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ORIGINAL ARTICLE

Elevated serum γ-glutamyltransferase predicts the development of impaired glucose metabolism in middle-aged and elderly Chinese

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Abstract The aim of this article is to prospectively investigate the association of the liver enzyme γ-glutamyltransferase (GGT) with the development of diabetes and impaired glucose regulation (IGR) in a Chinese population. Seven hundred and sixty normoglycaemic subjects aged 40 years or older randomly selected from an urban community of Shanghai received a baseline investigation in May 2005. The participants were invited to receive a standard 75-g oral glucose tolerance test (OGTT) in November 2008. Incident diabetes and IGR were determined according to the 1999 WHO criteria. Serum GGT levels were significantly associated with incident diabetes or combined diabetes and IGR prospectively. After extensive adjustment, the diabetes risk was significantly increased with incrementing serum GGT quartiles (P value for trend = 0.0027). As compared with the lowest quartile of GGT, the highest quartile had an adjusted hazard ratio of 1.30 (95% CI 1.03–1.65) for developing combined diabetes and IGR. Furthermore, a high serum GGT level at baseline was independently associated with an increase in the index of homeostasis model assessment of insulin resistance (HOMA-IR) at follow-up. Serum GGT concentration, even within its normal range, is a risk marker for developing impaired glucose metabolism in middle-aged and elderly Chinese.

Keywords γ-Glutamyltransferase · Type 2 diabetes · Impaired glucose regulation

Introduction

Type 2 diabetes is a major health problem worldwide. The liver, as a critical player in the process of nutrient metabolism, has drawn tremendous attention to metabolic disorders, including type 2 diabetes. Excess deposition of fat in the liver, in term of nonalcoholic fatty liver disease (NAFLD), is now regarded as the hepatic manifestation of metabolic syndrome [1]. Also, NAFLD is the most common cause of elevated liver enzyme levels in general populations without known liver diseases [2]. These interrelations between obesity, NAFLD, metabolic syndrome, insulin resistance, and liver enzymes raise the possibility that elevated liver enzyme concentrations predict the development of impaired glucose metabolism.

γ-Glutamyltransferase (GGT), one of the liver enzymes, has been widely used as an indicator of liver dysfunction and a biological marker of alcohol intake [3]. In addition, serum GGT levels are well adopted in epidemiological studies. Strong cross-sectional associations between serum GGT concentrations and many cardiovascular risk factors, including obesity, physical inactivity, hypertension,

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dyslipidemia, and type 2 diabetes, were reported in several population studies [4, 5]. In addition, a number of prospective studies [6–12] also showed that baseline serum GGT was an independent risk marker for the development of type 2 diabetes, metabolic syndrome, cardiovascular diseases, and even all-cause mortality. However, the predictive association of serum GGT with type 2 diabetes was rarely studied in Chinese population. Moreover, there were few studies regarding the association of serum GGT with the development of impaired glucose regulation (IGR). The underlying mechanisms remain to be elucidated. To address these critical issues, we prospectively investigated the association of serum GGT with development of type 2 diabetes and IGR in middle-aged and elderly Chinese.

Subjects, materials and methods

Study subjects

The subjects were recruited from Baoshan, Shanghai, as reported previously [13, 14]. In May 2005, 760 subjects aged 40 years or older, with normal glucose regulation (NGR) ascertained by oral glucose tolerance test (OGTT), were included in this study at baseline. Questionnaires were used to obtain the information about lifestyle and medical history. Anthropometric measurements were conducted by senior physicians. Blood and urine samples were collected from each participant for biochemical measurements. In November 2008, all the participants were invited to receive OGTT assessment except those who had been diagnosed as type 2 diabetes and taken anti-diabetic drugs. Type 2 diabetes and IGR were defined according to the 1999 WHO criteria. A total of 570 subjects (75%) responded and participated in the final visit. Forty-four subjects were excluded from the present analysis due to lack of fasting or 2h post-load plasma glucose measurements ($n = 11$), known liver diseases such as hepatitis, cirrhosis, or malignancy ($n = 9$), serum GGT levels more than 3 SDs above the mean of the study population (i.e., GGT > 113 IU/l, $n = 8$), and alcohol consumption exceeding 210 g/week ($n = 16$), which is considered as heavy drinking [15]. Thus, 526 subjects were eventually included in the present analysis. The mean follow-up duration was three and half years.

