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The association of gamma-glutamyltransferase and C-reactive protein with IFG/IGT in Chinese adults in Qingdao, China

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ABSTRACT

Background: Serum gamma-glutamyltransferase (GGT) and C-reactive protein(CRP) have been previously shown to be associated with impaired fasting glucose/impaired glucose tolerance (IFG/IGT), but such an association has not been well verified, and is examined in a non-diabetic Chinese population.
Methods: A population-based cross-sectional study was conducted in 2006 in Qingdao, China. Data of 1143 men and 1689 women aged 35–74 years and free of diabetes at baseline were analyzed. Multivariable logistic regression analysis was performed to estimate the odds ratio (OR) and its 95% confidence interval (CI).
Results: Compared with the lowest quartile, the ORs (95%CI) for IFG/IGT corresponding to the highest quartile were 0.89(0.61,1.28) in men and 0.87(0.64,1.18) in women for CRP and 2.12(1.40,3.38) and 1.87(1.32,2.62) for GGT, when the two were fitted simultaneously in a model adjusting for age, school years, alcohol-drinking, smoking, family history of diabetes, systolic blood pressure, waist circumference, triglycerides and high-density lipoprotein.
Conclusions: The elevated GGT, but not CRP, was independently associated with the presence of the IFG/IGT in both genders in this Chinese population.

1. Introduction

Serum γ-glutamyltransferase (GGT) is commonly used as a marker of alcohol consumption or liver disease [1] and synthesized in epithelial cells of the intrahepatic duct [2]. Several prospective studies have shown that serum GGT predicted the development of diabetes [3–7]. Moreover, recent studies have shown that serum GGT concentrations were associated with impaired fasting glucose/impaired glucose tolerance (IFG/IGT) [8–10].

C-reactive protein (CRP) is a non-specific biomarker of acute inflammation and is produced primarily in the liver. Several studies had shown that serum CRP may be involved in the development of IFG/IGT [11–13]. Because both GGT and CRP are produced in liver and strongly associated with obesity and excess deposition of fat in the liver, it is, thus, important to know whether the association of GGT and CRP with elevated glucose levels is mediated through obesity as well as other factors that are associated with the both. This may help to understand the underlying mechanism of the deterioration in glucose metabolism. In this study, the association of serum GGT and CRP levels with the presence of the IFG/IGT is examined in a Chinese population living in Qingdao, China.

2. Methods

2.1. Study population

A total of 6100 individuals aged 35–74 y who had lived in Qingdao City for at least 5 y were recruited in 2006 with stratified random cluster sampling from 3 urban districts (Shinan, Shibei and Sifang) and 3 rural districts (Huangdao, Jiaonan and Jimo). Among them, 5355 individuals participated in the study, with a response rate of 87.8%. The inclusion criteria for the current study were : 1) non-diabetic; 2) both fasting plasma glucose (FPG) and 2-h plasma glucose (2 h PG) values available; 3) no data missing for body mass index

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(BMI), waist circumference (WC), blood pressure measurements, CRP, GGT. A total of 2832 (1143 men) subjects with full requirement were included.

