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Relationships between Ɣ-glutamyltransferase and insulin resistance, glucose effectiveness, and first- and second-phase insulin secretion in young adults

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ABSTRACT *Type 2 diabetes mellitus (T2DM) is more prevalent in young adults. T2DM affects insulin resistance (IR), glucose effectiveness (GE), and first- and second-phase insulin secretion (FPIS and SPIS, respectively). Ɣ-glutamyltransferase (Ɣ-GT), an inflammatory marker, is related to IR, but whether Ɣ-GT is related to FPIS, SPIS, or GE is unclear. We investigated the associations of Ɣ-GT with these four factors. We noted that Ɣ-GT positively correlates with IR, SPIS, and FPIS, and negatively correlates with GE in young population without diabetes (18-27 years, 23188 men and 29230 women). GE is most tightly related to Ɣ-GT (r = -0.375 for men, r = -0.176 for women). GE should not be overlooked in both sexes.*

KEYWORDS : Insulin resistance, insulin secretion, glucose effectiveness, -glutamyltransferase

Introduction

The overall global prevalence of type 2 diabetes (T2DM) is predicted to dramatically increase from 382 million in 2013 to 592 million by 2035 (Forouhi & Wareham, 2014). The related morbidity and mortality are thus major threats to individual health and also burden health providers. There is evidence that this phenomenon is related to the simultaneously higher prevalence of obesity and the westernization of our lifestyles. What is more disturbing is that this trend is now not only found in adults, but that the age of onset of T2DM is also decreasing. T2DM is more prevalent among adolescents, children, and young adults worldwide than it was decades ago (Pinhas-Hamiel & Zeitler, 2005). Thus, early detection and prevention of T2DM in the younger population has become one of the most important public health challenges for health providers and governments.

Insulin resistance (IR) and insulin secretion are known to underlie the pathophysiology of T2DM. However, other two important facts are commonly overlooked. First, insulin secretion occurs in two phases, which are called first- and second-phase insulin secretion (FPIS and SPIS, respectively) (Cheng, Andrikopoulos, & Gunton, 2013). Second, impaired glucose effectiveness (GE) also contributes to the deterioration of glucose metabolism (Aizawa, Yamauchi, & Yamada, 2014). Even though there is evidence indicating that FPIS, SPIS, and GE play important roles in glucose metabolism, only a handful of studies have focused on these factors (Lorenzo et al., 2011; Succurro et al., 2011).

Earlier, Ɣ-glutamyltransferase (Ɣ-GT) was commonly regarded as a diagnostic tool for liver dysfunction, which is often caused by chronic alcohol consumption. Recently, a tight relationship between Ɣ-GT and oxidative stress (Lee, Blomhoff, & Jacobs, 2004) was revealed. Ɣ-GT is thus now recognized as a marker for cardiovascular risk. More interestingly, many studies also suggest that higher Ɣ-GT is correlated with the incidence of diabetes (Danielsson & Lister, 2009; Fujita, Ueno, & Hata, 2010). A possible explanation for this connection is that higher Ɣ-GT is related to increased IR and decreased ß-cell function (Arase et al., 2015; Bianchi et al., 2010). However, until now, little was known regarding whether Ɣ-GT affects GE, IR, GE, and FPIS or SPIS.

Using previously published methods, we measured the above four components in a group of healthy young adults without diabetes. We had two goals. Our first aim was to answer whether there is a relationship between Ɣ-GT and any of the four diabetes-related factors. Our second goal was to evaluate the relative impacts of Ɣ-GT impact on these factors.

Methods:

MJ Health Screening Centers are private clinics located throughout Taiwan. These clinics provide regular health examinations to their members. From enrolled 23,188 men and 29,230 women 18 to 27 years of age from these clinics between 1999 and 2008. All data from the study participants were collected anonymously and informed consent was obtained from all participants. Routine health checkups were arranged at the time of the study. After the institutional review board of MJ Health Screening Centers approved the study protocol, data were obtained from the centers.

We excluded participants who were obese (BMI ≧ 25 kg/m2) and those who were undergoing treatment for high blood pressure or glucose or lipid dysfunctions. On the basis of the criteria of the World Health Organization (Alberti & Zimmet, 1998), all participants were divided into two groups based on the presence of metabolic syndrome (MetS). There were 1,793 men with MetS and 21,395 men without MetS. There were 523 women with MetS and 28,707 women without MetS. The participants were then grouped into four groups according to the quartiles of Ɣ-GT levels in order for us to determine the effects of Ɣ-GT.

