ORIGINAL ARTICLE

Association between serum gamma glutamyl transferase and fasting blood glucose in Chinese people: A 6-year follow-up study

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ABSTRACT

Aims/Introduction: In this study, we aimed to investigate the relationships between gamma-glutamyl transferase (GGT) and fasting blood glucose (FBG) during a 6-year follow-up study of participants, and to determine whether GGT is a risk factor for FBG.

Materials and Methods: A total of 1,369 individuals from the health examination survey in the urban area of Xuzhou, central China, were followed up for 6 years. The patients were divided into four groups based on their baseline GGT levels (in quartiles). The one-way analysis of variance (ANOVA) method was used to compare the differences between the variables and baseline. The relationship between GGT and FBG levels was investigated using repeated measurements ANOVA.

Results: The grouping of baseline GGT levels affected the changes in blood glucose during the 6-year follow-up study. In the GGT quartile subgroups, the annual mean increase in FBG levels showed a positive relationship with baseline GGT levels. This trend was even more aggregated in the highest baseline GGT group. Interactions among time course, baseline FBG and GGT groups in different participants together affected the change of FBG levels during the follow-up period. The repeated measures ANOVA suggested that different baseline GGT groups were still significantly associated with increased FBG levels. GGT is a risk factor that affects FBG levels($P < 0.001$).

Conclusions: The annual mean increase in FBG levels showed a positive relationship with baseline GGT levels. Higher baseline GGT levels resulted in a faster annual mean increase in FBG. Thus, GGT can be used for the early detection of FBG-related disorders of glucose metabolism for clinical application.

INTRODUCTION

As a liver enzyme involved in the synthesis and catabolism of glutathione[1], gamma-glutamyl transferase (GGT) plays a crucial role in maintaining adequate levels of intracellular glutathione, which is considered a marker of oxidative stress[2]. Along with its diagnostic use in obstructive biliary disease and liver disease, GGT has garnered increasing attention, mainly owing to its association with other diseases, such as diabetes, atherosclerosis, cardiovascular diseases, metabolic syndrome and cancer[3]. Recently, a large-scale longitudinal study from Korea showed that increased serum GGT concentrations can be used to predict the progression of diabetes[4]. Even though many clinical studies have focused on the potential relationship between the risk of type 2 diabetes mellitus and GGT, the results remain controversial[5–7]. Furthermore, there are only a few follow-up studies on the relationship between fasting blood glucose (FBG) and GGT. In the present study, we aimed to investigate the relationships between GGT and FBG during a 6-year follow-up, and evaluated whether GGT is a risk factor for FBG.

STUDY POPULATION

The present study is a prospective cohort study based on the health examination population in the urban area of Xuzhou, central China. This study was approved by the Ethics Committee of the Central Hospital of Xuzhou, China, and informed consent

was obtained from all participants. A total of 1,369 individuals with laboratory results and questionnaires were considered for the study. The exclusion criteria were as follows: the participants with abnormal FBG (<3.9 mmol/L and >6.1 mmol/L), participants who suffered from diabetes, cancer, hepatic cirrhosis or were pregnant, and previous history of coronary heart disease, alcoholic liver disease, other liver diseases, viral hepatitis, chronic kidney disease, alcoholics, alcohol intake >70 g/week for women and >140 g/week for men. They were followed up for 6 years from 2010 to 2016, and had a yearly health examination at the Physical Examination Center of Xuzhou Central Hospital. During the 6-year follow-up period, 31 abnormal FBG, 19 cancers, 10 hepatic cirrhosis, 17 pregnancies, 22 coronary heart diseases, 24 alcoholic liver diseases, 22 viral hepatitis, 18 chronic kidney disease, 15 alcoholics and 124 cases of incomplete follow-up due to various reasons were recorded. Finally, the prospective analysis included 1,067 participants (421 men and 646 women) aged 20–84 years at baseline examination.