The study protocol was approved by the Institutional Review Board of Rui-Jin Hospital, and informed consent was obtained from each participant.

Definition and anthropometric measurements

Medical history and anthropometric measurements were obtained at baseline and the final visit. A family history of diabetes was defined as having a mother, father, sister, brother, son, or daughter with diagnosed diabetes. The current smoking or drinking states were defined as 'yes' if the subject smoked cigarettes or consumed alcohol regularly in the past 6 months. The information about alcohol consumption included the type of alcoholic beverage, the frequency of alcohol consumption on a weekly basis, and the usual amount consumed daily. Weekly alcohol consumption (grams of ethanol per week) was calculated accordingly. However, most participants were non-drinkers (90.7%); a small proportion of participants were light drinkers (4.6%, alcohol consumption <70 g/week) and moderate drinkers (4.7%, alcohol consumption between 70 and 210 g/week). Waist circumference was measured at umbilical level. Body mass index (BMI) was calculated as body weight in kilograms divided by body height squared in meters (kg/m^2). Blood pressure was measured at the non-dominant arm in a seated position three times consecutively at 1-min interval after at least 5-min rest using an automated electronic device (OMRON Model1 Plus, Omron Company, Kyoto, Japan). The three readings were averaged for analysis. All participants were informed to fast for at least 10 hours before blood samples were collected. Two-point (0 and 2h) OGTT with a 75-g glucose load was performed. Plasma and serum were aliquoted and stored at −80°C until assayed.

Biochemical measurements

Plasma glucose, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT, triglycerides, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were measured using an autoanalyser (Beckman CX-7 Biochemical Autoanalyser, Brea, CA, USA). The white blood cell (WBC) count was determined using an automated cell counter. Serum insulin was measured by a radioimmunoassay (Sangon Company, Shanghai, China). The index of homeostasis model assessment of insulin resistance (HOMA-IR) was calculated according to the formula: HOMA-IR = fasting insulin concentrations (mIU/l) × fasting plasma glucose concentrations (mmol/l)/22.5. Serum C-reactive protein (CRP) concentrations were measured using highly sensitive competitive immunoassay (antigens and antibodies from BioCheck, Foster City, CA, USA).

Statistical analysis

The chi-squared test and one-way analysis of variance were used to analyze statistical differences amongst characteristics of the study participants according to (1) glycaemic

states at follow-up and (2) serum GGT at baseline. Categories of GGT were defined by the following quartiles: <18, 18–22, 22–31, and ≥31 IU/l for men and <16, 16–19, 19–25, and ≥25 IU/l for women. The following skewed variables were logarithmically transformed before analysis: fasting insulin, HOMA-IR, triglycerides, CRP, WBC, ALT, AST, and GGT.

For each participant, person-years of follow-up were calculated from the date of enrollment to the date of the development of type 2 diabetes or the date of follow-up, whichever occurred first. Cox proportional hazards models were used to evaluate the association between serum GGT and the development of impaired glucose metabolism. Subjects in the two lower quartiles (quartiles 1–2) of GGT were combined for diabetes analysis due to a limited number of cases. The data were adjusted first for age and sex (model 1) and then for the following multiple covariates: age, sex, family history of diabetes, current smoking and drinking states, BMI, blood pressure, HDL cholesterol, and triglycerides (model 2). The data were also additionally adjusted for fasting glucose and insulin concentrations (model 3) and were finally adjusted for CRP levels (model 4). Tests of linear trend across increasing quartiles of GGT were conducted by treating the quartiles as a continuous variable. Results were presented as hazard ratios (HRs) and 95% confidence interval (CI).

Possible interactions between GGT and demographic or metabolic factors in the development of combined diabetes and IGR were explored in stratified analyses and by adding interaction terms to Cox proportional hazards models. GGT was fitted as a continuous variable, and HRs were computed for an increase of 1 SD of log GGT for each strata of the interaction variables, including sex, age (<61.3 vs. ≥61.3 years, representing the median split), family history of diabetes, current drinking states, obesity (BMI <24.4 vs. ≥24.4 kg/m^2, representing the median split), and insulin sensitivity (HOMA-IR <1.82 vs. ≥1.82, representing the 75th percentile).