Senior nursing staff obtained all participants' medical histories. The information in the medical history included current medications, responses to a thorough questionnaire, and results of a physical examination. BMI was calculated as the subject's body weight (kg) divided by the square of the subject's height (m). Waist circumference (WC) was checked horizontally at the level of the natural waist, which was identified as the level at the hollow molding of the trunk when the trunk was laterally concave. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using standard mercury sphygmomanometers on the right arm of each subject while the subject was seated.

Blood was drawn from the antecubital vein for biochemical analysis after the subject had fasted for 10 h. After drawing the blood sample, the plasma was separated within 1 h and stored at -30°C. Later, fasting plasma glucose (FPG), lipid profiles, and γ-GT levels were analyzed. FPG was measured using the glucose oxidase method (YSI 203 glucose analyzer, Yellow Springs Instruments, Yellow Springs, USA). Using the dry multilayer analytical slide method and a Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Tokyo, Japan), total cholesterol and triglycerides (TG) levels were measured. Concentrations of serum high-density lipoprotein cholesterol (HDLC) and low-density lipoprotein cholesterol (LDLC) were measured using an enzymatic cholesterol assay following dextran sulfate precipitation.

The equations used to calculate IR, FPIS, SPIS, and GE are as follows. All units are in international units.

$IR = \log_{10}(1.439 + 0.018 \times sex - 0.003 \times age + 0.029 \times BMI - 0.001 \times SBP + 0.006 \times DBP + 0.049 \times TG - 0.046 \times HDLC - 0.0116 \times FPG) \times 10^{3.333}$ (Wu et al., 2014)

$FPIS = 10^{(1.477 - 0.119 \times FPG + 0.079 \times BMI - 0.523 \times HDLC)}$ (J. D. Lin et al., 2015)

$SPIS = 10^{(-2.4 - 0.088 \times FPG + 0.072 \times BMI)}$ (Y.-T. Lin et al., 2015)

$GE = (29.196 - 0.103 \times age - 2.722 \times TG - 0.592 \times FPG) \times 10^{-3}$ (Chen et al., 2016)

Statistical analysis:

Statistical analyses were performed using SPSS 19.0 (IBM, Inc., Armonk, NY, USA). Data are presented as means ± standard deviations. All data were tested for normal distribution by using the Kolmogorov–Smirnov test and for homogeneity of variances by using the Levene's test. If data were not normally distributed, they were log-transformed before analysis. To evaluate the differences between the normal and metabolic syndrome groups, we performed t –tests. One-way analysis of variance was used to analyze the differences between the mean values of the four groups, arranged from the highest to the lowest level of γ-GT. The post-hoc Bonferroni method was used for between-group comparisons.

Simple correlations were calculated to evaluate the relationships between two independent variables, such as γ-GT and GE, and the slopes of these relationships were obtained at the same time. Owing to the difference in the units and scales used for these measurements, it was not possible to compare their slopes, which represent the rate changes of each of the factors in response to increasing γ-GT levels. To solve this problem, we compared the slopes of uniquely designed lines. For example, we took the highest value of FPIS as 100% and the lowest value as 0%. Other values falling between these two extremes were calculated as percentages. Using this method, different units used for the different factors were all changed to percentages, which allowed us to compare the different factors (Fig. 1). Among the four factors, only GE had a negative correlation with γ-GT. To compare the slope of GE with those of the other three factors, we plotted a mirror-line (or reciprocal) from the 4th quadrant to the 1st quadrant with the same slope.

Results

The demographic data and the parameters derived from our equations are shown in Table 1. It is not surprising that all of these measures were higher in subjects with MetS. The exceptions were GE and HDLC, which were significantly lower in both men and women with MetS. When evaluating the effects of γ-GT levels (quartiles, Table 2), similar findings to those shown in Table 1 were observed. In other words, when the levels of γ-GT increased, all of the parameters increased significantly and simultaneously. Again, the exceptions were GE and HDLC, whose levels tended to decline with increasing γ-GT. The results of simple correlation analyses between γ-GT and the other four factors are shown in Table 3. It should be noted that GE correlated most tightly with γ-GT ($r = -0.375$, $p < 0.001$ for men, $r = -0.176$, $p < 0.001$ for women) in both sexes. However, the obtained r values could not be compared directly, since different measures had different units.

