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GLUTAMIC PYRUVIC TRANSAMINASE IS ASSOCIATED WITH GLUCOSE EFFECTIVENESS IN CHINESE YOUNG ADULT

Clinical Research

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ABSTRACT

INTRODUCTION: Type 2 diabetes (T2D) is one of the most commonly disease found in the elderlies and its prevalence is obviously related to age. So there are very few studies on diabetes among young adults. Therefore, to understand the underlying pathophysiology for T2D is of main interest to the health providers and government. At present, it is generally agreed that here three major perturbations that could cause glucose intolerance, i.e., insulin resistance, insulin secretion and glucose effectiveness (GE). Here, it should be pointed out that GE is often over looked. In the present study, our aim is to evaluate the relationship between liver function enzyme glutamic pyruvic transaminase (GPT) and GE in the young adult.

METHODS: We randomly enrolled 22,971 men and 28,740 women who were aged between 18 to 28 years old from the private chain-clinics in 2013 and 2015. Subjects with different GPT were grouped. Scatter plots and slope were done in the current study.

RESULTS: Most of the metabolic associated parameters were higher in subjects with metabolic syndrome including GPT. On the contrary, HDL-C and GE were lower in subjects with metabolic syndrome. We further divided the study participants into 4 groups according to the level of GPT and similar results were also seen. Statistically significant negative results were found in linear model. Scatter plot were performed and obvious negative correlation were demonstrated. Moreover, slope changes in GE according to the level of GPT still showed a negative relationship between GPT and GE. In this relationship, men had tighter correlation than women was identified.

CONCLUSION: Our data suggest that there is a negative relationship between GPT and GE in young Chinese adult. Moreover, men with tighter correlation than women. Whether it is the cause or the effect remains further study to explore and clarify.

KEYWORDS

GPT, GE, diabetes, young, adult

INTRODUCTION

Diabetes mellitus is the seventh leading cause of death globally. Ninety percent of the diabetic population suffers from type-2 diabetes (T2D) [1]. The prevalence of T2D has been increasing drastically recently in Taiwan as well as many other countries [2, 3]. Rising rates of obesity have led to an increasing prevalence of T2D in young people [4]. In the same time, it is on the top five causes of death in Taiwan for many years [2, 5]. Early in 1946, Gray et al. were the first to find that there is a positive relationship between higher liver function and the occurrence of T2D [6]. After this first publication, many other researchers repeatedly confirmed their results [7-9]. Since liver is one of the major organs involved in glucose homeostasis and abnormal liver function might trigger the vicious cascade for glucose intolerance which eventually leads to T2D [10].

Abnormal liver function is often seen in clinical practice. It is estimated that the prevalence of abnormal liver function is around 10-21% [11]. Among them, the most common causes of abnormal glutamic pyruvic transaminase (GPT) is non-alcoholic fatty liver disease which is around 50-90% [12]. Other than this, it should also be noted that Taiwan is an endemic area for viral hepatitis. The prevalence of HBV infection is around 15-20% [13, 14]. These patients also have abnormal liver function. Therefore, it important to know the relationships between abnormal liver function and T2D.

At present, it is generally agreed that here three major perturbations that could cause glucose intolerance, i.e., decreased insulin action (insulin resistance; IR), insulin secretion and glucose effectiveness (GE) [15]. Here, it should be pointed out that GE is often over looked. Shortly, it is the ability of glucose to increase its uptake and suppress gluconeogenesis in the liver. According to Best et al. it is responsible to 60% of glucose clearance in normal subjects and 99% in T2D [16]. This is not surprising and could be understood since in these patients, the both IR and decreased insulin secretion are quite severe and unable to maintain normal glucose tolerance. However, it is interesting to note that very few studies were concentrate on the role of GE. According to our knowledge, the relationship between GE and GPT has never been explored yet.

T2D is one of the most commonly disease found in the elderlies and its prevalence is obviously related to age [3]. So there are very few studies on diabetes among young adults. Therefore, to understand the underlying pathophysiology for T2D is of main interest to the health providers and government.

In the present study, we enrolled 51711 subjects who had no histories of diabetes or taking any medications for diabetes, hypertension and/or dyslipidemia. Our aim is to evaluate the relationship between GPT and GE in the young adult.

METHODS

MJ Health Screening Centers are a private chain of clinics located in Taiwan that provide regular health examinations for their members. We randomly enrolled 22,971 men and 28,740 women who were aged over 18 years old and under 28 years old from the private chain-clinics in 2013 and 2015. All study participants were anonymous and informed consent was obtained from all participants. Data were provided by MJ Health Screening Centers for research purpose only, and the institutional review board of MJ Health Screening Center approved the study protocol. Participants who were on any medications known to affect blood pressure, glucose and lipids levels were excluded. The participants were further divided into two groups: with and without metabolic syndrome, according to the World Health Organization criteria. To observe the effect of liver function, the groups were further subdivided into quartiles, according to the level of GPT.

On the day of the study, a senior nursing staff recorded the subject's medical history, including information on any current medications, and a physical examination was performed. Waist circumference (WC) was measured horizontally at the level of the natural waist. BMI was calculated as the subject's body weight (kg) divided by the square of the subject's height (m). Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by standard mercury sphygmomanometers on the right arm of each subject while seated.

