Relationship Between Serum Gamma-Glutamyltransferase Levels and Prehypertension in Chinese Adults: The Cardiometabolic Risk in Chinese Study

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The authors aimed to investigate the relationship between serum gamma-glutamyltransferase (GGT) and prehypertension, as well as the modification of other metabolic risk factors in a large cohort of Chinese individuals. The data were collected via a community-based health examination survey in central China. Blood pressure, body mass index (BMI), and levels of GGT, fasting blood glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lipid indicators were measured. In total, data from 18,302 patients with available biomarkers were included in the present study. Elevated blood pressure was associated with increased GGT concentration ($P<.001$). After adjusting for age, sex, BMI, fasting blood glucose, lipid indicators, AST, and family history of hypertension, the association between GGT levels and prehypertension remained significant ($P=.021$). The adjusted odds ratios (95% confidence interval) for prehypertension across quintiles of GGT level were 1.00, 1.057 (1.012–1.334), 1.068 (0.916–1.254), 1.024 (0.851–1.368), and 1.272 (1.027–1.593), respectively. In stratified analyses, the association between GGT levels and prehypertension was significant in women but was not significant in men. Moreover, additive effect of BMI and age on the effect of GGT levels on prehypertension (both P for interaction $<.001$) was observed. In summary, GGT levels were positively associated with prehypertension in women, independent of other metabolic factors. Furthermore, BMI and age may amplify the effects of GGT levels on prehypertension. These findings suggest that monitoring the levels of GGT could help in the diagnosis and monitoring of prehypertension. *J Clin Hypertens (Greenwich).* 2014;16:760–765.

Several observational studies have reported on the association of elevated gamma-glutamyltransferase (GGT) levels with diabetes,[1] metabolic syndrome,[2] and cardiovascular disease.[3] Similarly, several cross-sectional and longitudinal studies have also noted a relatively independent association between elevated serum GGT levels and hypertension.[4–6] However, data on the association between GGT levels and prehypertension are limited, particularly in Chinese patients. In the present study, we aimed to examine the association between GGT levels and prehypertension in a large cohort of Chinese individuals with a normal range of blood pressure (BP) and to assess the interactions between GGT levels and other cardiovascular metabolic risk factors.

METHODS

Study Population

In 2012–2013, we conducted a community-based health examination survey for individuals who were randomly selected from 22,726 residents living in the urban area of central China. Written informed consent was obtained from all participants. The study was reviewed and approved by the ethics committee of the Central Hospital of Xuzhou, Jiangsu, China. Patients with viral hepatitis, autoimmune liver disease, liver cirrhosis, malignant tumors of the liver, biliary tract disease, and history of heavy drinking (alcohol intake: men, >20 g/d; women, >10 g/d) were excluded. In addition, patients with systemic disease leading to fatty liver, diabetes, fasting glucose level ≥7.0 mmol/L, 2-hour oral glucose tolerance test value ≥11.1 mmol/L, those who could potentially develop hypertension (systolic BP [SBP] ≥140 mm Hg and/or diastolic BP [DBP] ≥90 mm Hg), and those who were taking or had recently taken medication that would result in elevating serum alanine transaminase (ALT) and GGT levels were excluded. Thus, in total, 18,302 patients with appropriate and sufficient data were finally enrolled in this study.

Assessment of BP and Prehypertension

Using a standard mercury sphygmomanometer, physicians recorded BP values 3 times consecutively on the right arm, which was placed at the level of the heart, with the patient sitting still for more than 5 minutes. The 3 measurements were recorded at 60-second intervals. The average of the 3 values of SBP and DBP was used in our analyses. Prehypertension was defined

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as SBP between 120 mm Hg and 139 mm Hg or DBP between 80 mm Hg and 89 mm Hg according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).[7]

Assessment of Biomarkers and Covariates

Height and body weight were measured with the participants in a standing position without shoes or heavy outer garments. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Biomarkers were measured in all participants. A venous blood sample was drawn from all patients after an overnight fast (at least 10 hours). After blood was drawn, samples were transferred into glass tubes and allowed to clot at room temperature for 1 to 3 hours. Immediately after clotting, serum was separated by centrifugation for 15 minutes at 3000 rpm. Fasting blood samples were collected for measuring the levels of GGT, fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and aspartate aminotransferase (AST), and ALT. All biochemical assays were performed enzymatically on an autoanalyzer (Type 7600, Hitachi Ltd, Tokyo, Japan).