Table 1. Demographic and biochemical data and data regarding diabetes-related factors in subjects with or without metabolic syndrome

Age (year)	MetS (-)	MetS (+)	p
Men			
N	21,395	1,793	
Age (year)	24.2 ± 2.6	24.6 ± 2.5	<0.001
BMI (kg/m^2)	22.4 ± 3.3	28.8 ± 4.6	<0.001
SBP (mmHg)	118.4 ± 12.4	133.4 ± 13.1	<0.001
DBP (mmHg)	68.3 ± 8.8	77.3 ± 10.5	<0.001
FPG (mg/dl)	93.5 ± 7.4	101.7 ± 18.8	<0.001
Triglyceride (mg/dl)	86.5 ± 42.6	174.5 ± 75.9	<0.001
HDL-C (mg/dl)	51.8 ± 11.6	39.5 ± 8.2	<0.001
Logγ-GT	1.20 ± 0.31	1.46 ± 0.37	<0.001
FPIS (μU/min)	118.0 ± 205.5	590.7 ± 1420.0	<0.001
GE (10^{-2} dL min^{-1} kg^{-1})	0.0210 ± 0.0014	0.0180 ± 0.0025	<0.001
SPIS (pmol/mmol)	0.068 ± 0.075	0.222 ± 0.417	<0.001
IR (10^{-4} min^{-1} pmol^{-1} L^{-1})	3.685 ± 0.023	3.736 ± 0.027	<0.001
Women			
N	28,707	523	
Age (year)	24.2 ± 2.4	24.2 ± 2.6	0.599
BMI (kg/m^2)	20.1 ± 2.8	29.0 ± 5.5	<0.001
SBP (mmHg)	106.5 ± 11.2	125.7 ± 14.1	<0.001
DBP (mmHg)	62.9 ± 8.1	73.5 ± 10.8	<0.001
FPG (mg/dl)	89.8 ± 7.8	102.0 ± 23.2	<0.001
Triglyceride (mg/dl)	67.9 ± 29.2	146.6 ± 67.5	<0.001
HDL-C (mg/dl)	62.7 ± 14.1	43.3 ± 7.9	<0.001
Logγ-GT	0.997 ± 0.271	1.239 ± 0.340	<0.001
FPIS (μU/min)	59.4 ± 106.1	645.6 ± 1349.8	<0.001
GE (10^{-2} dL min^{-1} kg^{-1})	0.0217 ± 0.0010	0.0188 ± 0.0023	<0.001
SPIS (pmol/mmol)	0.047 ± 0.045	0.263 ± 0.475	<0.001
IR (10^{-4} min^{-1} pmol^{-1} L^{-1})	3.667 ± 0.020	3.734 ± 0.032	<0.001

MetS (-) = Without metabolic syndrome; MetS (+) = with metabolic syndrome; BMI: body mass index; SPB: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; HDL-C: high-density lipoprotein cholesterol; Logγ-GT: log γ-glutamyl transpeptidase; FPIS: first phase insulin secretion; SPIS: second phase insulin secretion; GE: glucose effectiveness; IR: insulin resistance.

Data are shown as mean ± standard deviation.

Table 2. Demographic and biochemical data and data regarding diabetes-related factors for quartiles of log γ-glutamyl transpeptidase

	Logγ-GT 1	Logγ-GT 2	Logγ-GT 3	Logγ-GT 4	Logγ-GT 5	
Men						
n	5,632	5,631	5,631	5,631	22,525	
Age (year)	23.7 ± 2.7[2,3,4]	24.0 ± 2.6[1,3,4]	24.4 ± 2.5[1,2,4]	24.7 ± 2.3[1,2,3]	24.2 ± 2.6	<0.001
Body mass index (kg/m^2)	21.3 ± 2.6[2,3,4]	21.9 ± 2.9[1,3,4]	23.0 ± 3.5[1,2,4]	25.4 ± 4.5[1,2,3]	22.9 ± 3.8	<0.001
Systolic blood pressure (mmHg)	116.9 ± 12.5[2,3,4]	118.3 ± 12.6[1,3,4]	119.8 ± 12.9[1,2,4]	123.1 ± 13.6[1,2,3]	119.5 ± 13.1	<0.001
Diastolic blood pressure (mmHg)	67.5 ± 8.8[3,4]	67.9 ± 8.7[3,4]	69.1 ± 9.0[1,2,4]	71.3 ± 9.9[1,2,3]	68.9 ± 9.2	<0.001

