Original Article

Relationship between serum gamma-glutamyltransferase activity and cardiometabolic risk factors in metabolic syndrome

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Abstract

Objectives: The objective of this study was to examine the associations of serum gamma-glutamyltransferase (GGT) levels with the metabolic syndrome (MetS) and its components in Saudi adults. **Methods:** The study comprised 400 participants (70 men and 330 women), aged between 40 and 88 years, randomly selected from the medicine clinics at the King Abdulaziz University Hospital in Jeddah, Saudi Arabia, in a cross-sectional study design. A standardized questionnaire was used to determine demographics variables, general health, lifestyle habits, and medical history. Anthropometric and biochemical variables measurements were taken for all study participants. MetS was defined according to the American Heart Association/National Heart, Lung, and Blood Institute report, by the presence of abdominal obesity. **Results:** Higher means for triglycerides and insulin resistance indices ($P < 0.0001$) was found among those in the second, third, and fourth GGT quartiles as compared with their counterparts in the first quartile. McAuley index ($\beta = -0.239$, $P < 0.0001$, 95% confidence interval: −4.1–−1.5) was shown to be a major determinant of circulating GGT in a multivariate analysis. **Conclusion:** Elevated serum GGT could be a cardiometabolic risk factor either as a mediator of low-grade systemic inflammation and as a mediator of oxidative stress through mediation of extracellular glutathione transport into cells of organ systems.

Keywords: Gamma-glutamyltransferase, metabolic syndrome, Saudi adults, oxidative stress, inflammation

Introduction

Metabolic syndrome (MetS) is defined by a clustering of risk factors for cardiovascular disease (CVD), that include abdominal obesity, dyslipidemia, hypertension, and impaired glucose tolerance, all of which increase the risk of CVD and diabetes mellitus.[1] MetS has been acknowledged as one of the major public-health problems globally.[2]

Gamma-glutamyltransferase (GGT) has long been considered an indicator of hepatobiliary dysfunction and alcohol abuse.[3] Recently, several epidemiology studies have shown that GGT participates in common pathophysiological processes, including oxidative stress and lipid peroxidation, which are important to the pathogenesis and development of insulin resistance and the MetS.[4-6] Furthermore, when GGT was tested along with other hepatic markers, GGT was the major predictor of type 2 diabetes.[7-9] It is clear that the pathways by which biomarkers such as GGT are associated with the causation and/or complications of the MetS represent a rich field for research. It is also possible that GGT is a risk factor and a prognostic indicator of CVD. Further information is needed in regard to the magnitude of risk associated between GGT activity and the individual cardiometabolic disorders. Such a relationship could help to explain the high prevalence of MetS.

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Nevertheless, the relationship remains uncertain and has not been well researched yet. Therefore, the aim of this study was to examine the associations of serum GGT levels with the MetS and its components in Saudi adults.

Methods

The study was approved by the Ethical Committee of King Abdulaziz University Hospital (KAUH) and was carried out in accordance with recommendations from the Declaration of Helsinki. Verbal consent form was provided by all study participants.

A total of 400 Saudi participants (70 men and 330 women), aged between 40 and 88 years, were randomly recruited in a cross-sectional study, between February 2014 and July 2016, from the Department of Internal Medicine Clinics at KAUH, Jeddah, Saudi Arabia, during visits for routine checkups, or for evaluation of cardiovascular risk factors.

Those with a known history of liver disease (e.g., acute and chronic active hepatitis, liver cirrhosis), biliary tract diseases, cardiovascular events (unstable angina, myocardial infarction, and stroke), heart failure, peripheral vascular diseases, cardiovascular surgery, malignant diseases, acute infectious, or inflammatory disorders were all excluded from the study. The demographic, lifestyle, medical history, and use of medications of participants were assessed using an interviewer-based structured questionnaire. The medical history included whether there was a diagnosis and/or treatment of diabetes, hypertension, dyslipidemia, and heart diseases. Lifestyle habits assessed by the questionnaire included supplementation use, smoking history, and physical activity level.