Statistical Analyses

In all analyses, parameters with non-normal distributions were used after log-transformation. The measured data are expressed as mean±standard deviation. The relationship between GGT levels and metabolic markers was examined using one-way analysis of variance. We used unconditional logistic regression for estimating the odds ratios (ORs) for prehypertension risk, after adjusting for covariates including age, sex, BMI, and biomarkers. The interactions between GGT levels and other factors were also assessed using logistic regression. The joint effects between GGT levels and BMI on the risk of prehypertension were examined using the linear regression models. All reported *P* values were two-tailed. A *P* value of <.05 was considered statistically significant. Data management and statistical analysis were conducted using SAS statistical software (version 9.1.3; SAS Institute, Inc., Cary, North Carolina).

RESULTS

Correlation Between GGT Concentration and the Clinical Characteristics of the Study Population

The study participants had an average age of 41.7±2.24 (range, 18–91) years and a mean BMI of 23.7 kg/m². The mean SBP and DBP values were 118 mm Hg (range, 80–139 mm Hg) and 75.9 mm Hg (range, 49–89 mm Hg), respectively. A total of 12,040 (65.8%) individuals had prehypertension. Table I presents the baseline characteristics of the study participants according to quintiles of the GGT levels. Weight, height, BMI, and levels of fasting blood glucose, log triglyceride, total cholesterol, LDL-C, log AST, and log ALT showed statistically significant differences between the GGT quintile groups. As the GGT level increased, an increasing trend in all these values was noted (*P*<.001), except for HDL-C, which showed a decreasing trend (*P*<.001).

Correlations Between GGT Concentration and BP

Table II shows that the risk of prehypertension increased along with the elevated levels of GGT, which remained significant even in a multivariate-adjusted model. In an age-adjusted and sex-adjusted model, the ORs (95% confidence interval [CI]) of prehypertension across increasing quintiles of GGT were 1.00, 1.338

TABLE I. Baseline Characteristics of Participants According to Quintile Groups of Serum GGT Level (N=18,302)

	GGT Level (Quintiles), U/L						
Variables	Q1 (GGT≤13.0)	Q2 (13.0<GGT≤17.0)	Q3 (17.0<GGT≤23.0)	Q4 (23.0<GGT≤36.0)	Q5 (GGT>36.0)	*F* Value	*P* Value for Trend
No.	5162	3712	3610	3106	2712		
Age, y	40.49±10.59	41.74±12.15	42.22±12.48	41.25±12.59	40.04±12.05	1.36	.064
Weight, kg	58.46±8.32	63.78±9.85	68.67±10.56	72.56±10.78	75.68±10.91	10.25	<.001
BMI, kg/m²	22.18±2.67	22.90±2.95	23.73±3.06	24.53±3.04	25.54±3.04	8.67	<.001
Height, cm	161.83±6.25	163.68±7.27	167.48±8.00	170.47±7.37	172.33±6.39	12.65	<.001
Fasting glucose, mmol/L	5.16±1.11	5.24±1.15	5.31±1.16	5.32±1.02	5.29±0.80	9.65	<.001
HDL-C, mmol/L	1.47±0.32	1.42±0.31	1.31±0.31	1.24±0.30	1.18±0.28	14.52	<.001
LDL-C, mmol/L	2.71±0.74	2.91±0.80	3.01±0.80	3.10±0.80	3.18±0.82	25.65	<.001
Log triglyceride	−0.08±0.21	−0.01±0.24	0.07±0.25	0.13±0.26	0.23±0.26	7.64	<.001
Total cholesterol, mmol/L	4.45±0.83	4.60±0.88	4.67±0.92	4.71±0.89	4.84±0.93	15.25	<.001
Log AST	1.23±0.12	1.26±0.13	1.28±0.14	1.30±0.13	1.33±0.14	16.42	<.001
Log ALT	1.17±0.21	1.23±0.22	1.29±0.23	1.35±0.22	1.43±0.24	9.87	<.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

TABLE II. Association Between Serum GGT Levels and the Risk of Prehypertension by Logistic Regression Analysis