Fasting plasma glucose (mg/dl)	92.9 ±	7.9[2,3,4]	93.7 ±	8.7[1,3,4]	94.2 ±	8.5[1,2,4]	95.7 ±	10.8[1,2,3]	94.1 ±	9.1	<0.001
Triglyceride (mg/dl)	72.5 ±	30.6[2,3,4]	80.4 ±	36.7[1,3,4]	93.7 ±	46.2[1,2,4]	126.6 ±	67.9[1,2,3]	93.3 ±	51.8	<0.001
HDL-C (mg/dl)	51.8 ±	11.4[3,4]	52.1 ±	11.7[3,4]	50.9 ±	11.9[1,2,4]	48.4 ±	11.9[1,2,3]	50.8 ±	11.8	<0.001
Logγ-GT	0.998 ±	0.085[2,3,4]	1.158 ±	0.035[1,3,4]	1.294 ±	0.046[1,2,4]	1.589 ±	0.192[1,2,3]	1.260 ±	0.243	<0.001
FPIS (μU/min)	86.0 ±	75.3[3,4]	101.1 ±	117.1[3,4]	140.6 ±	199.1[1,2,4]	287.9 ±	832.0[1,2,3]	153.9 ±	440.6	<0.001
GE (10^{-2} dL min^{-1} kg^{-1})	0.0215 ±	0.0010[2,3,4]	0.0212 ±	0.0013[1,3,4]	0.0207 ±	0.0015[1,2,4]	0.0196 ±	0.0022[1,2,3]	0.0207 ±	0.0017	<0.001
SPIS (pmol/mmol)	0.053 ±	0.030[2,3,4]	0.060 ±	0.045[1,3,4]	0.076 ±	0.073[1,2,4]	0.131 ±	0.250[1,2,3]	0.080 ±	0.137	<0.001
IR (10^{-4} min^{-1} $pmol^{-1}$ L^{-1})	3.677 ±	0.019[2,3,4]	3.681 ±	0.021[1,3,4]	3.689 ±	0.024[1,2,4]	3.708 ±	0.031[1,2,3]	3.689 ±	0.027	<0.001
Women											
n	7,034		7,033		7,033		7,033		28,133		
Age (year)	24.1 ±	2.5[4]	24.1 ±	2.5[3,4]	24.2 ±	2.4[2,4]	24.4 ±	2.4[1,2,3]	24.2 ±	2.4	<0.001
Body mass index (kg/m^2)	19.9 ±	2.3[3,4]	20.0 ±	2.6[3,4]	20.2 ±	2.8[1,2,4]	21.1 ±	4.3[1,2,3]	20.3 ±	3.1	<0.001
Systolic blood pressure (mmHg)	105.6 ±	11.0[2,3,4]	106.3 ±	11.0[1,3,4]	106.9 ±	11.4[1,2,4]	108.4 ±	12.4[1,2,3]	106.8 ±	11.5	<0.001
Diastolic blood pressure (mmHg)	62.7 ±	8.1[4]	62.7 ±	8.0[4]	62.8 ±	8.3[4]	63.9 ±	8.7[1,2,3]	63.0 ±	8.3	<0.001
Fasting plasma glucose (mg/dl)	89.0 ±	6.9[2,3,4]	89.7 ±	8.4[1,3,4]	90.3 ±	7.7[1,2,4]	91.2 ±	10.6[1,2,3]	90.0 ±	8.5	<0.001
Triglyceride (mg/dl)	63.7 ±	25.6[2,3,4]	65.7 ±	26.2[1,3,4]	68.0 ±	29.8[1,2,4]	80.4 ±	41.7[1,2,3]	69.4 ±	32.2	<0.001
HDL-C (mg/dl)	61.6 ±	13.4[2,3]	62.7 ±	13.7[1,4]	63.0 ±	14.3[1,4]	62.0 ±	15.5[2,3]	62.3 ±	14.3	<0.001
Logγ-GT	0.829 ±	0.090[2,3,4]	0.970 ±	0.030[1,3,4]	1.073 ±	0.032[1,2,4]	1.291 ±	0.166[1,2,3]	1.041 ±	0.194	<0.001
FPIS (μU/min)	52.5 ±	47.2[4]	54.4 ±	71.1[4]	59.7 ±	90.5[4]	112.9 ±	386.2[1,2,3]	69.9 ±	204.4	<0.001
GE (10^{-2} dL min^{-1} kg^{-1})	0.0218 ±	0.0009[2,3,4]	0.0217 ±	0.0009[1,3,4]	0.0216 ±	0.0010[1,2,4]	0.0212 ±	0.0014[1,2,3]	0.0216 ±	0.0011	<0.001
SPIS (pmol/mmol)	0.043 ±	0.023[3,4]	0.044 ±	0.032[3,4]	0.047 ±	0.039[1,2,4]	0.069 ±	0.151[1,2,3]	0.051 ±	0.081	<0.001
IR (10^{-4} min^{-1} $pmol^{-1}$ L^{-1})	3.666 ±	0.017[3,4]	3.666 ±	0.019[3,4]	3.667 ±	0.021[1,2,4]	3.674 ±	0.030[1,2,3]	3.668 ±	0.023	<0.001