Waist circumference was measured at the plane across the iliac crests, which usually represents the narrowest part of the torso. Systolic and diastolic blood pressures were measured in the sitting position on the right arm three times using a standard zero mercury sphygmomanometer after at least 10–15 min of rest. Then, the average of the three readings was obtained.

MetS was defined according to the American Heart Association/National Heart, Lung, and Blood Institute report, by the presence of abdominal obesity (waist circumference >88 cm in women) with at least two of the following: triglycerides of 150 mg/dl (1.7 mmol/L) or greater, high-density lipoprotein (HDL) cholesterol levels <50 mg/dl (1.29 mmol/L) in women, fasting glucose of 110 mg/dl (6.1 mmol/L) or greater, or blood pressure of 130/85 mmHg or greater.[10]

Venous blood samples were obtained after fasting for at least 12 h. Samples centrifuged and serum, refrigerated at 2–8°C, and analyzed within 24 h. Levels of fasting blood glucose (FBG), plasma insulin, triglyceride, total cholesterol, HDL cholesterol, and liver function test were measured in the routine biochemistry laboratory of the KAUH. Fasting lipid profile, FBG, and liver enzymes were measured by an enzymatic colorimetric method using an automated chemistry analyzer (Dimension Vista System, Siemens, Germany). Low-density lipoprotein cholesterol was calculated using the Friedewald formula. Fasting plasma insulin concentration was measured with a chemiluminescence method (Modular E170 immunoassay analyzer, Roche, USA). High-sensitivity C-reactive protein (hs-CRP) was measured by immunoturbidimetric assay (Behring Nephelometer-BNA2, Siemens, USA).

Insulin resistance was determined using a number of indices including the homeostatic model assessment of insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index (QUICK-I), McAuley's index, and insulin sensitivity index (ISI).[11-14]

Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as a total number (percentage). If necessary, logarithmic transformation was performed to achieve a normal distribution. Differences of clinical and metabolic features among groups were calculated using ANOVA test and/or Kruskal–Wallis test for parametric and nonparametric variables, respectively. The correlation analysis was performed by calculating the Pearson's or Spearman coefficient correlation for parametric and nonparametric variables, respectively. Multiple linear regression analyses were applied to determine the relationship between GGT and the risk for MetS. Differences were considered statistically significant at two-sided $P < 0.05$. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 21 (SPSS, Inc., Chicago, IL, USA).

Results

A total of 400 individuals, aged 40–88 years, including 70 men and 330 women, participated in this cross-sectional study. In total, 260 (65%) participants were identified as having MetS.

Sex-specific serum GGT values (66.05 ± 11.2 U/L for men and 31.31 ± 1.94 U/L for women) are within KAUH laboratory reference ranges.

Clinical characteristics of the study population across GGT quartiles are shown in Table 1 Participants in the third and fourth quartiles had significantly higher means of waist circumference ($P < 0.05$) and serum insulin levels ($P < 0.05$) than those in the first quartile. Higher means for triglycerides, HOMA-IR, QUICK-I, McAuley index, and ISI ($P < 0.0001$ in all) was found among those in the second, third, and fourth quartiles as compared with their counterparts in the first quartile.

Comparisons of GGT levels were made among groups of participants classified as having 0, 1, 2, 3, 4, or 5 components of MetS [Figure 1]. Although nonsignificant, the greater the number of clustered risk factors of MetS, the higher the mean levels of GGT.

Table 1: Clinical characteristics of the study population across GGT quartiles (N=400)