	Normotensive Controls, No. (%)	Prehypertension Cases, No. (%)	Model 1		Model 2		Model 3	
			OR	95% CI	OR	95% CI	OR	95% CI
Q1	2725 (52.8)	2437 (47.2)	1	1	1	1	1	1
Q2	1401 (37.7)	2311 (62.3)	1.338	1.221–1.467	1.183	1.075–1.301	1.057	1.012–1.334
Q3	1027 (28.4)	2583 (71.6)	1.594	1.438–1.766	1.223	1.099–1.361	1.068	0.916–1.254
Q4	685 (22.1)	2421 (77.9)	2.025	1.805–2.272	1.362	1.206–1.538	1.024	0.851–1.368
Q5	424 (15.6)	2288 (84.4)	2.974	2.607–3.393	1.736	1.510–1.996	1.272	1.027–1.593
P for trend			<.001		<.001		.021	

Abbreviations: CI, confidence interval; GGT, gamma-glutamyltransferase; OR, odds ratio. Model 1: Adjusted for age and sex. Model 2: Adjusted for sex, age, fasting glucose levels, and body mass index. Model 3: Adjusted for age, sex, body mass index, and levels of fasting glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, aspartate aminotransferase, and family history of hypertension.

(1.221–1.467), 1.594 (1.438–1.766), 2.025 (1.805–2.272), and 2.974 (2.607–3.393) (*P* for trend <.001). In model 3, after further adjusting for BMI and the levels of fasting glucose, total cholesterol, triglycerides, HDL-C, LDL-C, AST, and family history of hypertension, the ORs (95% CI) were 1.00, 1.057 (1.012–1.334), 1.068 (0.916–1.254), 1.024 (0.851–1.368), and 1.272 (1.027–1.593) (*P* for trend=.021).

Interactions Between GGT Level and Prehypertension According to Age and Sex

After stratified analysis, the associations between GGT level and prehypertension remained significant in women, but were not significant in men. Furthermore, we examined the associations between GGT level and prehypertension in different age groups: younger than 35 years, 35 to 46 years, and older than 46 years (Table III). We noted that the associations were significant in individuals older than 46 years (*P*=.019), but not in those younger than 35 years and those between 35 and 46 years. The interaction between GGT levels and age in relation to prehypertension risk was significant (*P* for interaction <.001).

BMI Modifies the Associations Between GGT Concentration and Prehypertension

We assessed the interactions between GGT levels and other metabolic factors (BMI and levels of fasting blood glucose, LDL-C, and total cholesterol) and performed stratified analyses (Table III). While considering the power of the present study for the stratified analyses, we grouped the strata factors, fasting blood glucose levels, and lipid indicator values into 3 categories (tertiles): low, median, and high levels. We found significant interactions between GGT levels and BMI in relation to prehypertension risk (*P* for interaction <.001). Moreover, the association between GGT levels and prehypertension was significant in the groups with high (*P*<.001) and median BMI levels (*P*=.016); however, this association was not statistically significant in those with low BMI levels (*P*=.290). The tests for the interaction of fasting blood glucose, LDL-C, and total cholesterol levels did not yield significant results (*P* for interaction=.202, .501, and .895, respectively).

Joint Effects of GGT Levels and BMI on Prehypertension

We also examined the joint effects of GGT levels and BMI on prehypertension (Figure). These 2 markers showed an additive pattern in relation to the risk of prehypertension. Compared with patients in the group with the lowest levels for both markers, individuals in the group with highest levels of the 2 markers had a 2.29-fold higher prevalence risk ratio of prehypertension.

DISCUSSION

In clinical and epidemiological studies, GGT has been found to be positively associated with metabolic syndrome.[8,9] Shankar and colleagues[10] reported a clear positive association between GGT levels and prehypertension among adult men and women in the United States. Previous studies indicated this association in Korean and Japanese men but not in women.[11,12] However, no large-scale studies have assessed whether GGT is independently associated with prehypertension in the Chinese population. Our data showed a significant association between GGT level and the risk of prehypertension in women in a large Chinese population. In the stratified analyses, there were significant interactions between GGT level and risk of prehypertension according to age and BMI.