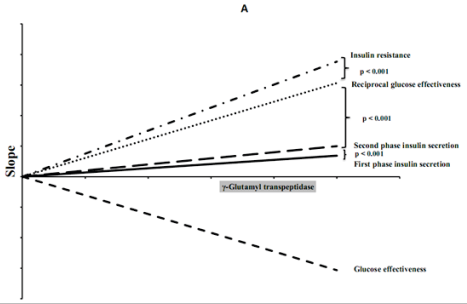
Logγ-GT: log γ-glutamyl transpeptidase; FPIS: first-phase insulin secretion; SPIS: second-phase insulin secretion; GE: glucose effectiveness; IR: insulin resistance. Data are shown as mean ± standard deviation.

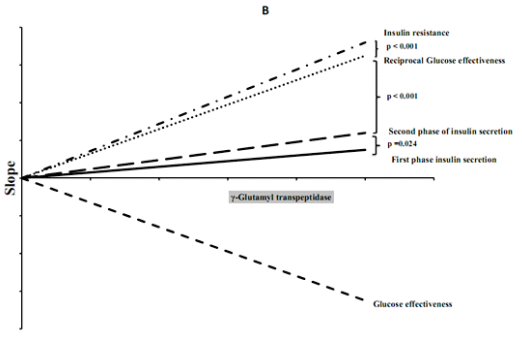
Table 3: Simple correlations between log γ-glutamyl transpeptidase, first phase insulin secretion, second phase insulin secretion, glucose effectiveness, and insulin resistance in both sexes

Diabetic Factor	r	p
Men		
First-phase insulin secretion	0.281	<0.001
Glucose effectiveness	−0.375	<0.001
Second-phase insulin secretion	0.242	<0.001
Insulin resistance	0.359	<0.001
Women		
First-phase insulin secretion	0.101	<0.001
Glucose effectiveness	−0.176	<0.001
Second-phase insulin secretion	0.111	<0.001
Insulin resistance	0.111	<0.001

The most important finding in the present study and the relative relationships between Y-GT and the four factors are shown in Figure 1. Again, as mentioned in the Methods section, all of the measurements were transformed into a scale of 100% before they were compared, as they had different units. GE is the only factor that was reciprocally plotted due to its negative correlation with Y-GT. In Figure 1, it is clear that all four factors are significantly correlated with Y-GT. GE had the tightest relationship with Y-GT in both sexes. The slopes of the factors are significantly different from each other.

Figure 1. Comparison of slopes for percentages of patients with selected diabetic factors in both sexes. (A) Data for men and (B) data for women.





Discussion

In the present study, we not only show that all four factors discussed above are related to Y-GT, but also describe the relative weights of these relationships. Specifically, GE correlates most tightly with Y-GT, and followed by IR, SPIS, and FPIS. To our knowledge, this is the first study to report the association between GE and Y-GT. We also differentiated the effects of Y-GT on FPIS vs. SPIS.

Our finding of the positive correlation between Y-GT and IR is not novel. Ryoo et al. have carried out a similar study in Korean men. In that longitudinal study, the authors showed that the group with the highest Y-GT levels (≥41 U/L) had a 1.58-fold higher chance of having IR than the group with the lowest Y-GT levels (< 18 U/L) after adjusting for confounding factors (Ryoo, Oh, Kim, Park, & Choi, 2014). These results are in line those of the present study. However, Ryoo et al. did not report whether there is a linear correlation between Y-GT and homeostasis model assessment HOMA-IR, which would have been a much more precise method for describing the relationship between the two continuous parameters. There are three mechanisms that may explain this relationship. First, Y-GT may be an indicator of increasing fat in the liver (Stranges, Trevisan, Dorn, Dmochowski, & Donahue, 2005). Fatty liver is in turn strongly associated with a higher risk for IR (Tiikkainen et al., 2002; Westerbacka et al., 2004). Second, elevated -GT activity is associated with sarcopenia and sarcopenic obesity (Hong, Lee, &

Kim, 2015), which is also related to increased IR (Cleasby, Jamieson, & Atherton, 2016). The last possibility is that higher Ɣ-GT might reflect an increase in oxidative stress (Lee et al., 2004), which is a well-known contributor to IR (Meigs et al., 2007).