	GGT Quartiles				*p*
	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	
F: M ratio (n)	90:10	84:16	82:18	74:26	<0.0001
Waist circumference (cm)	99.8±1.3	102.5±1.5	104.6±1.9¥	105.2±1.5¶	<0.05
SBP (mmHg)	138.6±2.5	138.6±2.9	143.4±2.4	142.6±2.7	NS
DBP (mmHg)	76.9±1.1	75.7±1.7	80.2±1.5	80.4±1.6	NS
Total cholesterol (mmol/L)	4.52±0.1	4.71±0.1	4.82±0.1	4.61±0.1	NS
Triglycerides (mmol/L)	1.45±0.1	1.71±0.1*	1.93±0.1¥	2.05±0.1¶	<0.0001
HDL-C (mmol/L)	1.29±0.03	1.31±0.04	1.24±0.04	1.19±0.04	NS
LDL-C (mmol/L)	2.58±0.1	2.63±0.1	2.71±0.1	2.52±0.1	NS
FBG (mmol/L)	6.50±0.3	7.29±0.3*	8.03±0.4¥	8.22±0.5¶	<0.05
Fasting insulin (μU/ml)	12.8±1.0	14.2±1.6	16.5±1.4¥	18.8±1.6¶§	<0.05
HOMA-IR	4.12±0.6	5.19±0.9*	6.27±0.7¥†	6.55±0.6¶§	<0.0001
QUICK-I	0.33±0.01	0.32±0.01*	0.31±0.01¥†	0.31±0.01¶§	<0.0001
McAuley index	6.73±0.2	6.25±0.2*	5.87±0.2¥	5.61±0.2¶§	<0.0001
ISI	196.4±13.3	156.2±13.0*	126.8±10.9¥†	138.5±18.5§¶	<0.0001
hs-CRP (mg/L)	0.57±0.06	0.50±0.06	0.66±0.07	0.72±0.07	NS

Data are given as mean ± standard deviation. Continuous variables are compared by Kruskal-Wallis test. DBP: diastolic blood pressure; FBG: fasting blood glucose, HDL-C: high density lipoprotein cholesterol, HOMA-IR: Homeostasis model assessment insulin resistance index, hs-CRP: high sensitivity-C reactive protein, ISI: insulin sensitivity index, LDL-C: low density lipoprotein cholesterol, NS: non-significant, QUICK-I: Quantitative insulin sensitivity check index, SBP: systolic blood pressure. * *P*<0.05 (first & second quartiles), ¥*P*<0.05 (first & third quartiles), ¶*P*<0.05 (first & forth quartiles), †*P*<0.05(second & third quartiles), §*P*<0.05 (second & forth quartiles).

Table 2: Correlation between serum GGT and cardio-metabolic risk factors in the study population, partially adjusted for age and gender (N=400)

	r	*p*
Waist circumference (cm)	0.152	0.009
hs-CRP (mg/L)	0.118	0.042
Triglycerides (mmol/L)	0.228	<0.0001
HDL-cholesterol (mmol/L)	-0.137	0.018
Fasting blood glucose (mmol/L)	0.232	<0.0001
Fasting insulin (μU/ml)	0.246	<0.0001
HOMA-IR	0.317	<0.0001
QUICK-I	-0.317	<0.0001
McAuley index	-0.311	<0.0001
ISI	0.319	<0.0001

HDL-C: high density lipoprotein cholesterol, HOMA-IR: Homeostasis model assessment insulin resistance index, hs-CRP: high sensitivity-C reactive protein, ISI: insulin sensitivity index, LDL-C: low density lipoprotein cholesterol, QUICK-I: Quantitative insulin sensitivity check index

Table 2 summarizes the correlations between serum GGT and cardiometabolic risk factors in the study population, partially adjusted for age and gender (*r* ranging from 0.1 to 0.3). Of all MetS components, blood pressure values failed to show a correlation with GGT levels. Fasting insulin, hs-CRP, and all insulin resistance indices showed a significant correlation with GGT levels ($P < 0.05$).

Stepwise multiple regression analysis for serum GGT was conducted in a model that included all independent variables with *P* value up to 0.1 to demonstrate their contribution to GGT level. Only one independent variable that explained 5.7% of the variation in GGT values; McAuley index, exponential (2.63–0.28 in insulin [μU/ml] −0.31 in triglycerides [mM/ml]), ($\beta = -0.239$, $P < 0.0001$, 95% confidence interval: −4.1–−1.5) was shown to be a major determinant of circulating GGT.