WC was measured at the middle point between the lowest rib cage and top of the iliac crest to the nearest 0.1 cm. Three consecutive blood pressure readings, apart for at least 30 sec, were taken from the right arm of seated subjects, and the average of the three readings was used in the data analysis. Smoking status was classified as current smokers (smoking daily regardless of the amount and type of smoking) and non-smokers (including ex-smoking, smoking now and then and not smoking at all). Alcohol-drinking status was defined as current drinkers (drink frequently regardless of the amount and type of alcohol) and non-drinkers (including ex-drinkers, drinking now and then or not drinking at all). Family history of diabetes was defined as having at least one of parents, sibling or offsprings with diabetes. School years were divided into 2 levels of ≤9 and >9 y. Occupational activities were categorized into light (managerial staff), moderate (teacher/doctor/nurse) and heavy (worker or farmer). All subjects without a prior history of diabetes underwent a standard 2-h 75 g oral glucose tolerance test (OGTT). Blood samples were transported in a dark box with ice to the laboratory no more than 6 h after drawing and stored at −80 °C.The lab assays were performed in the central laboratory of Qingdao Hiser Medical Center using Olympus AU analyzers (Tokyo, Japan). Plasma glucose levels were determined by the glucose oxidase method. CRP, fasting serum triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) were determined by enzymatic method. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation. GGT and alanine aminotransferase (ALT) was measured by using an International Federation of Clinical Chemistry (IFCC) method. Haemoglobin A1c (HbA1c) was measured using an immunoturbidimetry method (Tina-qu.a A1C HIT 917 large; Roche Diagnostics). The HbA1c concentration was calculated by using the formula provided by Roche Diagnostics: [calculated HbA1c (%) = 0.81 × HbA1c (test result) + 2.39] to match the values with those found in the new IFCC standardization procedure, and a conventional high performance liquid chromatography (HPLC) method [14]. The calculated HbA1c was subsequently used in the data analysis. The Ethic Committee of Qingdao Municipal Hospital approved the study. Verbal or written consent was obtained from each participant prior to the data collection.

2.2. Classification of diabetes

IFG/IGT was defined according to the 2006 World Health Organization (WHO)/International Diabetes Federation (IDF) criteria [15]. Subjects who reported a history of diabetes and who were under treatment with either insulin or oral anti-diabetic agents were considered as previously diagnosed diabetes regardless of their plasma glucose levels. Newly diagnosed diabetes was defined if FPG ≥ 7.0 mmol/l and/or 2 h PG ≥ 11.1 mmol/l. Both previously diagnosed and newly diagnosed diabetes were excluded from the data analysis. Among non-diabetic individuals, IFG/IGT was defined if FPG between 6.1–6.9 mmol/l and/or 2 h PG between 7.8–11.0 mmol/l, and normal glucose tolerance (NGT) defined as FPG of <6.1 mmol/l and 2 h PG of <7.8 mmol/l.

2.3. Statistical analysis

A χ^2 test for categorical variables and the general linear model (GLM) procedure for continuous variables were used to compare differences in prevalence and in age-adjusted means among different glucose categories. Multivariable logistic regression analysis was used to investigate the relationship of IFG/IGT with serum CRP and GGT levels in men and women, adjusting for age, school years, alcohol-drinking, smoking, family history of diabetes, WC, systolic blood pressure (SBP), HDL-C and TG. The serum CRP and GGT levels were divided into four groups according to sex-specific quartiles. Odds ratios (ORs) and 95% confidence interval (CI) for IFG/IGT was estimated for quartiles 2–4 as compared with the lowest quartile. For all analyses, variables with skewed distribution, such as CRP and GGT, were logarithmically transformed before data analysis.

Table 1
Baseline characteristics of participants according to glucose tolerance categories.