In order to examine whether increased serum GGT levels at baseline were associated with a subsequent decrease in insulin sensitivity, the predictive effect of baseline GGT concentrations on change (follow-up adjusted for baseline) in HOMA-IR was evaluated using multiple linear regression models. Models were adjusted for sex and change in waist circumference. Insulin measurements at follow-up were available in 457 participants, and none of the diabetes progressors was using insulin at the time of final visit.

Significance tests were two-tailed, and a P value of <0.05 was stated as statistically significant. All analyses were performed using SAS version 8.1 (SAS Institute Inc., Cary, NC, USA).

Results

Clinical and biochemical characteristics at baseline

In three and half years, 19 subjects developed type 2 diabetes and 93 developed IGR. The clinical characteristics of the study subjects at baseline are shown in Table 1. The participants who progressed to IGR or diabetes had much more risk factors at baseline as compared with non-progressors, including an older age, higher BMI and waist circumference, higher fasting and 2h post-load plasma glucose levels and serum triglycerides. In particular, the progressors of IGR and diabetes had significantly higher serum ALT, AST, and GGT levels. Moreover, the participants who developed diabetes had higher serum ALT ($P < 0.05$) and GGT ($P < 0.01$) as compared with those who developed IGR.

Clinical and biochemical characteristics of the participants according to baseline GGT quartiles are shown in Table 2. The cross-sectional analysis revealed that serum GGT concentrations were well associated with a variety of metabolic disorders, including higher BMI and waist circumference, higher blood pressure, higher fasting and 2h post-load plasma glucose levels, higher HOMA-IR, dyslipidemia, and higher CRP levels and WBC counts.

Serum GGT in association with the development of impaired glucose metabolism

Elevated serum GGT was strongly associated with an increased risk of type 2 diabetes in both simple and multivariate analyses (Table 3). After adjustment for a wide range of covariates, the association did not materially change in direction or magnitude. The hazard ratios for type 2 diabetes in quartiles 3 and 4 of GGT levels were 2.56 (95% CI 0.47–13.92) and 2.71 (95% CI 1.37–5.36), respectively, as compared with combined quartiles 1–2 (P value for trend = 0.0027). It was also shown that serum GGT was significantly associated with the risk of combined diabetes and IGR with a hazard ratio for the highest quartile versus the lowest quartile of 1.30 (95% CI 1.03–1.65). Although serum GGT was not statistically associated with the development of IGR, directions of the associations were positive and consistent with those of diabetes or combined diabetes and IGR.

The subjects with type 2 diabetes and IGR were combined for analysis since they had some risk factors in common [16]. The associations of serum GGT with the risk of combined diabetes and IGR in subgroups of sex, age, family history of diabetes, current drinking states, obesity, and insulin sensitivity are shown in Fig. 1. There were no significant interactions of any of the above variables with the associations between serum GGT and combined

Table 1 Baseline characteristics of participants, according to glycaemic states at follow-up

Characteristics	Normal glucose regulation	Impaired glucose regulation	Type 2 diabetes	*P* value
n	414	93	19	
Age (years)	60.8 ± 9.3	63.9 ± 9.9†	60.6 ± 8.6	0.02
Female *n* (%)	271 (65.5)	65 (69.9)	12 (63.2)	0.67
Family history of diabetes (%)	7.0	9.7	10.5	0.33
Current smoking (%)	13.3	7.5	15.8	0.41
Current drinking (%)	9.7	6.5	15.8	0.95
Body mass index (kg/m^2)	24.2 ± 3.1	25.3 ± 3.3†	26.2 ± 3.5†	0.0004
Waist circumference (cm)	81.5 ± 8.0	84.2 ± 8.7†	87.9 ± 10.0‡	0.0002
Systolic blood pressure (mmHg)	132 ± 21	142 ± 23‡	132 ± 19	0.0009
Diastolic blood pressure (mmHg)	77 ± 11	79 ± 10	78 ± 8	0.48
Fasting plasma glucose (mmol/l)	5.26 ± 0.49	5.46 ± 0.40‡	5.46 ± 0.26	0.0005
2h post-load plasma glucose (mmol/l)	5.97 ± 1.00	6.66 ± 0.77$^{\|}$	6.42 ± 0.98*	<0.0001
HOMA-IR	0.96 (0.46–1.71)	1.29 (0.56–2.08)	1.96 (0.89–2.45)	0.08
HDL cholesterol (mmol/l)	1.53 ± 0.38	1.47 ± 0.36	1.44 ± 0.33	0.27
Triglycerides (mmol/l)	1.10 (0.79–1.53)	1.40 (0.95–2.13)$^{\|}$	1.30 (0.91–1.73)	0.0002
C-reactive protein (mg/l)	1.7 (0.7–3.3)	1.7 (0.7–3.7)	2.1 (0.9–4.0)	0.40
ALT (IU/l)	9 (8–11)	10 (8–13)	12 (9–17)$^{\dagger,\#}$	0.002
AST (IU/l)	22 (20–26)	24 (21–28)*	25 (19–38)*	0.008
GGT (IU/l)	19 (16–26)	22 (18–30)†	30 (22–48)$^{\|,\P}$	<0.0001