Previous studies have indicated that elevated serum GGT levels are associated with an increased risk of metabolic syndrome and type 2 diabetes.[13–16] Insulin resistance may play an important role in the pathophysiological mechanism of these findings. Compensatory hyperinsulinemia can activate the mitogen-activated protein kinase pathway, resulting in enhancement of vasoconstriction, proinflammation, increased sodium and water retention, and the elevation of BP.[16] In addition, insulin increases sodium reabsorption in the kidney and promotes sympathetic nerve activity, which can cause hypertension.[17] Moreover, the evidence of a

TABLE III. Adjusted ORs of Prehypertension According to GGT Level Quintiles by Stratification for Sex, Age, BMI, and Levels of Fasting Glucose and Lipids

		GGT Level (Quintiles), U/L							
Variables		Q1 (GGT≤13.0)	Q2 (13.0<GGT≤17.0)	Q3 (17.0<GGT≤23.0)	Q4 (23.0<GGT≤36.0)	Q5 (GGT>36.0)	*P* Value for Trend	*P* Value for Interaction	R^2
Sex	Women; n=8234	1	1.078 (0.927–1.25)	1.120 (0.913–1.37)	1.254 (0.950–1.65)	1.663 (1.130–2.44)	.01	0.418	0.096
	Men; n=10,068	1	1.316 (1.018–1.70)	1.128 (0.880–1.44)	1.125 (0.863–1.46)	1.303 (0.961–1.76)	.508		
Age, y	Low (<35); n=6555	1	1.171 (0.935–1.46)	1.067 (0.812–1.40)	1.056 (0.758–1.47)	1.360 (0.882–2.09)	.379	<0.001	0.157
	Median (35–46); n=6054	1	1.070 (0.872–1.31)	1.097 (0.862–1.39)	1.088 (0.826–1.43)	1.304 (0.934–1.82)	.198		
	High (>46); n=5690	1	1.224 (0.973–1.54)	1.165 (0.910–1.49)	1.321 (0.991–1.76)	1.553 (1.096–2.20)	.019		
BMI, kg/m^2	Low (<22.2); n=6112	1	1.094 (0.909–1.31)	0.929 (0.734–1.17)	0.796 (0.594–1.06)	0.988 (0.655–1.49)	.29	<0.001	0.149
	Median (22.2–24.9); n=6102	1	1.227 (0.995–1.51)	1.244 (0.983–1.57)	1.300 (0.982–1.72)	1.550 (1.104–2.17)	.016		
	High (>24.9); n=6088	1	1.410 (1.040–1.91)	1.532 (1.119–2.09)	1.837 (1.307–2.58)	2.258 (1.522–3.35)	<.001		
Fasting glucose, mmol/L	Low (<4.88); n=6176	1	1.119 (0.915–1.36)	1.264 (0.990–1.61)	1.322 (0.987–1.77)	1.616 (1.107–2.36)	.008	0.202	0.134
	Median (4.88–5.29); n=5943	1	1.187 (0.961–1.46)	1.097 (0.861–1.39)	0.961 (0.723–1.27)	1.181 (0.825–1.69)	.757		
	High (>5.29); n=5951	1	1.142 (0.883–1.47)	0.960 (0.727–1.26)	1.146 (0.836–1.57)	1.314 (0.911–1.89)	.234		
Total cholesterol, mmol/L	Low (<4.21); n=5852	1	1.128 (0.919–1.38)	1.093 (0.856–1.39)	0.959 (0.703–1.30)	1.409 (0.911–2.17)	.434	0.895	0.161
	Median (4.21–4.94); n=5783	1	1.337 (1.081–1.65)	1.292 (1.010–1.65)	1.617 (1.214–2.15)	1.764 (1.235–2.52)	.001		
	High (>4.94); n=5777	1	0.985 (0.770–1.26)	0.948 (0.723–1.24)	0.931 (0.691–1.25)	1.092 (0.772–1.54)	.834		
LDL-C, mmol/L	Low (<2.59); n=4086	1	1.195 (0.987–1.44)	1.150 (0.913–1.44)	1.101 (0.815–1.48)	1.223 (0.825–1.81)	.272	0.501	0.152
	Median (2.59–3.25); n=4032	1	1.094 (0.880–1.35)	1.129 (0.879–1.45)	1.342 (1.009–1.78)	1.800 (1.257–2.57)	.002		
	High (>3.25); n=4054	1	1.197 (0.917–1.56)	1.053 (0.789–1.40)	1.000 (0.730–1.37)	1.116 (0.772–1.61)	.957		

Abbreviations: GGT, gamma-glutamyltransferase; LDL-C, low-density lipoprotein cholesterol. Analyses were adjusted for the following covariates: age, body mass index (BMI), sex, and biomarkers when they were not the strata variables.