	Men		Women	
	NGT	IFG/IGT	NGT	IFG/IGT
Number (%)	783 (68.5)	360 (31.5)	1124 (66.5)	565(33.5)
Age (y)	47.9(47.5, 49.3)	50.9(50.3, 51.5)*	48.3(48.0,48.6)	55.3(54.6,56.0)*
School y >9 (%)	57.9	49.2*	36.5	25.3*
Current smoking (yes, %)	50.1	53.6	1.3	2.2
Alcohol-drinking (yes, %)	49.3	47.8	1.6	0.5
Family history of diabetes (yes, %)	10.5	16.4*	16.4	22.8*
Occupational activity (%)				
Light	15.2	14.2	14.7	15.9
Moderate	46.0	53.1	61.8	64.0
Heavy	38.8	32.8	23.5	20.1
Body mass index (kg /m^2)	25.3(25.0, 25.5)	26.3(26.0, 26.6)*	25.1(24.9, 25.3)	26.5(26.2, 26.7)*
Waist circumference (cm)	86.1(85.4, 86.7)	89.6(88.6, 90.5)*	80.1(79.5, 80.6)	83.8(83.0, 84.5)*
Systolic blood pressure (mmHg)	130(129, 131)	136(134, 138)*	126(125,127)	137(135, 139)*
Diastolic blood pressure (mmHg)	86(85, 87)	88(87, 89)*	82(81,83)	86(85, 87)*
Fasting plasma glucose(mmol/l)	5.09(5.05, 5.13)	5.94(5.87, 6.01)*	5.16(5.13, 5.19)	5.86(5.80, 5.91)*
2 h post-load plasma glucose (mmol/l)	5.61(5.54, 5.69)	7.65(7.48, 7.81)*	5.97(5.91, 6.03)	8.00(7.88,8.14)*
Haemoglobin A1c(%)	5.61(5.59,5.63)	5.59(5.56,5.62)	5.52(5.50,5.54)	5.50(5.48,5.52)
Low density lipoprotein cholesterol (mmol/l)	2.93(2.86, 2.99)	3.06 (2.97, 3.14)	2.94(2.88, 2.99)	3.15(3.07, 3.22)*
High density lipoprotein cholesterol (mmol/l)	1.65(1.62, 1.69)	1.54(1.50, 1.58)*	1.73(1.69,1.76)	1.60 (1.57, 1.63)*
Triglyceride (mmol/l)	1.29(1.24, 1.34)	1.61(1.52,1.69)*	1.08(1.04, 1.12)	1.29(1.21,1.35)*
Total cholesterol (mmol/l)	5.16(5.09, 5.23)	5.36(5.26, 5.46)*	5.13(5.07, 5.19)	5.33(5.25, 5.40)*
C-reactive protein (mg/dl)	0.85(0.75, 0.95)	0.94 (0.74, 1.14)	0.68(0.60, 0.76)	0.89(0.81,0.97)*
Alanine aminotransferase (U/l)	12.7(12.1, 13.4)	13.5(11.6, 15.4)	10.8 (10.2, 11.3)	11.9(10.7, 13.2)
Gamma–glutamyltransferase (U/l)	26.5 (24.8, 29.2)	33.9(30.4, 37.4)*	14.6(14.2, 15.0)	17.8(17.1, 18.5)*

Data are age-adjusted mean (95% confidence interval) or percentage as noted. Geometric mean for C-reactive protein and Gamma-glutamyltransferase.*P<0.05, NGT vs. IFG/IGT within the same gender.

Table 2
Standard β coefficients and R square (R^2) for C-reactive protein (CRP) and gamma-glutamyltransferase (GGT) in association with fasting, 2 h plasma glucose concentrations (mmol/l) and haemoglobin A1c (%).

	Fasting plasma glucose		2 h plasma glucose		Haemoglobin A1c	
	Standard β coefficients	R^2	Standard β coefficients	R^2	Standard β coefficients	R^2
Men (n = 1143)						
CRP (mg/dl)	0.05	0.001	0.01	0.003	0.006	0.001
GGT(U/l)	0.11†	0.034	0.15†	0.016	0.001	0.001
Women (n = 1689)						
CRP (mg/dl)	0.15	0.011	0.06*	0.027	0.008	0.003
GGT(U/l)	0.10†	0.035	0.08 †	0.032	0.005	0.000

Adjusted for age, school years, family history of diabetes, waist circumference, systolic blood pressure, triglycerides and high density lipoprotein cholesterol. CRP and GGT are logarithmic transformed.
* $P<0.01$, † $P<0.001$.

All analyses were performed using SPSS (Version15.0; SPSS Inc, Chicago, IL). A $P<0.05$ (2 tailed) was considered statistically significant.