Data are means ± SD, medians (interquartile ranges) for skewed variables, or proportions for categorical variables. Differences were assessed using ANOVA (for continuous variables) or χ^2 (for categorical variables) tests; ANOVA tests were performed on natural log transformation of the following skewed variables: HOMA-IR, triglycerides, CRP, ALT, AST and GGT

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$, $^{\|}$ $P < 0.0001$ compared with the group of normal glucose regulation; $^{\#}$ $P < 0.05$, ¶ $P < 0.01$ compared with the group of impaired glucose regulation

diabetes and IGR (all interaction term $P > 0.05$). However, directions of the associations were almost entirely positive.

With regard to the association between serum ALT concentrations and diabetes risk, no significant findings were obtained (Supplementary Table 1).

Serum GGT in association with the change of insulin sensitivity

Relationship between serum GGT at baseline and the change in HOMA-IR is shown in Table 4. A high serum GGT level at baseline was associated with an increment of HOMA-IR during follow-up independent of baseline HOMA-IR and change in waist circumference ($\beta = 0.20$; $P = 0.0007$).

Discussion

The present study has evaluated serum GGT as a predictive marker for the development of impaired glucose metabolism in middle-aged and elderly Chinese. The major findings in our study were: (1) an elevated serum GGT level, even within its normal range, was an important and significant risk marker for incident type 2 diabetes or combined diabetes and IGR, independent of commonly measured diabetes risk factors; (2) serum GGT levels were closely and positively linked to a series of metabolic risk factors; (3) a high GGT level at baseline was associated with a future decline in insulin sensitivity by HOMA-IR. The subjects with alcohol consumption more than 210 grams per week were excluded since heavy alcohol drinking was well associated with the increase of liver enzymes [17].

In the present study, both the cross-sectional and the prospective association of elevated serum GGT levels and type 2 diabetes in Chinese were indicated as in other populations [4–10]. Moreover, serum GGT levels in our study were also an independent predictor of developing combined diabetes and IGR. However, this association was not shown between serum ALT concentrations and type 2 diabetes. In order to investigate the underlying factors for the development of type 2 diabetes in association with serum GGT, we further assessed the association of baseline serum GGT with the change of insulin sensitivity during follow-up measured by HOMA-IR. The HOMA-IR is a well-validated measurement for insulin resistance and well correlated with reference techniques such as the euglycaemic clamp

Table 2 Baseline characteristics of participants, according to serum GGT at baseline

