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Original Article

# Association between serum gamma-glutamyltransferase levels and hyperuricemia

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**Abstract**

**Aim:** Although the the contribution of gamma-glutamyltransferase (GGT) to hyperuricemia (hUA) has been previously shown in literature, there is not any study showing the contribution of GGT to hUA in a Turkish population. The aim of this study was to investigate both the association between GGT and uric acid (UA) and the contribution of GGT to hUA in the Turkish population.

**Materials and Methods:** This retrospective study was conducted in Antalya, Turkey. A total of 14049 subjects (5521 males and 8528 females) aged > 40 years were recruited and divided into four subgroups according to serum GGT quartiles. Patient demographic data and laboratory results of biochemical parameters were obtained from electronic medical records. Linear regression analysis was applied to GGT quartiles with UA and binary logistic regression analysis was applied to GGT quartiles with hUA.

**Results:** Firstly, serum UA levels were increased across GGT quartiles ($p < 0.001$). Linear regression models showed GGT in the fourth quartile was strong associated with a 0.22 mmol/L (95% confidence interval (CI) 0.16- 0.29, $p = 0.001$) increase in UA after adjustment. Logistic regression analysis revealed that compared with subjects in the lowest GGT quartile, the adjusted odds ratio (OR) for hyperuricemia in the fourth quartile was 2.62 (95% CI 2.27- 3.01, $p = 0.001$) after adjustment for age, sex, creatinine, total cholesterol (TC), high density lipoprotein (HDL) cholesterol, triglyceride (TG), glycosylated hemoglobin (HbA1c) and alanine aminotransferase (ALT).

**Conclusions:** Serum GGT is closely associated with serum UA and might contributes greatly to hUA.

**Keywords:** Cardiovascular disease; Gamma-glutamyl transferase; uric acid

## INTRODUCTION

GGT is a cell surface enzyme mainly found in the liver, which has an essential role in glutathione metabolism. Conventionally, GGT is used chiefly as a biomarker of hepatobiliary disease, alcohol consumption and non-alcoholic fatty liver disease (NAFLD). However, in recent years increased levels of GGT have been found to be associated with type II diabetes mellitus (type II DM), cardiovascular risk factors, and metabolic syndrome (MS) (1,2). Furthermore, increased GGT activity is also associated with coronary heart disease (CHD) and cardiovascular mortality (3,4).

UA, the final product of purine metabolism, is used routinely as a biochemical parameter especially in the diagnosis of gouty arthritis and kidney stones. A growing number of current studies show that hyperuricemia is implicated in CHD, type II DM, and MS (5).

There are significant number of studies in literature that have analysed the association between UA and GGT in populations with different ethnicity and clinical characteristics. However, the contribution of GGT to hUA has been investigated in a limited number of studies (6-8). One of these studies indicated that increased serum GGT is an independent predictor of subsequent development of hUA (6). Although, there is a study that has demonstrated the relationship between GGT and hUA (9), to the best of our knowledge there is not any study that shows the contribution of GGT to hUA in a Turkish population. The present study is the first to investigate both the association between GGT and UA and the contribution of GGT to hyperuricemia in the Turkish population.

## MATERIALS and METHODS

### Study Design

This study was conducted in Heath and Science University Antalya Traning and Research Hospital. Patients presenting at the internal medicine and family medicine outpatient clinics between January 2018 and December 2019 were enrolled in the study. Inclusion criteria were age > 40 years, with no history of hepatobiliary and renal disease. All patients had blood work that included measurement

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of 11 biochemical parameters (GGT, UA, glucose, creatinine, Total Cholesterol (TC), Triglycerides (TGs), high density cholesterol (HDL-C), Low-density lipoprotein cholesterol (LDL-C), Haemoglobin A1c ($HbA_1c$), Aspartate aminotransferase (AST), Alanin aminotransferase (ALT)) that were analysed on the same day in a fasting state. A total of 14049 participants (5521 males and 8528 females) were eligible for the study. Approval for the study was granted by the Ethics Committee of our hospital.

