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Serum gamma-glutamyl transferase is associated with the elevated uric acid levels in normotensive Chinese adults

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ABSTRACT

Background: Although both serum gamma-glutamyltransferase (GGT) and uric acid are correlated with hypertension, studies on the association between serum GGT and uric acid in normotensive individuals are rare. In this study, we tried to reveal this relationship in normotensive Chinese adults.
Methods: Four hundred seven normotensive adults were recruited. The subjects were divided into 3 subgroups according to serum GGT tertiles. Anthropometric parameters as well as systolic blood pressure (SBP), diastolic blood pressure (DBP), uric acid, GGT, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood glucose, blood lipids, and fasting insulin were measured. Insulin resistance was assessed using HOMA-IR index.
Results: Uric acid was increased in parallel with increasing serum GGT ($P < 0.001$). After correction for age, sex, smoking and alcohol consumption, serum GGT was positively associated with uric acid ($r = 0.42$, $P < 0.001$), SBP ($r = 0.22$, $P < 0.001$), and DBP ($r = 0.19$, $P < 0.001$). When compared with lowest GGT tertile, the odds ratio of the middle tertile for the increased serum uric acid was 3.43 (95% *CI*, 1.39–8.47) and 7.29 (95% *CI*, 1.57–33.82) for the highest tertile after adjustment for age, sex, BMI, smoking, alcohol consumption, SBP, DBP, creatinine and HOMA-IR.
Conclusions: Serum GGT is strongly associated with the increased uric acid concentrations in normotensive Chinese adults.

1 . Introduction

It has been demonstrated that, serum gamma-glutamyltransferase (GGT), previously regarded as a biomarker of liver dysfunction or excess alcohol intake [1], is associated with various risk factors for cardiovascular diseases, such as obesity, increased blood pressure, dyslipidemia, and hyperglycemia [2]. Furthermore, multiple lines of evidence have shown that serum GGT concentrations are involved in the occurrence and development of cardiovascular and metabolic diseases, including metabolic syndrome, coronary artery disease (CAD), hypertension, and type 2 diabetes mellitus [3–5]. Increased GGT activity is also implicated in higher cardiovascular mortality and all-cause mortality [6,7]. In addition, even in the upper reference range, serum GGT concentrations are found to be closely related with the onset of metabolic syndrome [4,5].

In recent years, the correlation between serum GGT and hypertension has attracted the attention of investigators from different countries. It has been found that serum GGT is involved in the higher incidence of hypertension in Hong Kong Chinese [8], Japanese [9], Korean adults [10], and US adults [11]. These findings have indicated that serum GGT concentrations are related to increased blood pressure in hypertensive patients. However, hitherto, few data are available on the link between serum GGT and blood pressure concentrations in normotensive individuals.

Hyperuricemia is very common in patients with cardiovascular diseases [12], especially in hypertension [13]. Evidences from epidemiological surveys and clinical trials have shown that serum uric acid is not only an independent risk factor for hypertension but also a contributor to the occurrence of hypertension [14–16]. Since GGT and uric acid both are involved in cardiovascular diseases and the increased blood pressure, some correlation might exist between each other. A study reported that GGT was positively related with serum uric acid in community-dwelling Japanese population [17], in which patients with hypertension were involved. However, it is uncertain whether serum GGT independently contributes to the increased serum uric acid concentrations in individuals with normal blood pressure.

Therefore, the present study was designed to examine the potential impact of GGT on the increased serum uric acid in normotensive individuals. Relationships among GGT, blood pressure, and other cardiovascular risk factors were also observed.

Abbreviations: DBP, diastolic blood pressure; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment index-insulin resistance; SBP, systolic blood pressure.

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2 . Subjects and methods

2.1 . Study population

A total of 510 consecutive subjects with normal blood pressure, from the Wuhan General Hospital Health Check-up Center, were enrolled in this study from June 2014 to August 2014. Doppler ultrasonography scan of the liver was performed in all the subjects. The participants were excluded if they had hypertension, pre-diabetes, diabetes mellitus, non-alcoholic fatty liver disease, liver cirrhosis,liver cancer, renal dysfunction, urinary tract infection, congestive heart failure, and malignant neoplasms. Also, the subjects were excluded if they were taking any medications such as uric acid-lowering agents, thiazide diuretic, lipid-lowering agents, hepatotoxic agents, and so forth. Finally, 407 participants (235 males and 172 females), aged from 30 to 70 y, were eligible for this study. The mean age of them was 46.85 ± 8.77 y.

Normotension was defined as systolic blood pressure(SBP) < 140 mm Hg and diastolic blood pressure (DBP) < 90 mm Hg. Questionnaires were sent to all the participants to confirm lifestyle details, including smoking and alcohol intake history. Persons who had smoked more than one cigarette daily for at least one year were considered as cigarette smokers. Those who had consumed alcohol more frequently than once a week were considered as drinkers. The study was approved by the ethics committee of our hospital, and written informed consent forms were signed by all the participants.

2.2 . Anthropometry and serum parameters

Anthropometry indexes, including body height, weight, waist circumference and hip circumference were measured using a normative protocol. Body mass index (BMI) was calculated as weight (kilogram, kg) divided by square of height (m^2). Waist-to-hip ratio was evaluated by waist circumference (cm) divided by hip circumference (cm). Blood pressure was measured 3 times by a specially assigned nurse using a mercury sphygmomanometer. During 2 different visits, SBP and DBP were determined after at least 30 min rest.