MATERIALS AND METHODS
The study participants were assigned to four groups (Q1, Q2, Q3 and Q4) based on their baseline GGT levels (in quartiles). We first carried out a cross-sectional analysis of the sample population to explore the relationship between FBG and serum GGT in terms of values at baseline, age, weight, body mass index (BMI), systolic blood pressure, triglycerides, diastolic blood pressure, total cholesterol, low-density lipoprotein and high-density lipoprotein. All participants were followed up regularly and subjected to annual physical examinations by experienced physicians, who also guided them in their efforts to develop a healthy lifestyle. Next, we analyzed the change in the FBG level during a 6-year follow-up analysis according to a quartile of the baseline GGT levels. Finally, we analyzed the relationship between basic GGT subgroups, time course and baseline FBG.

All participants underwent professional anthropometric measurements, including blood pressure, height and weight. After sitting for 5 min, the systolic blood pressure and diastolic blood pressure of the right upper arm were measured with a mercury barometer. The arm and heart were at the same level, measured three times and the average value was considered for analysis. The height and weight were measured while the participants were wearing thin clothes and pants, and without any shoes. As an indicator of relative weight, BMI was calculated by dividing weight by height squared in meters. A uniform questionnaire was designed by qualified physicians to record the age, sex, general health, and history of medication and alcohol consumption. The blood samples were obtained from the antecubital vein in the morning after a 12-h overnight fast. The biochemical indicators were measured by using an enzymatic method on the Hitachi 7,600 Automatic Biochemical Analyzer (Hitachi Ltd., Tokyo, Japan).

STATISTICAL ANALYSIS
Data management and statistical analysis were carried out using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean and standard deviation. All measured data were found to obey normal distribution after the normal test. The participants were assigned to four groups based on the baseline GGT levels (in quartiles). One-way ANOVA was applied to compare the differences in variables with the baseline. The relationship between the GGT levels and FBG levels was examined through repeated measurements ANOVA. All P-values were double-tailed, and $P < 0.05$ was considered to show statistical significance.

RESULTS
Clinical characteristics based on the quartiles of serum GGT
The mean ± standard deviation (SD) age of the participants was 47.49 ± 9.60 years, and more than half of the participants were women (646 of 1,067; 60.54%). The participants were grouped based on the following baseline GGT quartile: Q1 <12 IU/L, 12 < Q2 < 16 IU/L, 16 < Q3 < 22 IU/L and Q4 >22 IU/L for women. Q1 <20 IU/L, 20 < Q2 < 27 IU/L, 27 < Q3 < 42 IU/L and Q4 >42I U/L for men. The baseline clinical and biochemical characteristics are presented in Table 1. We found positive relationships among the baseline serum GGT levels and age, weight, BMI, systolic blood pressure,

Table 1 | General clinical characteristics according to quartile of baseline gamma-glutamyl transferase groups

	Q1 ($n = 281$)	Q2 ($n = 301$)	Q3 ($n = 241$)	Q4 ($n = 244$)	F	P for trend
Age (years)	43.79 ± 10.40	48.08 ± 10.65	48.63 ± 9.46	49.93 ± 9.61	18.73	<0.001
Weight (kg)	61.48 ± 10.90	62.89 ± 10.29	66.46 ± 11.34	67.84 ± 11.59	19.26	<0.001
BMI (kg/m²)	22.49 ± 2.73	23.41 ± 3.00	24.55 ± 2.93	25.24 ± 3.32	43.35	<0.001
SBP (mmHg)	117.60 ± 11.92	121.84 ± 15.49	125.80 ± 16.01	128.54 ± 17.33	23.56	<0.001
DBP (mmHg)	75.22 ± 9.77	77.65 ± 9.91	79.80 ± 11.06	81.19 ± 9.90	17.39	<0.001
TC (mmol/L)	4.54 ± 0.79	4.87 ± 0.86	4.93 ± 0.84	5.23 ± 0.90	29.40	<0.001
TG (mmol/L)	1.02 ± 0.63	1.29 ± 0.74	1.74 ± 1.63	2.18 ± 2.02	38.20	<0.001
HDL (mmol/L)	1.57 ± 0.38	1.52 ± 0.37	1.44 ± 0.34	1.44 ± 0.37	9.26	<0.001
LDL (mmol/L)	2.72 ± 0.65	3.00 ± 0.74	3.00 ± 0.72	3.16 ± 0.80	17.28	<0.001