**Biochemical Measurements**

Patient demographics (age and gender) and laboratory results of biochemical parameters, analyzed for routine clinical care were obtained from electronic medical records. Serum GGT levels were measured with the methodology recommended by the International Federation of Clinical Chemistry (IFCC) (10) and serum UA levels were estimated based on the modification of Fossati method (11) using an automatic analyzer (Beckman AU5800; Beckman Coulter Diagnostics, USA). ALT, AST, creatinine, TC, TGs, LDL-C, HDL-C concentrations were analyzed enzymatically with an automatic analyser (Beckman AU5800; Beckman Coulter Diagnostics, USA). If TG levels > 4.52 mmol/L then LDL cholesterol levels were calculated according to the formula: LDL = TC -(HDL + TG -5) (12). Serum glucose levels were measured using the hexokinase method (Beckman AU5800; Beckman Coulter Diagnostics, USA). $HbA_1c$ was measured with an automatic glycohemoglobin analyzer (Tosoh HLC 723 G8; Tosoh Bioscience, Japan) with the principle of high-performance liquid chromatography.

**Statistical Analysis**

The study population was divided into 4 groups according to the quartiles of serum GGT levels (GGT data set was sorted in to numerical order from smallest to largest, then ordered data set cut in to four equal parts at three points including median value). Baseline characteristics of the groups were analyzed by the Kruskal-Wallis test for continuous variables (GGT, UA) and by the chi-square test for categorical variables. The association between the GGT quartiles (≤ 15, 16-21, 22-32, ≥ 33 U/L) and UA (dependent variable) was explored using the adjusted multiple linear regression method. Logistic regression was used to assess the contribution of GGT to hUA (> 0.36 mmol/L in females and > 0.43 mmol/L in males) at four different GGT quartiles. In both regression analyses, three models were formed. In Model 1 an unadjusted analysis was applied. In Model 2, age and gender, and in Model 3, creatinine, TC, HDL-C, TG, $HbA_1c$,AST and ALT were adjusted. The regression analysis was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for hUA development for each quartile of serum GGT. Normally distributed data were shown as mean ± standard deviation (SD). Data that were not normally distributed were shown as median values Interquartile range,(IQR). Categorical variables were expressed as number (n) and percentage (%). Comparisons across the GGT quartiles for the baseline characteristics of individuals were made using the ANOVA test for continuous variables and Kruskal-Wallis test for non-normally distributed variables. All statistical analyses were performed using the SPSS version 17.0. All statistical tests were considered significant at $p < 0.05$.

## RESULTS

The total 14049 subjects comprised 61% females and 39% males with a median age of 59 years (IQR: 50-68 years). The demographic and biochemical characteristics of the study population across the GGT quartiles are presented in Table 1.

It was shown that percentiles of males were increased in parallel with GGT quartiles ($p < 0.001$). Serum UA levels were increased with increasing GGT quartiles ($p < 0.001$). Subjects in the highest GGT quartiles exhibited increased fasting glucose, creatinine, TGs, $HbA_1c$, ALT and AST levels when compared with subjects in the lowest quartile ($p < 0.001$). HDL-C concentrations were decreased significantly in subjects with higher GGT concentrations ($p < 0.001$).

