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 (β = −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.[3] 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.[1]

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.[14] 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. 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.

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).

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’s 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 | 1st Quartile | 2nd Quartile | 3rd Quartile | 4th Quartile | p        |
|---------------|--------------|--------------|--------------|--------------|----------|
| 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     | 4.8±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       |

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]), (β = −0.239, P < 0.0001, 95% confidence interval: −4.1–−1.5) was shown to be a major determinant of circulating GGT.

Discussion

MetS consists of clustering of atherogenic factors. 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.

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. Although high levels of GGT have been postulated to be directly atherogenic, 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. A number of studies have also shown that the serum level of GGT directly correlates with an increased risk of MetS. This was demonstrated by the significant correlations between GGT levels and all MetS components, independent of age and gender, except for blood pressure values. 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.

**Gamma-glutamyl transferase associations with inflammatory markers**

Another important finding was the association between GGT and hs-CRP. A number of studies have also shown that the circulating GGT, is a key target organ for the development of the MetS. As proposed by Ortega et al., 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.

**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. 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.

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.

**References**

1. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: A joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; International atherosclerosis society; and international association for the study of obesity. Circulation 2009;120:1640-5.

2. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. J Am Coll Cardiol 2010;56:1113-32.

3. Nemesánszky E, Lott JA. Gamma-glutamyltransferase and its isoenzymes: Progress and problems. Clin Chem 1985;31:797-803.

4. André P, Balkau B, Vol S, Charles MA, Eschwège E, DESIR Study Group, et al. Gamma-glutamyltransferase activity and development of the metabolic syndrome (International diabetes federation definition) in middle-aged men and women: Data from the epidemiological study on the insulin resistance syndrome (DESIR) cohort. Diabetes Care 2007;30:2355-61.

5. Targher G. Elevated serum gamma-glutamyltransferase activity is associated with increased risk of mortality, incident type 2 diabetes, cardiovascular events, chronic kidney disease and cancer - A narrative review. Clin Chem Lab Med 2010;48:147-57.

6. Turgut O, Tandogan I. Gamma-glutamyltransferase to determine cardiovascular risk: Shifting the paradigm forward. J Atheroscler Thromb 2011;18:177-81.

7. Cho NH, Jang HC, Choi SH, Kim HR, Lee HK, Chan JC, et al. Abnormal liver function test predicts type 2 diabetes: A community-based prospective study. Diabetes Care 2007;30:2566-8.

8. Ford ES, Schulze MB, Bergmann MM, Thamer C, Joost HG, Boeing H, et al. Liver enzymes and incident diabetes: Findings from the European prospective investigation into cancer and nutrition (EPIC)-potsdam study. Diabetes Care 2008;31:1138-43.

9. Sato KK, Hayashi T, Nakamura Y, Harita N, Yoneda T, Endo G, et al. Liver enzymes compared with alcohol consumption in predicting the risk of type 2 diabetes: The Kansai healthcare study. Diabetes Care 2008;31:1230-6.

10. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic
syndrome: An American heart association/National heart, lung, and blood institute scientific statement: Executive summary. Crit Pathw Cardiol 2005;4:198-203.

11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC, et al. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.

12. Hanson RL, Pratley RE, Bogardus C, Narayan KM, Roumain JM, Imperatore G, et al. Evaluation of simple indices of insulin sensitivity and insulin secretion for use in epidemiologic studies. Am J Epidemiol 2000;151:190-8.

13. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, et al. Quantitative insulin sensitivity check index: A simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000;85:2402‑10.

14. McAuley KA, Williams SM, Mann JI, Walker RJ, Lewis-Barned NJ, Temple LA, et al. Diagnosing insulin resistance in the general population. Diabetes Care 2001;24:460‑4.

15. Tracy RP. Inflammation, the metabolic syndrome and cardiovascular risk. Int J Clin Pract Suppl 2003;134:10‑7.

16. González AS, Guerrero DB, Soto MB, Díaz SP, Martinez-Olmos M, Vidal O, et al. Metabolic syndrome, insulin resistance and the inflammation markers C‑reactive protein and ferritin. Eur J Clin Nutr 2006;60:802‑9.

17. Wei D, Chen T, Gao Y, Tian H. Serum gamma-glutamyltransferase and ferritin are related to insulin resistance: A Population-based study. Clin Lab 2015;61:1157-61.

18. Emdin M, Passino C, Michelassi C, Donato L, Pompella A, Paolicchi A, et al. Additive prognostic value of gamma-glutamyltransferase in coronary artery disease. Int J Cardiol 2009;136:80-5.

19. Mason JE, Starke RD, Van Kirk JE. Gamma-glutamyl transferase: A novel cardiovascular risk biomarker. Prev Cardiol 2010;13:36-41.

20. Liu CF, Gu YT, Wang HY, Fang NY. Gamma-glutamyltransferase level and risk of hypertension: A systematic review and meta-analysis. PLoS One 2012;7:e48878.

21. Onat A, Can G, Örnek E, Çiçek G, Ayhan E, Doğan Y, et al. Serum γ-glutamyltransferase: Independent predictor of risk of diabetes, hypertension, metabolic syndrome, and coronary disease. Obesity (Silver Spring) 2012;20:842-8.

22. Du G, Song Z, Zhang Q. Gamma-glutamyltransferase is associated with cardiovascular and all-cause mortality: A meta-analysis of prospective cohort studies. Prev Med 2013;57:31-7.

23. Lee DS, Evans JC, Robins SJ, Wilson PW, Albano I, Fox CS, et al. Gamma glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk: The framingham heart study. Arterioscler Thromb Vasc Biol 2007;27:127-33.

24. Kunutsor SK, Apekey TA, Seddoh D. Gamma glutamyltransferase and metabolic syndrome risk: A systematic review and dose-response meta-analysis. Int J Clin Pract 2015;69:136-44.

25. Stranges S, Trevisan M, Dorn JM, Dmochowski J, Donahue RP. Body fat distribution, liver enzymes, and risk of hypertension: Evidence from the western New York study. Hypertension 2005;46:1186-93.

26. Ortega E, Koska J, Salbe AD, Tataranni PA, Bunt JC. Related articles, links serum gamma-glutamyl transpeptidase is a determinant of insulin resistance independently of adiposity in Pima Indian children. J Clin Endocrinol Metab 2006;91:1419-22.

27. Wei D, Chen T, Li J, Gao Y, Ren Y, Zhang X, et al. Association of serum gamma-glutamyl transferase and ferritin with the metabolic syndrome. J Diabetes Res 2015;2015:741731.

28. Aksakal E, Tanboga IH, Kurt M, Kaygın MA, Kaya A, Isik T, et al. The relation of serum gamma-glutamyl transferase levels with coronary lesion complexity and long-term outcome in patients with stable coronary artery disease. Atherosclerosis 2012;221:596-601.