For men, Q1: gamma-glutamyl transferase (GGT) <12 IU/L, Q2: 12 < GGT < 16 IU/L, Q3: 16 < GGT < 22 IU/L, Q4: GGT >22 IU/L; for women, Q1: GGT < 20 IU/L, Q2: 20 < GGT <27 IU/L, Q3: 27 < GGT <42 IU/L, Q4: GGT > 42 IU/L. *F*-value is the statistical value of the *F*-test. BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic pressure; TC, total cholesterol; TG, triglycerides.

Table 2 | The horizontal comparison results of fasting blood glucose (mmol/L) level according to quartile of baseline gamma-glutamyl transferase level

	Q1	Q2	Q3	Q4	F	P
Baseline	5.09 ± 0.02	5.13 ± 0.02	5.20 ± 0.03	5.19 ± 0.03	3.68	0.012
Follow up 1 year	5.11 ± 0.03	5.09 ± 0.03	5.08 ± 0.04	5.16 ± 0.04	0.95	0.414
Follow up 2 years	5.25 ± 0.04	5.27 ± 0.04	5.29 ± 0.04	5.45 ± 0.04	4.78	0.003
Follow up 3 years	5.20 ± 0.04	5.19 ± 0.04	5.22 ± 0.03	5.22 ± 0.04	0.16	0.926
Follow up 4 years	5.17 ± 0.04	5.29 ± 0.04	5.28 ± 0.04	5.35 ± 0.04	3.53	0.014
Follow up 5 years	5.27 ± 0.04	5.30 ± 0.04	5.30 ± 0.05	5.40 ± 0.05	1.53	0.206
Follow up 6 years	5.29 ± 0.06	5.36 ± 0.05	5.43 ± 0.06	5.60 ± 0.06	4.92	0.002

Adjusted age, weight, F-value is the statistical value of the F-test. For men, Q1: gamma-glutamyl transferase (GGT) <12 IU/L, Q2: 12 < GGT < 16 IU/L, Q3: 16 < GGT < 22 IU/L, Q4: GGT > 22 IU/L; for women, Q1: GGT < 20 IU/L, Q2: 20 < GGT <27 IU/L, Q3: 27 < GGT <42 IU/L, Q4: GGT > 42I U/L. BMI, blood pressure and lipids; FBG, fasting blood glucose.

diastolic blood pressure, total cholesterol, triglycerides, and low-density lipoprotein levels. Only GGT and high-density lipoprotein cholesterol levels showed a negative relationship ($P < 0.001$).

FBG changes at baseline and 6-year follow up
Changes in FBG at baseline and 6-year follow up after the participants were grouped by quartile according to the baseline serum GGT levels are shown in Table 2. After adjusted age, weight, BMI, blood pressure and lipids, FBG levels at baseline ($P < 0.05$), 2-year follow up ($P < 0.01$), 4-year follow -up ($P < 0.05$) and 6-year follow up ($P < 0.01$) were positively correlated with GGT levels. This indicated that the grouping of baseline GGT levels affected the changes in FBG during the 6-year follow-up period.

As shown in Figure 1, during the 6-year follow-up period, FBG levels were proportional to follow-up duration in all baseline GGT quartile subgroups. In the four GGT quartile subgroups, a positive relationship was noted between the annual mean increase of the FBG levels and the baseline GGT levels, and the relationship was more noticeable in the highest baseline GGT group (Q4).