**Table 1. Baseline characteristics of the study population according to gender**

| | Total (n=14,049) | Male (n=5,521) | Female(n=8,528) | p value |
|---|---|---|---|---|
| Age (y) | 59 (50-68) | 61 (52-70) | 58 (49-67) | < 0.001* |
| Fasting glucose (mmol/L) | 5.55 (5-6.66) | 5.72 (5.11-7.05) | 5.5 (5.0-6.49) | < 0.001* |
| Creatinine (mmol/L) | 80.44 (70.72-92.82) | 91.94 (83.1-102.54) | 73.37 (67.18-82.21) | < 0.001* |
| Total Cholesterol (mmol/L) | 5.3 ± 1.2 | 5.04 ± 1.2 | 5.46 ± 1.18 | < 0.001* |
| HDL-cholesterol (mmol/L) | 1.29 ± 0.32 | 1.16 ± 0.27 | 1.38 ± 0.32 | < 0.001* |
| Triglyceride (mmol/L) | 1.46 (1.05-2.05) | 1.52 (1.07-2.19) | 1.42 (1.04-1.98) | < 0.001* |
| LDL-Cholesterol (mmol/L) | 3.26 ± 0.98 | 3.09 ± 0.99 | 3.36 ± 0.96 | < 0.001* |
| $HbA_1c$ (%) | 6 (5.6-6.6) | 6.1 (5.7-6.8) | 6 (5.6-6.5) | < 0.001* |
| ALT (U/L) | 18 (14-25) | 21 (15-29) | 17 (13-23) | < 0.001* |
| AST (U/L) | 21 (18-25) | 22 (18-27) | 20 (17-24) | < 0.001* |
| GGT (U/L) | 21 (15-31) | 26 (19-39) | 18 (14-26) | < 0.001* |
| Uric Acid (mmol/L) | 0.3 (0.26-0.37) | 0.34 (0.29-0.4) | 0.29 (0.24-0.34) | < 0.001* |

Data are presented as mean ± standard deviation, median ($25^{th}$-$75^{th}$) or percentile of participants
*Statistically significant difference male and female for ANOVA

**Table 2. Baseline characteristics of the study population across GGT quartiles**

| | GGT Q1 (n=3,630) | GGT Q2 (n=3,624) | GGT Q3 (n=3,311) | GGT Q4 (n=3,484) | p value |
|---|---|---|---|---|---|
| Age (years) | 57 (47-68) | 61 (52-69) | 60 (52-68) | 58 (51-67) | < 0.001* |
| Male (%) | 17.3 | 34 | 49.5 | 58 | < 0.001* |
| Fasting glucose (mmol/L) | 5.27 (4.83-5.88) | 5.5 (5-6.44) | 5.77 (5.16-7.05) | 6 (5.22-7.88) | < 0.001* |
| Creatinine (mmol/L) | 75.14 (67.18-84.86) | 79.56 (69.84-91.94) | 82.21 (72.49-93.7) | 85.75 (75.14-97.24) | < 0.001* |
| Total Cholesterol (mmol/L) | 5.29 ± 1.16 | 5.29 ± 1.18 | 5.3 ± 1.2 | 5.31 ± 1.28 | 0.808 |
| HDL-cholesterol (mmol/L) | 1.4 ± 0.32 | 1.3 ± 0.31 | 1.24 ± 0.29 | 1.22 ± 0.31 | < 0.001* |
| Triglyceride (mmol/L) | 1.2 (0.89-1.6) | 1.4 (1.05-1.95) | 1.61 (1.17-2.27) | 1.72 (1.21-2.51) | < 0.001* |
| LDL-Cholesterol (mmol/L) | 3.28 ± 0.95 | 3.26 ± 0.96 | 3.24 ± 0.97 | 3.23 ± 1.03 | 0.102 |
| $HbA_1c$ (%) | 5.8 (5.5-6.2) | 6 (5.7-6.5) | 6.1 (5.7-6.8) | 6.3 (5.8-7.3) | < 0.001* |
| ALT (U/L) | 15 (12-18) | 17 (13-22) | 20 (15-26) | 21 (18-25) | < 0.001* |
| AST (U/L) | 19 (17-22) | 20 (17-24) | 21 (18-25) | 24 (20-32) | < 0.001* |
| Uric Acid (mmol/L) | 0.27 (0.23-0.32) | 0.3 (0.26-0.36) | 0.32 (0.27-0.38) | 0.34 (0.28-0.4) | < 0.001* |

Data are presented as mean ± standard deviation, median (IQR) or percentile of participants
*Statistically significant difference GGT quartiles for ANOVA

As shown in Table 2, age and fasting glucose, creatinine, TGs, $HbA_1c$, ALT, AST, GGT, UA levels were significantly higher in males than females. TC, HDL-C, and LDL-C levels were significantly lower in males than females.