Characteristics	GGT quartiles				*P* value
	1 (lowest)	2	3	4 (highest)	
n	138	131	124	133	
GGT (IU/l)	14 (13–15)	18 (17–19)	23 (22–24)	37 (31–46)	
Age (years)	61.1 ± 9.6	61.6 ± 9.4	61.6 ± 9.7	61.1 ± 9.1	0.95
Female *n* (%)	101 (73.2)	90 (68.7)	70 (56.5)	87 (65.4)	0.053
Family history of diabetes (%)	5.8	7.6	8.9	8.3	0.40
Current drinking (%)	6.5	9.2	9.7	12.0	0.13
Body mass index (kg/m^2)	23.5 ± 3.3	24.5 ± 2.9*	24.7 ± 3.1†	25.0 ± 3.1‡	0.0008
Waist circumference (cm)	79.3 ± 7.6	81.8 ± 8.2*	83.3 ± 8.4$^{\|}$	84.5 ± 8.3$^{\|}$	<0.0001
Systolic blood pressure (mmHg)	130 ± 21	135 ± 23*	134 ± 21	137 ± 22†	0.052
Diastolic blood pressure (mmHg)	75 ± 11	78 ± 10*	79 ± 11†	79 ± 9‡	0.0024
Fasting plasma glucose (mmol/l)	5.14 ± 0.53	5.37 ± 0.42$^{\|}$	5.40 ± 0.39$^{\|}$	5.31 ± 0.51†	<0.0001
2h post-load plasma glucose (mmol/l)	5.90 ± 1.06	6.11 ± 0.93	6.14 ± 1.00*	6.29 ± 0.97†	0.013
HOMA-IR	0.78 (0.37–1.34)	1.02 (0.44–1.94)†	1.27 (0.67–2.12)$^{\|}$	1.29 (0.61–2.09)$^{\|}$	<0.0001
HDL cholesterol (mmol/l)	1.59 ± 0.40	1.48 ± 0.35*	1.52 ± 0.40	1.46 ± 0.35†	0.025
Triglycerides (mmol/l)	0.94 (0.68–1.26)	1.07 (0.82–1.63)†	1.19 (0.85–1.60)†	1.46 (1.02–2.05)$^{\|}$	<0.0001
C-reactive protein (mg/l)	1.0 (0.5–2.3)	1.8 (0.8–3.1)*	2.0 (0.8–4.3)$^{\|}$	2.3 (1.0–5.3)$^{\|}$	<0.0001
White blood cell (×10^9/l)	5.00 (4.20–5.80)	5.60 (4.60–6.40)*	5.55 (4.80–6.60)†	5.70 (4.90–6.65)‡	0.0005
ALT (IU/l)	8 (7–9)	9 (7–11)†	10 (8–12)$^{\|}$	12 (10–17)$^{\|}$	<0.0001
AST (IU/l)	21 (19–23)	22 (19–25)	23 (20–26)‡	26 (21–31)$^{\|}$	<0.0001

Data are means ± SD, medians (interquartile ranges) for skewed variables, or proportions for categorical variables. Differences were assessed using ANOVA (for continuous variables) or χ^2 (for categorical variables) tests; ANOVA tests were performed on natural log transformation of the following skewed variables: HOMA-IR, triglycerides, CRP, WBC, ALT and AST. The cutoff points for GGT quartiles were <18, 18–22, 22–31, and ≥31 IU/l for men and <16, 16–19, 19–25, and ≥25 IU/l for women

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$, $^{\|}$ $P < 0.0001$ compared with the group of quartile 1

(0.58–0.88) [18]. We observed that serum GGT appeared to be associated with both insulin resistance and later decline in insulin sensitivity. Given the interactions between elevated serum GGT, NAFLD, and insulin resistance, the most obvious explanation for our findings is that raised GGT levels reflect fatty change in the liver and in turn the pathophysiological changes predating the development of type 2 diabetes. In addition, our results demonstrated a positive association between serum GGT and chronic inflammatory markers such as CRP and WBC. In this study, we found that CRP concentrations and WBC counts were significantly increased across GGT quartiles, and GGT was positively correlated with CRP ($r = 0.17$; $P = 0.0001$) and WBC ($r = 0.18$; $P < 0.0001$) after adjustment for HOMA-IR.

The observation that serum ALT, a more specific liver enzyme for NAFLD, was not significantly associated with the development of type 2 diabetes suggested other underlying mechanisms possible. In addition, several prospective studies showed that serum GGT level at baseline was also an independent risk marker for the development of other cardiometabolic disorders such as metabolic syndrome, myocardial infarction, ischemic stroke, and cardiac death [10–12, 19–21]. Accordingly, elevated serum GGT levels were thought to reflect inflammation, which is associated with impairment of insulin signaling in the liver and other peripheral tissues. Thus, elevated serum GGT may reflect a subclinical inflammation, which contributed to one of the underlying mechanisms for diabetes development.