## Interactions between time course, baseline FBG levels and baseline GGT levels
As shown in Table 3, the baseline FBG level was used as a covariate in ANOVA with repeated measurements. We found that 'time course' affected the change in FBG levels. There were interactions between time course, baseline FBG levels and baseline GGT groups in different individuals, which together affected the change in FBG levels during the follow up.

GGT is a risk factor affecting FBG levels
Considering that the baseline FBG level might affect subsequent FBG levels, the effect of this factor was eliminated by carrying out repeated measures ANOVA. As shown in Table 4, different baseline GGT groups were significantly associated with increased FBG levels during the follow-up period, indicating GGT as a risk factor affecting FBG levels ($P < 0.01$).

DISCUSSION
A large cross-sectional and longitudinal analysis from Korea showed that GGT concentration in the serum was closely related to impaired fasting glucose regulation (IFG)[8]. In the present general population-based 6-year follow-up study, we
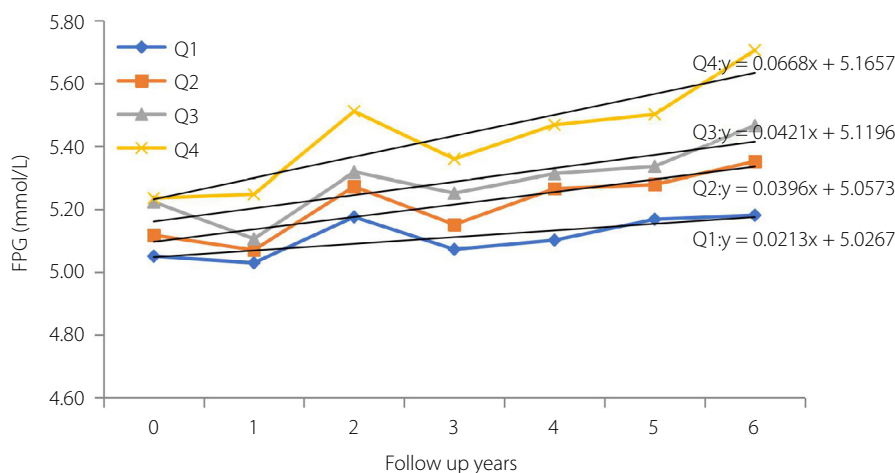
Figure 1 | The change of fasting blood glucose (FBG) in the follow up study according to quartile of baseline gamma-glutamyl transferase groups.

Table 3 | The fasting blood glucose change with test of within-subjects

	Type III Sum of squares	d.f.	Mean square	*F*	*P*
Time course	4.14	3.98	1.05	3.61	0.006
Time course × baseline FBG	6.43	3.98	1.63	5.60	<0.001
Time course × baseline GGT groups	6.16	11.84	0.52	1.79	0.045

There were interactions between time course, baseline fasting blood glucose (FBG) and gamma-glutamyl transferase (GGT) groups in this repeated measurements ANOVA (*P* < 0.05). d.f., degrees of freedom.

Table 4 | Relationship between baseline gamma-glutamyl transferase groups and fasting blood glucose levels during follow up after using repeated measures ANOVA

	Type III sum of squares	d.f.	Mean square	*F*	*P*
Intercept	79.95	1	79.95	57.58	<0.001
Baseline FBG	550.32	1	550.32	396.32	<0.001
GGT quartile Groups	36.57	3	12.19	8.78	<0.001

Different baseline gamma-glutamyl transferase (GGT) groups were still significantly associated with increased fasting blood glucose (FBG) levels during follow up (*P* < 0.01).

showed an association between GGT and FBG in the Chinese population. The baseline FBG levels, and 2-year, 4-year and 6-year follow-ups were positively correlated with the baseline GGT levels. The correlation indicated that the grouping of baseline GGT levels affected changes in blood glucose during the 6-year follow-up period. In the four GGT quartile subgroups, the annual mean increase in FBG levels was positively correlated with baseline GGT levels. Higher baseline GGT levels resulted in a faster annual mean increase in FBG levels.