The association between the GGT quartiles and UA (dependent variable) was explored using the adjusted multiple linear regression method. A steady increase was determined in UA moving from the second to the fourth quartiles (Table 3).

**Table 3. Multiple Linear regression analysis of GGT quartiles and Uric Acid**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| Quartile 1 (ref) | 1.0 | 1.0 | 1.0 |
| Quartile 2 | 0.16 (0.1, 0.23), p < 0.001 | 0.12 (0.07, 0.19), p < 0.001 | 0.1 (0.07, 0.14), p < 0.001 |
| Quartile 3 | 0.25 (0,2, 0.32), p < 0.001 | 0.18 (0.12, 0.24), p < 0.001 | 0.16 (0.11, 0.24), p < 0.001 |
| Quartile 4 | 0.33 (0.26, 0.39), p < 0.001 | 0.25 (0.18, 0.31), p < 0.001 | 0.22 (0.16, 0.29), p < 0.001 |

Model 1: unadjusted
Model 2: adjusted for age and gender
Model 3: model 2 + adjusted for creatinine, TC, HDL-C, TGs, $HbA_1c$, ALT

GGT levels in the higher quartiles were associated with higher ORs of having elevated UA (> 0.36 mmol/L in females and > 0.43 mmol/L in males) (Table 4).

According to the results of logistic regression analysis, the unadjusted ORs for hUA was determined as 1.62 (%95 CI, 1.43- 1.84) for the second quartile, 1.76 (%95 CI, 1.54- 2.00) for the third quartile and 2.31 (%95 CI, 2.04- 2.62) for the fourth quartile when compared with the lowest quartile as the reference category. In both Model 2 and Model 3 the adjusted odds ratios of hUA increased with higher quartiles compared to the first quartile.

**Table 4. Odds ratio of hyperuricemia with GGT quartiles from logistic regression analysis**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| Quartile 1 (ref) | 1.0 | 1.0 | 1.0 |
| Quartile 2 | 1.62 (1.43, 1.84), p < 0.001 | 1.67 (1.47, 1.91), p < 0.001 | 1.6 (1.4, 1.84), p < 0.001 |
| Quartile 3 | 1.76 (1.54, 2.00), p < 0.001 | 2.03 (1.77, 2.32), p < 0.001 | 1.91 (1.66, 2.2), p < 0.001 |
| Quartile 4 | 2.31 (2.04, 2.62), p < 0.001 | 2.94 (2.58, 3.35), p < 0.001 | 2.62 (2.27, 3.01), p < 0.001 |

Model 1: unadjusted
Model 2: adjusted for age and gender
Model 3: model 2 + adjusted for creatinine, TC, HDL-C, TGs, $HbA_1c$, ALT

## DISCUSSION

In the present study, a comparison was made of the blood biochemical and demographic characteristics across GGT quartiles in a population derived from a cross-sectional survey. It was demonstrated that the association between GGT and UA presented a dose-response association. Logistic regression analysis showed that GGT quartiles were positively correlated with hUA and the association remained significant after adjustment for possible confounding factors, including age, gender, creatinine, TC, HDL-C, TGs, $HbA_1c$, and ALT. The results of this study demonstrated for the first time that increasing GGT levels are associated with hUA in a Turkish population.

In line with these findings, there have been several studies in literature that have shown an association between GGT and UA. In a six year prospective study which was done in 3310 Japanese men have demonstrated that increased serum GGT is an independent predictor of subsequent development of hUA (6). In a cross-sectional study of 407 normotensive Chinese adults, it was demonstrated that

GGT independently contributed to increased serum uric acid (7). In another cross-sectional study of 2486 Chinese females, it was shown that serum uric acid concentrations were significantly increased in subjects with higher serum GGT levels and serum GGT was positively associated with hUA after adjusting for possible confounding factors (8). Another study that used cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) 1988-1994 and NHANES 1999-2006, demonstrated that higher serum uric acid levels were associated with higher GGT levels (13). In a previous Turkish study of middle-aged, non-diabetic adults, it was shown that serum UA levels were associated with serum GGT levels as an inflammatory marker (9).