3. Results

The baseline characteristics of the study population were summarized in Table 1. Compared with individuals with NGT, those with IFG/IGT were older, more obese, having less school years and higher levels of SBP, diastolic blood pressure (DBP), serum TG, TC, LDL-C, but lower HDL-C in men and women. Family history of diabetes was more common in men and women with IFG/IGT than in those with NGT. There was no difference between participants with IFG/IGT and those with NGT in HbA1c level, tobacco and alcohol consumption. The mean serum GGT was higher in individuals with IFG/IGT than in those with NGT in both men and women, but the mean serum CRP level was higher only in female subjects with IFG/IGT (Table 1).

In both genders, the level of serum GGT was independently and positively correlated with FPG and 2hPG, while the serum CRP level was only significantly correlated with the 2hPG in women. Neither GGT nor CRP was associated with HbA1c levels. The correlation (R^2), a measure of goodness-of-fit of linear regression, was shown in Table 2. The multivariable adjusted ORs of having IFG/IGT was significantly higher in men within the top quartile of the GGT distribution and in women within the upper three quartiles of the GGT distribution than in those within the lowest GGT category, and the increase in ORs for the GGT remained unchanged when the CRP was fitted in the same model. The association between CRP and IFG/IGT was significant only in women, but attenuated significantly when GGT was entered to the model (Table 3). The results of the Table 3 were not changed substantially when BMI instead of the WC was fitted into the models.

Since we detected a significant interaction of the WC with the GGT ($P<0.001$) and the CRP ($P=0.037$) in women, a stratified analysis

Table 3
Odds ratio (95% confidence interval) for IFG/IGT in relation to quartiles of C-reactive protein (CRP) and gamma-glutamyltransferase (GGT) concentration.

		Model 1	Model 2	Model 3	Model 4
Men					
CRP	Number				
Q1 (≤0.50 mg/ml)	288	1	1	1	1
Q2 (0.51–0.90 mg/ml)	296	0.95(0.68,1.31)	0.86(0.61,1.20)	0.85(0.61,1.19)	0.85(0.62,1.22)
Q3 (0.91–1.70 mg/ml)	274	1.18(0.84,1.64)	1.07(0.76,1.51)	1.06(0.75,1.50)	1.06(0.75,1.49)
Q4 (>1.70 mg/ml)	285	1.10(0.78,1.55)	0.90(0.62,1.31)	0.88(0.66,1.31)	0.89(0.61,1.28)
P for trend		$P=0.535$	$P=0.612$	$P=0.621$	$P=0.673$
GGT					
Q1 (≤18 U/l)	272	1	1	1	1
Q2 (19–27 U/l)	301	1.07(0.67,1.74)	0.99(0.61,1.61)	0.98(0.61,1.61)	0.99(0.61,1.61)
Q3 (28–42 U/l)	283	1.27(0.83,1.96)	1.08(0.70,1.67)	1.07(0.69,1.67)	1.06 (0.67,1.64)
Q4 (>42 U/l)	287	2.79(1.83,4.24)	2.13(1.38,3.30)	2.12(1.37,2.37)	2.12(1.40,3.38)
P for trend		$P=0.000$	$P=0.000$	$P=0.000$	$P=0.000$
Women					
CRP					
Q1 (≤0.40 mg/ml)	413	1	1	1	1
Q2 (0.41–0.80 mg/ml)	438	1.06(0.82,1.37)	0.95(0.71,1.23)	1.12(0.71,1.84)	0.93(0.71,1.22)
Q3 (0.81–1.60 mg/ml)	420	1.36(1.16,1.76)	1.24(1.06,1.61)	1.35(1.03,1.60)	1.15(0.87,1.53)
Q4 (>1.60 mg/ml)	418	1.42(1.14,1.62)	1.59 (1.16,2.05)	1.79(1.25,2.90)	0.87(0.64,1.18)
P for trend		$P=0.000$	$P=0.023$	$P=0.034$	$P=0.206$
GGT					
Q1 (≤12 U/l)	443	1	1	1	1
Q2 (13–15 U/l)	417	1.64(1.29,2.07)	1.36(1.05,1.74)	1.35(1.05,1.74)	1.35(1.04,1.72)
Q3 (16–21 U/l)	422	2.08(1.63,2.64)	1.57(1.20,2.02)	1.56(1.20,2.01)	1.56(1.19,2.00)
Q4 (>21 U/l)	407	2.53(1.85,3.46)	1.95(1.41,2.70)	1.88(1.35,2.65).	1.87(1.32,2.62)
P for trend		$P=0.000$	$P=0.000$	$P=0.000$	$P=0.000$