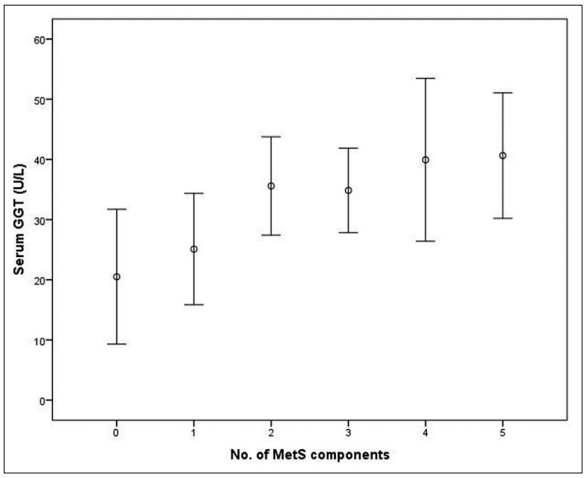

Figure 1: Error bars of 95% confidence intervals of mean and standard deviation of serum gamma-glutamyltransferase in the study population (*n* = 400) categorized by the number of MetS component(s)

Discussion

MetS consists of clustering of atherogenic factors.[10] In addition, a large number of biochemical and anthropometric parameters have been reported to be associated with the MetS, including parameters of obesity and products released by adipose tissue, plasma insulin levels, liver enzymes, and CRP.[15-17]

Epidemiology studies have indicated that serum GGT concentrations may be related to the development and clinical progression of CVD, even after adjustment for alcohol consumption.[6,18-21] Although high levels of GGT have been postulated to be directly atherogenic,[22] as have several other biomarkers for the MetS, a direct role in causation of atherosclerosis remains to be determined. As shown in Figure 1, higher GGT levels are accompanied by the additive effect

of MetS components and potentially greater risk for subsequent development of type 2 diabetes.

Gamma-glutamyl transferase associations with metabolic syndrome components

There is growing evidence that the liver, the primary source of circulating GGT, is a key target organ for the development of the MetS.[23] A number of studies have also shown that the serum level of GGT directly correlates with an increased risk of MetS.[4,23,24] This was demonstrated by the significant correlations between GGT levels and all MetS components, independent of age and gender, except for blood pressure values [Table 2]. Although it has been previously proposed that the connection between GGT and MetS could be attributed to an association of higher GGT levels with hypertension.[20,25]

Gamma-glutamyl transferase associations with inflammatory markers

Another important finding was the association between GGT and hs-CRP [Table 2]. As proposed by Ortega *et al.*[26] a higher GGT production could be secondary to a low-grade hepatic inflammation induced by hepatic steatosis. Alternatively, excess fat in the liver could enhance oxidative stress, leading to overconsumption of glutathione with a compensatory increase in GGT synthesis. The documented predictability of MetS by GGT activity suggests that, as a reflection of oxidative stress, elevated GGT levels are actively involved in the pathogenesis of MetS.[24]

Gamma-glutamyl transferase association with insulin resistance indices

Higher GGT levels were repeatedly reported to be associated with insulin resistance and thus greater risk for type 2 diabetes.[17,20,27] Irrespective of all cardiometabolic risk factors, only the McAuley index showed to be a major determinant of circulating GGT in a stepwise multiple regression models. Such elevations of serum GGT might indicate to be due to ectopic liver fat and/or secondary hepatic inflammation.[22,28]

Strengths and limitations of this study should be acknowledged. The current findings must be interpreted with caution due to the cross-sectional study design, which does not allow us to make inference about the causality for the effects. Nevertheless, the large sample size ensures sufficient evidence in investigating the associations of serum GGT with the MetS and its components.

Conclusion

Elevated serum GGT could be a cardiometabolic risk factor either as a mediator of low-grade systemic inflammation and as a mediator of oxidative stress through the mediation of extracellular glutathione transport into cells of organ systems. Whether it is implicated as a cause or as a reflection of a metabolic abnormality remains to be discovered. Further longitudinal studies are needed to find out the exact mechanisms underlying the association between GGT and MetS components.

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Conflicts of interest

There are no conflicts of interest.

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