The liver plays a crucial role in regulating blood glucose levels, especially in the fasting state[9]. Thamer *et al.*[10] showed that increased serum GGT levels might predict glucose intolerance through hepatic insulin resistance, they observed an association between reduced insulin sensitivity and increased liver fat that might explain the increased risk of diabetes in individuals with increased serum GGT concentrations. An increased serum GGT concentration might indicate an early glucose metabolism disorder after excluding the possibility of liver diseases[11]. Consistent with our findings, the present 6-year follow-up study showed a significant association between the baseline GGT levels and FBG, independent of age, weight, BMI, blood pressure, and lipids.

The early intervention of fasting hyperglycemia can effectively reduce the risk of type 2 diabetes, which is crucial for reducing the long-term medical burden[12]. Hence, understanding the risk factors of fasting hyperglycemia is practically important. In prediabetes, blood glucose levels are higher than the normal range, but are not high enough to be diagnosed as diabetes. Furthermore, the condition is characterized by reduced glucose tolerance or IFG. However, elevated FBG within the normal range is positively associated with IFG risk[13,14]. Relevant studies have shown that patients with IFG possess a significantly higher risk of developing diabetes[15]. In a previous study, we confirmed

that serum GGT levels were positively correlated with IFG in Chinese adults, and this trend was not affected by other confounding factors[16]. The present 6-year follow-up study in China evaluated the relationship between GGT and FBG. We noted that an annual mean increase in the FBG levels had a positive relationship with the baseline GGT levels.

Previous studies have shown GGT as a marker of oxidative stress and an increasing GGT concentration within its normal range as a predictor of incident diabetes[4,17]. As oxidative stress increases with age[18], we examined whether baseline GGT levels modified the relationship between time course and FBG levels. The present results showed that due to differences in baseline GGT levels, FBG levels varied with the increasing follow-up time. These results showed that the grouping of baseline GGT levels affected changed in blood glucose levels during the 6-year follow-up period.

The present study was a 6-year follow up containing several participants. Compared with cross-sectional studies, the follow-up study provided more important information on the relationship between GGT and FBG levels. However, the study had some limitations. First, the study was based on the data from a health examination survey in the urban area of Xuzhou, central China, and it cannot represent the entire Chinese population. Second, the observation period was only 6 years. Long-term and large-scale prospective studies can overcome this limitation. Third, a misclassification bias might exist because of the single measurement of biomarkers. Finally, several potential confounders, such as diet, social class, educational attainment and other lifestyle factors in adulthood (tobacco smoking and the lack of physical exercise), were not assessed in the present study.

In conclusion, the present study showed that baseline FBG levels, and 2-year, 4-year and 6-year follow ups were positively correlated with GGT levels. The grouping of baseline GGT

levels affected changes in blood glucose during the 6-year follow-up period. Individuals with different baseline FBG levels in different baseline GGT groups might have different FBG levels during the follow-up period than others. In the four GGT quartile subgroups, the annual mean increase in FBG levels was positively related to baseline GGT levels. Therefore, GGT levels, an easy and convenient measurement, can be used for early detection in FBG-related disorders of glucose metabolism in the clinical field.

DISCLOSURE
The authors declare no conflict of interest.
Approval of the research protocol: This study approved by the Ethics Committee of the Central Hospital of Xuzhou, China.
Informed consent: Written informed consent was obtained from all participants.
Registry and the registration no. of the study/trial: N/A.
Animal Studies: N/A.

DATA AVAILABILITY STATEMENTS
We certify that we have participated sufficiently in the work to take public responsibility for the appropriateness of the design and method, the research, analysis, and interpretation of the data. The primary data used to support the findings of this study are restricted by the Ethics Committee of the Central Hospital of Xuzhou, China, to protect patient privacy. Data are available from Dr Jun Liang for researchers who meet the criteria for access to confidential data.

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