Recent experimental studies have shown that GGT plays an important role in intracellular antioxidation. It is reported that GGT participated in the maintenance of intracellular antioxidant defenses by mediating extra-cellular glutathione into the cells [22]. Therefore, increases in GGT activity could be a response to oxidative stress, indicating increased transport of glutathione into cells. GGT was also histologically detected within the coronary plaque [23] which provided evidence that GGT participated directly in oxidation of LDL within the plaque and therefore in atherogenesis. In addition, the Coronary Artery Risk Development in Young Adults (CARDIA) study [24, 25] showed that serum GGT had concentration–response relations even within normal range with markers of oxidative stress such as F2-isoprostanes. Hence, elevated serum GGT concentrations could be an indicator of oxidative stress, which is also a cause for development of diabetes.

Table 3 Incidence rates and relative risks for the development of impaired glucose metabolism by baseline serum GGT

Type 2 diabetes	GGT at baseline			
	Quartiles 1–2[a]	Quartile 3	Quartile 4	*P* for trend
Cases/number at risk	3/269	4/124	12/133	
Person-years (PY)	950.4	438.0	469.5	
Crude rate per 1000 PY	3.16	9.13	25.56	
Adjusted HRs				
Model 1	1.00	2.50 (0.55–11.37)	2.74 (1.45–5.18)	0.0010
Model 2	1.00	2.79 (0.58–13.48)	2.80 (1.44–5.48)	0.0023
Model 3	1.00	2.48 (0.46–13.49)	2.75 (1.40–5.41)	0.0027
Model 4	1.00	2.56 (0.47–13.92)	2.71 (1.37–5.36)	0.0027

Impaired glucose regulation[b]	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* for trend
Cases/number at risk	12/138	25/128	28/120	28/121	0.0016
Person-years (PY)	487.2	452.6	424.1	426.9	
Crude rate per 1000 PY	24.63	55.24	66.02	65.59	
Adjusted HRs					
Model 1	1.00	2.04 (1.02–4.06)	1.58 (1.12–2.23)	1.32 (1.05–1.66)	0.014
Model 2	1.00	1.72 (0.85–3.49)	1.53 (1.07–2.17)	1.22 (0.96–1.57)	0.089
Model 3	1.00	1.47 (0.71–3.03)	1.38 (0.95–2.00)	1.20 (0.93–1.54)	0.17
Model 4	1.00	1.47 (0.71–3.03)	1.46 (1.00–2.13)	1.20 (0.93–1.54)	0.15

Combined diabetes and IGR	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* for trend
Cases/number at risk	12/138	28/131	32/124	40/133	
Person-years (PY)	487.2	463.2	438.0	469.5	
Crude rate per 1000 PY	24.63	60.45	73.06	85.20	
Adjusted HRs					
Model 1	1.00	2.22 (1.13–4.36)	1.68 (1.20–2.35)	1.44 (1.16–1.79)	0.0006
Model 2	1.00	1.97 (0.98–3.96)	1.62 (1.15–2.29)	1.35 (1.07–1.70)	0.0098
Model 3	1.00	1.67 (0.82–3.39)	1.48 (1.03–2.13)	1.30 (1.03–1.65)	0.026
Model 4	1.00	1.67 (0.82–3.40)	1.56 (1.08–2.25)	1.30 (1.03–1.65)	0.022

[a] Subjects in the two lower quartiles (quartiles 1 and 2) were combined for the analysis due to a limited number of diabetes cases

[b] Nineteen participants who developed type 2 diabetes were excluded from the analysis

Model 1: adjusted for age and sex

Model 2: model 1 further adjusted for family history of diabetes, current smoking and drinking states, BMI, blood pressure, HDL cholesterol and triglycerides

Model 3: model 2 further adjusted for fasting glucose and insulin concentrations

Model 4: model 3 further adjusted for CRP levels

To our knowledge, this is the first longitudinal study to investigate the association of serum GGT with the development of type 2 diabetes as well as IGR in Chinese. The strengths of our study included the prospective nature, determination of diabetes and IGR by OGTT for each individual subject both at baseline and the final visit, and the analysis of pre-diabetes occurrence. However, the present study definitely had several limitations. The sample size was relatively small, and the duration of follow-up was not very long. Moreover, although multivariate analyses were adopted in the observational prospective study to control the effect of known confounders on the association of serum GGT with the development of impaired glucose metabolism, some residual or undetected confounding factors could not be ruled out.