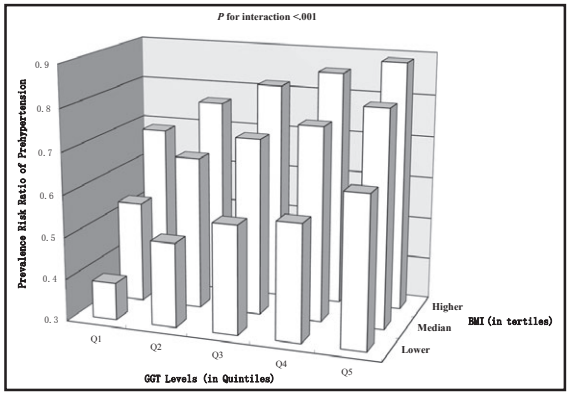

FIGURE. The association between gamma-glutamyltransferase (GGT) level (in quintiles), body mass index (BMI) (lower, median, and higher levels), and the risk of prehypertension. The multivariate-adjusted prevalence risk ratios are presented.

link between insulin resistance and an inappropriately overactive renin-angiotensin system has been implicated in the pathogenesis of hypertension.[18] Recent studies have shown that insulin increases the expression of arterial angiotensinogen and angiotensin type 1 receptor in cultured vascular smooth muscle cells,[18] which may represent another mechanism through which hyperinsulinemia promotes the development of hypertension.

In stratified analyses, our data showed that the association between GGT and prehypertension was significant only in women. There were substantial sex-based differences in fat distribution,[19,20] and the differences in free fatty acid (FFA) metabolism between men and women[21] may explain the sex differences observed. GGT levels are a potentially important indicator of abdominal fat distribution.[22] Women have a greater amount of adipose tissue in the total abdominal and abdominal subcutaneous regions,[19] and have greater rates of nonoxidative FFA disposal[21] compared with men. In addition, female sex was reported to be positively associated with mean neutrophil counts.[23] In the present study, we noted that women with increased adiposity had higher circulating neutrophil counts; neutrophils are a major component of the inflammatory process contributing to endothelial dysfunction activated by cytokines.[24] Furthermore, an elevated GGT level could reflect subclinical inflammation,[25] which could also represent the underlying mechanism. In addition, we observed that the association between GGT level and prehypertension was not significant in individuals younger than 46 years and in those with low BMI levels. GGT levels and BMI showed an additive pattern in their effect on elevated BP. In particular, the age-dependent increases in visceral adipose tissue may be a speculative reason for the age disparity. Increasing age is associated with a marked number of changes in body composition and a progressive increase in the amount of body fat mass.[26] The age-related shifts in body composition with an increase in body fat mass, particularly the accumulation of more internalized fat deposits, was associated with an increased risk of developing chronic disorders, including insulin resistance, and cardiovascular disease.[26,27] A sex difference in the association between GGT levels and prehypertension was found in the present study. We found that the association between GGT levels and prehypertension was significant only in women. However, a few studies have shown disparate outcomes in non-Chinese adults.[11–13] The ethnic and regional differences in the population studies may be speculative reasons for the difference between the studies.

Our results suggest that monitoring the levels of GGT could help in the diagnosis and monitoring of prehypertension. Through these measures, such individuals may adopt an intervention at an early stage, such as effective lifestyle modifications or use of medication to decrease GGT levels and the risk of prehypertension.

Study Limitations and Strengths

The large sample size was a major strength of the present study and ensured sufficient power for the investigation of complex interactions between serum GGT levels and other metabolic factors. However, our study has the following limitations. First, the cross-sectional nature of our study does not allow us to infer about the causality of the effects. To confirm that the associations between GGT levels and BP are independent of other metabolic risk factors, a prospective study is needed. Second, the individuals were restricted to those who were administered a community-based health examination survey; hence, the results of this study may not be applicable to the general population in China. Third, although we carefully adjusted for the potential confounding variables in the analyses, we did not collect information on dietary intake and lifestyle habits. Therefore, the residual confounding of these unmeasured variables may influence the associations.

CONCLUSIONS

In our study, GGT levels were positively associated with increased risk of prehypertension in Chinese women, independent of other metabolic risk factors. BMI and age showed a significant interaction with GGT levels in relation to prehypertension risk.

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