First of all, the observed relationship between GGT and UA can be attributed to the increment of both biochemical parameters in cardiometabolic diseases such as coronary artery disease, type II diabetes mellitus and MS. There are several studies in literature showing that GGT is associated with some CHD risk factors (1, 14), the incidence of CHD (15) and CHD-related mortality (3, 4, 15). In the same way, the associations between UA and CHD risk factors (16), the incidence of CHD (17) and CHD-related mortality (18) have been shown in several studies. There are also studies showing increased GGT (19) and UA (20) in type II DM and MS.

The increments seen in serum GGT and serum UA levels in CHD, Type II DM and MS have led to the need to explain by which mechanisms they are involved in the development of these diseases. Although the source of the association of GGT with CHD has not been clearly identified, some studies have shown that GGT contributes to the development of atherosclerotic plaque by generating ROS (21). Products of two reactions that catalyzed by GGT, cysteinylglycine (a prooxidant molecule), leukotriene C4 and leukotriene D4 (inflammatory mediators), could be partly responsible for high oxidative stress in CHD and type II DM (21,22). As there is known to be a close relationship between NAFLD and insulin resistance (23, 24), it is not surprising to observe elevated levels of serum GGT in type II DM and MS.

With regards to UA, experimental studies have shown that UA causes some changes in endothelial cells resulting in a predisposition to atherosclerosis (25). The associations between hUA and endothelial dysfunction and atherosclerosis have also been demonstrated in clinical studies (26). In type II DM and MS, the cause of the elevation of serum UA levels can be attributed to the decrement of renal UA clearance (27, 28), interruption of the glycolytic pathway (29) and over-activation of hexose monophosphate shunt (30). These pathophysiological events may be responsible for the association of GGT and UA levels with the onset of in CHD, Type II DM and MS.

The dose-response association between GGT and UA can be explained in different ways, taking advantage of this study data analysis and previous literature knowledge. First, the prevalence of CHD, Type II DM, and MS in the Turkish population over 40 years of age is high (31), which could partly explain the relationship between GGT and UA observed in the current study. In addition, the current study data showed that there was an increase in age, male gender, TC levels and a decrease in HDL-C levels according to GGT quartiles, indicating the increased risk of CHD. Furthermore, the increment in fasting glucose, $HbA_1c$ and TG levels according to GGT quartiles can be easily interpreted as an increased risk of Type II DM and MS. All these results of the current study provide important clues about the increased incidence of CAD, Type II DM, and MS according to GGT quartiles.

There are several limitations to this study. First, it must be said that the statistical results would have been more realistic and robust, if data had been included of waist circumference, fasting insulin and blood pressure, which are important cardiometabolic indicators. Second, since the study was cross-sectional, the causal relationship between GGT and UA could not be determined. As there was no information about the history of the patients, or medications they used drugs that, may change GGT and/or UA metabolism; such as thiazide and loop diuretics which may cause hyperuricemia, further refinement and more detailed analysis of the data was not possible.

## CONCLUSION

In conclusion, serum GGT levels were observed to be closely associated with serum UA levels and serum GGT levels were an independent predictor of hUA. To the best of our knowledge, this is the first study to have revealed the independent contribution of GGT to the elevated levels of UA in Turkish adults aged > 40 years. It would be beneficial to clarify the reasons for the relationship between GGT and UA to be able to open up its use in different pathologies such as CHD, type II DM, and MS apart from its traditional use.

*Competing interests: The authors declare that they have no competing interest.*

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*Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Antalya Education and Research Hospital Ethics Committee (Reference Number: 2017-241 19/10) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.*

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