In conclusion, the present study indicates that an elevated GGT level, even within normal range, is associated with an increased risk of impaired glucose metabolism. Although the underlying pathophysiological mechanisms are not very clear, it seems that insulin resistance, chronic low-grade systematic inflammation, and oxidative stress may be involved in this association between serum GGT and the development of type 2 diabetes and IGR.

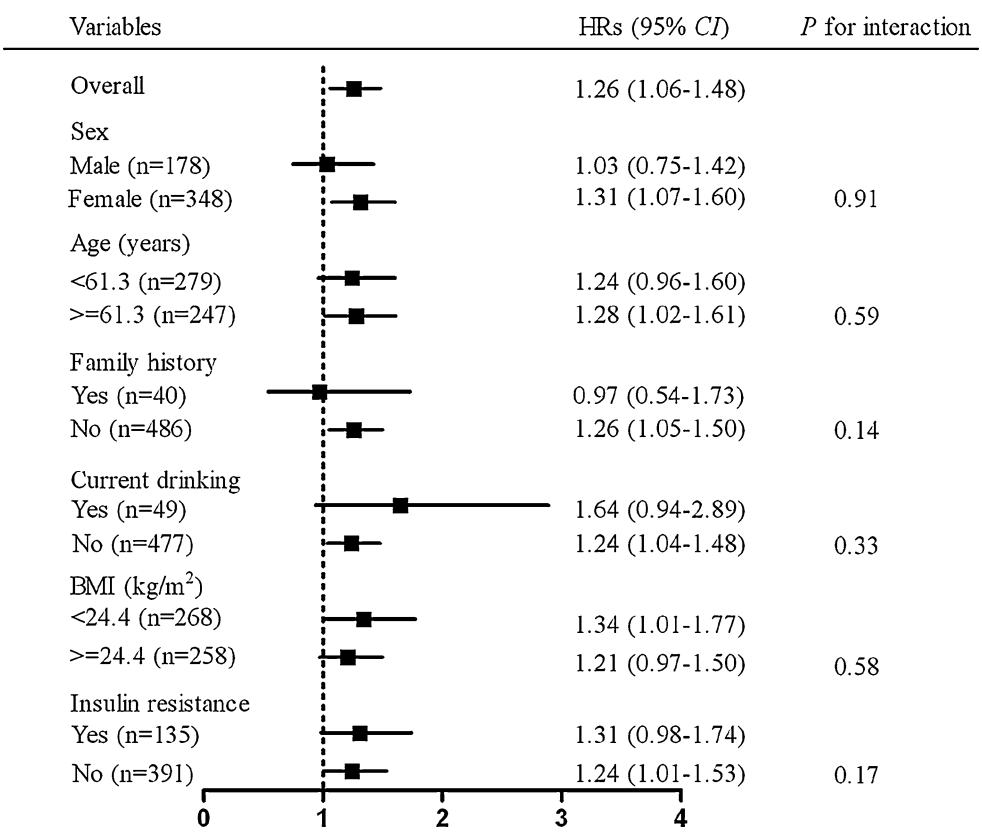

Fig. 1 Cox regression analyses of serum GGT with risk of combined diabetes and IGR by subgroups of sex, age, family history of diabetes, current drinking states, BMI, and insulin resistance. HRs refer to risks of combined diabetes and IGR associated with a 1-SD increment in the natural log of GGT and were adjusted for age, sex, family history of diabetes, current smoking and drinking states, and BMI

Table 4 Multiple regression analysis of relationship between serum GGT at baseline and the change (follow-up adjusted for baseline) in HOMA-IR (adjusted for sex and change in waist circumference)

HOMA-IR at follow-up	Determinant	β[a]	Standard error	*P* value
	Sex (male = 1; female = 2)	0.14	0.049	0.004
	Waist circumference at follow-up	0.018	0.0036	<0.0001
	Waist circumference at baseline	0.014	0.0041	0.0008
	HOMA-IR at baseline	0.13	0.027	<0.0001
	GGT at baseline	0.20	0.057	0.0007

[a] β represented the increase in HOMA-IR at follow-up according to 1-unit increase of baseline GGT and other co-variables

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