Model1: Adjusted for age, school years, alcohol-drinking, smoking, family history of diabetes, systolic blood pressure.
Model2: Model1+ waist circumference.
Model3: Model2+ triglyceride + high-density lipoprotein cholesterol.
Model4: GGT and CRP fitted simultaneously into the Model 3.

according to the level of WC (≥90 cm for men and ≥80 cm for women) [16] was performed. We found that the activities of serum GGT were positively associated with IFG/IGT in spite of obesity, with the OR of 1.32 (1.09,1.59) in men and 1.26 (1.04,1.51) in women within the low WC category and 1.45 (1.20, 1.72) and 1.30 (1.08, 1.52) respectively, in those within the high WC category corresponding to a one unit increase in GGT concentration (U/l). The association between the serum CRP and IFG/IGT was only detected in obese female subjects, and became non-significant after further adjustment for GGT.

4. Discussion

In this population-based cross-sectional study, we demonstrated that increased GGT levels were positively associated with the presence of IFG/IGT in both genders independent of other known risk factors including CRP. The positive association of CRP with IFG/IGT was observed in women only, but the association was significantly attenuated after further adjustment for GGT.

The impact of obesity was not explored either previously, probably due to the small sample size. An OR of 2.16 (95% CI [1.39, 3.37]) was reported in a Mexico City Diabetes Study for increased GGT levels with the incidence of IGT [9] and GGT remained an independent predictor of IFG/IGT (OR 2.62, 95%CI:1.13–6.07) in an Italian study including only 199 men and 301 women recruited from hospital [10]. In a Japanese study including men only, increased GGT level was found to be a significant predictor of incident IFG [8].

Several possible mechanisms may explain the association of the increased GGT activities with the development of IFG/IGT or diabetes. High GGT levels may indicate fat deposition in the liver which often causes hepatic insulin resistance, further systemic insulin resistance and hyperinsulinaemia [17,18]. Thus increased GGT could be a marker of the insulin resistance. Moreover, GGT plays an important role in the defensive response to oxidative stress. It is noteworthy that hyperglycemia, such as that shown by IFG/IGT, can induce the predominance of oxidative stress over antioxidative defense systems. Furthermore, the oxidative stress can contribute to more pronounced hyperglycemia such as IFG/IGT or diabetes [19].

The association between CRP with IFG/IGT was found in some studies [11–13], and more recent studies [7,20] had observed that the association of CRP with type 2 diabetes was entirely attenuated after adjusting for GGT. Our study further confirmed that the association of the CRP with IFG/IGT in women largely depended on the GGT levels, and there was no an independent association between the CRP and IFG/IGT in both genders.

The study has several strengths. First, all IFG/IGT subjects were defined according to the standard 2-hour oral glucose tolerance test. Second, this is a population-based study which is representative of the Chinese population in general. The sample size is large enough to enable data analysis separately for men and women. However, our study is cross-sectional which is not able to determine causality or a temporal relationship between elevated GGT (or CRP) levels and IFG/IGT.

In summary, increased GGT levels were independently associated with the presence of IFG/IGT in both genders after taking into consideration a wide range of potentially confounding factors. CRP was not independently associated with the IFG/IGT in this study population. Prospective studies are needed to further examine the relationship between hyperglycemia and the levels of serum CRP and GGT.

Abbreviations

IFG	impaired fasting glucose
IGT	impaired glucose tolerance
NGT	normal glucose tolerance
FPG	fasting plasma glucose
WC	waist circumference
OGTT	2-h 75 g Oral glucose tolerance test
GLM	general linear model

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