After an overnight fasting, venous blood samples were collected for the analysis of biochemical parameters and fasting insulin concentrations. Serum GGT concentration was measured enzymatically at 37 °C with an automatic analyzer (Olympus AU 5400, Japan). Serum uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol concentrations were measured with standard enzymatic methods. Fasting blood glucose (FBG) was determined by a glucose oxidase procedure. The intra-assay CVs for those assays mentioned above were 0.5 ~ 1.0% for GGT, ALT, and AST, 1.0 ~ 2.0% for TC, HDL-C, and FBG, 2 ~ 3% for TG and LDL-C, and 2.0 ~ 4.0% for UA and creatinine. The inter-assay CVs for those biochemical parameters were all less than 10%. Fasting insulin (FINS) was evaluated by human serum insulin radioimmunoassay kit (Guangzhou Atom High-tech Istope Pharmaceutical co., Ltd.), with an intra-assay CV < 10% and an inter-assay CV < 15%, respectively. Insulin resistance was calculated according to homeostasis model assessment index-insulin resistance index (HOMA-IR) [HOMA-IR = FBG (mmol/l) × FINS (mIU/l)/22.5].

2.3. Statistical analysis

The Kolmogorov–Smirnov test was used to determine the data distribution characteristics. Normally distributed data was shown as mean ± SD. Non-normally distributed data was presented as median (interquartile range) and was log transformed before further analysis. Categorical variables were presented as numbers and percentages. The subjects were sub-divided into 3 subgroups according to serum GGT tertiles. The differences among the 3 groups were compared using one-way ANOVA followed by Bonferroni's post hoc test. For all the subjects, correlation coefficients between serum GGT and other variables were calculated by Spearman or partial correlation analysis with or without correction for age, sex, smoking and alcohol intake. Binary logistic regression models, according to serum GGT tertiles (≤24.0, 24.1–39.0 and ≥39.1 U/l in males, and ≤15.0, 15.1–21.0 and ≥21.1 U/l in females), were built to determine the influence of serum GGT on the increased uric acid concentrations. If serum uric acid was higher than median value, that is, 348.2 μmol/l in males and 253.4 μmol/l in females, the increased serum uric acid was defined and used as the dependent variable in the regression models. In these models, potential confounding factors were controlled, including age, sex, BMI, smoking, alcohol intake, blood pressure, serum creatinine and HOMR-IR. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS statistical package (ver 17.0).

3 . Results

The subjects were sub-divided into the first tertile (T1) group, the second tertile (T2) group and the third tertile (T3) group according to serum GGT tertiles. For GGT concentrations, the cut-off values for T1, T2, and T3 are ≤24.0, 24.1–39.0 and ≥39.1 U/l in males, and ≤15.0, 15.1–21.0 and ≥21.1 U/l in females, respectively. The baseline characteristics of these participants are presented in Table 1. There was no significant difference in age, sex constituent ratio, smoking ratio, alcohol intake ratio, serum creatinine as well as SBP among the three groups. However, it was demonstrated that concentrations of uric acid were increased paralleled by serum GGT concentrations (one-way ANOVA, P < 0.001). Moreover, when compared with subjects in the lowest tertile of serum GGT, the ones in the highest tertile exhibited higher waist circumference, waist-to-hip ratio, BMI, DBP, FBG, ALT, AST, TC, TG, and LDL-cholesterol along with the increased fasting insulin and HOMA-IR (all $P < 0.01$). In contrast, HDL-C concentrations were decreased significantly in participants with higher GGT concentrations ($P < 0.01$).

In Table 2, it was found that serum GGT was significantly associated with uric acid concentrations ($r = 0.50$, $P < 0.001$). In addition, serum GGT concentrations were also positively associated with BMI, waist circumference, waist-to-hip ratio, SBP, DBP, FBG, serum creatinine, TC, TG, LDL-cholesterol, fasting insulin as well as HOMA-IR index (all $P < 0.01$). However, serum GGT concentrations showed inverse relationship with HDL-cholesterol ($r = -0.31$, $P < 0.001$). Even though age, sex, smoking and alcohol consumption were adjusted, serum GGT concentrations were still associated with uric acid concentrations ($r = 0.42$, $P < 0.001$), BMI ($r = 0.19$, $P < 0.001$), waist circumference ($r = 0.34$, $P < 0.001$), waist-to-hip ratio ($r = 0.34$, $P < 0.001$), SBP ($r = 0.22$, $P < 0.001$), DBP ($r = 0.19$, $P < 0.001$), FBG ($r = 0.25$, $P < 0.001$), serum creatinine ($r = 0.33$, $P < 0.001$), TC ($r = 0.16$, $P = 0.001$), TG ($r = 0.32$, $P < 0.001$), LDL-cholesterol ($r = 0.20$, $P < 0.001$), fasting insulin ($r = 0.32$, $P < 0.001$), HOMA-IR ($r = 0.36$, $P < 0.001$), and HDL-cholesterol ($r = -0.18$, $P < 0.001$).

Further, we explored the effect of serum GGT on the increased serum uric acid concentrations using logistic regression analysis method. As shown in Table 3, it was demonstrated that the unadjusted odds ratio (OR) for increased serum uric acid was 5.29 (95% *CI*, 3.08–9.09) for the middle tertile and 19.81 (95% *CI*, 10.83–36.22) for the highest tertile when compared with lowest one. With the lowest tertile as the conference, after correction for age, sex, BMI, smoking, alcohol consumption, SBP, DBP, creatinine and HOMA-IR, the adjusted OR of the middle tertile was 3.43 (95% *CI*, 1.39–8.47) and 7.29 (95% *CI*, 1.57–33.82) for the highest tertile. Additionally, the data showed that OR for higher serum uric acid increased gradually according to GGT tertiles. These findings suggested that serum GGT might play a role in the increased serum uric acid concentrations even after correction for confounding factors.