The biphasic nature of glucose-stimulated insulin secretion is influenced by several factors, including distinct pools of insulin granules and metabolic signaling (Henquin, Ishiyama, Nenquin, Ravier, & Jonas, 2002; Rorsman & Renstrom, 2003). To our knowledge, there is no study regarding the separate effects of Ɣ-GT on FPIS and SPIS. The closest study we could find was one by Succurro et al., who evaluated the relationships between liver enzymes and 1-h post-load plasma glucose levels in Caucasians without diabetes. In that cross-sectional study, insulin concentration after the first hour of the oral glucose tolerance test had a positive correlation with Ɣ-GT levels ($r = 0.15$, $p < 0.0001$) (Succurro et al., 2011). This finding is consistent with our results.

It should be noted that, in general, insulin secretion 10-15 minutes after a glucose challenge is considered as the FPIS (Curry, Bennett, & Grodsky, 1968). The results of the report by Succurro et al., which used insulin concentrations after 1 h, do not exactly correspond to FPIS. However, insulin secretion in the real physiological condition after a food challenge is more like a continuous increased secretion. Thus, the time point 1 h after glucose loading may be used as a surrogate for FPIS, even if it is not completely accurate. We found that Ɣ-GT is positively correlated with both phases of insulin secretion ($r = 0.281$ and $r = 0.242$, for FPIS and SPIS, $p < 0.001$ in men, $r = 0.101$ and $r = 0.111$, for FPIS and SPIS, $p < 0.001$ in women). The fat level in the liver may be the key to explaining these relationships. The level of Ɣ-GT is an indicator of intra-hepatic fat accumulation (Stranges et al., 2005) and liver fat is in turn tightly related to higher insulin secretion (Chai et al., 2014). Our study also indicates that compared to FPIS, SPIS is more tightly related to increases in Ɣ-GT levels.

GE is an independent predictor of future diabetes (Lorenzo et al., 2010). GE is attenuated during the development of non-diabetic hyperglycemia (Aizawa et al., 2014) and deteriorates more in the initial stages of the disease process (Lorenzo et al., 2011). Again, at present, there is no known study discussing the correlation between Ɣ-GT and GE. Our study is the first one to demonstrate that there is a positive correlation between Ɣ-GT and GE. It is also surprising to note that GE is most tightly related to Ɣ-GT than other factors ($r = -0.375$, $p < 0.001$ in men, $r = -0.176$, $p < 0.001$ in women). Although there is no evidence to support the idea that increased Ɣ-GT worsens GE, a possible mechanism underlying this potential phenomenon may involve free fatty acids (FFAs). It is well-documented that higher FFA levels indicate that more fat is stored in the liver (Zhang et al., 2014). Higher FFA levels are also positively correlated to Ɣ-GT. Hawkins et al. have in fact suggested that high levels of FFA may lead to the deterioration of whole-body and hepatic GE. Moreover, the untoward effects of GE mediated by FFA may be reversed by lowering FFA levels. There is solid evidence supporting this connection (Kishore et al., 2006). We thus have reason to believe that that there is a negative correlation between Ɣ-GT and GE, and that FFA underlies this relationship.

Although this study provides some interesting and novel information, there are limitations to our findings. First, the methods we used in this study may be less accurate than the "gold standard." However, since the number of participants in our cohort is quite large, we believe that this shortcoming may be justified. Second, it should be noted that we only enrolled Chinese subjects. Therefore, caution must be exercised when applying the findings to other ethnic groups. Third, this is only a cross-sectional study. In the future, it would be interesting to use the levels of Ɣ-GT to predict changes in the four factors under discussion over time. Finally, some of the new relationships described in the present study do not have cellular or animal studies that would support our conclusions. These studies are required to strengthen our findings.

In conclusion, we successfully showed that Ɣ-GT is positively correlated to IR, SPIS, and FPIS, and negatively correlated to GE. Among these diabetogenic factors, GE is most tightly correlated with Ɣ-GT in both sexes.

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