and environmental factors such as pollutants can affect GGT levels [7,34,35], we were unable to obtain this information. Finally, although the potential selection bias was minimized by selecting a work center–based population, the characteristics of the participants were all middle-aged Korean men, which may limit the generalization of the findings to non-Korean populations and/or to women.

In conclusion, our study indicates that a longitudinal increase in the GGT level, even within the GGT reference interval, may be an independent predictor for MetS, regardless of the baseline GGT level. Thus, longitudinal monitoring of GGT change may provide additional information for assessing the risk for incident MetS.

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