After fasting for 10 hours, blood samples were drawn for biochemical analyses. Plasma was separated from the blood within 1 hour of collection and stored at 30°C until analysis for fasting plasma glucose (FPG) and lipid profiles. FPG was measured using a glucose oxidase method (YSI 203 glucose analyzer, Yellow Springs Instruments, Yellow Springs, USA). Total cholesterol and triglyceride (TG) levels were measured using a dry, multilayer analytical slide method with the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Tokyo, Japan). Serum

high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) concentrations were analyzed using an enzymatic cholesterol assay, following dextran sulfate precipitation.

The GE was calculated by the following equation.
$GE=(29.196 - 0.103 \times age - 2.722 \times TG - 0.592 \times FPG) \times 10^{-3}$

All statistical analyses were performed using SPSS 19.0 (IBM Inc., Armonk, New York). Data are presented as mean ± standard deviation. All data were tested for normal distribution with the Kolmogorov–Smirnov test and for homogeneity of variances with Levene's test. If data were not normally distributed, data were log transformed prior to analysis. A t–test was performed to evaluate the differences between with and without metabolic syndrome groups. A one-way analysis of variance was used to evaluate the difference between the mean values of the four groups. A Bonferroni post-Hoc analysis was performed for the between group comparisons. A simple correlation was applied to evaluate the relationship between two independent variables. Concurrently, the slopes of these relationships could also be obtained. We took the highest value of GE as 100% and lowest was 0%, with values between these two extremes calculated as the corresponding percentage. In order to compare the slopes between these two lines to see if they are significantly separated from each other, the Chris's calculator was used (https://www.surrey.ac.uk/search? query=calculator&op=Search).

RESULTS

The demographic data were shown in the table 1. Most of the metabolic associated parameters were higher in subjects with metabolic syndrome including GPT. On the contrary, HDL-C and GE were lower in subjects with metabolic syndrome. Both genders showed similar results. We further divided the study participants into 4 groups according to the level of GPT from lower quadrant to the higher quadrant. Similar results were seen bot only the metabolic associated parameters but also in both genders (Table 2). When we correlate GPT with GE in a linear regression model, statistically significant negative results were found in both genders (Table 3). In the figure 3, scatter plot were performed and obvious negative correlation were demonstrated. Moreover, slope changes in GE according to the level of GPT still showed a negative relationship between GPT and GE. In this relationship, men had tighter correlation than women was identified.

DISCUSSION

In the present study, our data reveal that there is a negative relationship between GPT and GE in young Chinese. To our knowledge, this is the first study revealing these results in a group of relative healthy subjects without any possible confounding effects from the drugs for treating hypertension, dyslipidemia or diabetes.

The ambient glucose level is depended on three different forces: 1) hepatic glucose production; 2) insulin dependent glucose uptake (INGU), which represents insulin action or insulin sensitivity; 3) non-insulin dependent glucose uptake, which is GE. In subjects without diabetes, both insulin secretion and INGU are relatively normal. At this stage, with enough insulin concentration and intact insulin action, the blood glucose level could be easily maintained. However, when glucose intolerance takes place, these two factors become deteriorated which lead to the commencement of diabetes. Under this circumstance, two interesting things happen. First, GE is only remaining one that could still be functioning well which becomes the main factor to be responsible for glucose clearance. Second, higher plasma glucose will increase the percentage of glucose uptake through GE compared to those who have normal glucose level. This hypothesis has been proved by Best *et al*. who reported that GE contributes 66% glucose utilization in healthy subjects but 99% in patients with T2DM due to insulin resistance and impaired insulin secretion [16].

To explain the relationship between GPT and GE, obesity might be the key. Again, like it has been discussed in the previous paragraph, there has been no study focused on the GE and GPT. However, the notion that obesity is related to GPT has well been established [17, 18]. The first group who reported this association was in 1967 [17]. After several years of extensive research, this topic became less interesting and fewer publications are noted in the past two decades. The direct underlying mechanism is that obese subjects have greater –cell mass than the lean ones [19]. These studies did not separate the FPIS or SPIS. To our knowledge, the only study published confirmed that there is a positive relationship between BMI and SPIS was from our group recently [20].

Next, if obesity has a negative relationship with GE, this would fulfill the logic to explain our finding. Although the effect of BMI on GE has been demonstrated in several studies, the results remain controversial. In the present study, GE was negatively correlated with BMI (r = -0.082 for men and -0.069 for women) which is consistent with the results reported by Kautzky-Willer *et al*. and Lopes *et al*. [21, 22] but not with those reported by Healy *et al*. [23]. By conducting the FSIGT for measuring GE in white and African Americans, Healy *et al*. showed that no correlation was present in individuals with prediabetes. Plausible explanations for these inconsistent results include different ethnic populations, inclusion criteria, GE estimation methods, and the BMI (37.8 ± 6.3 kg/m^2) and young age (46.5 ± 11.2 years). In particularly, very few Chinese individuals have a comparable BMI.

There are limitations in this study. First, this is a cross-sectional study which doesn't show the cause-effective relationships. Compare to a longitudinal study, it provides less information. In the future, a well-designed, longitudinal study might further explore the true roles between them. Secondly, our equation to measure GE is less accurate compared to hyperglycemic clamp test. However, as mentioned before, it will cost tremendous man-power and budget to be done in such a large cohort. Thus, even though it is less satisfactory, our results should be reliable in such a large cohort. We believed that the benefit of the n number could compensate the shortness of the less-accurate method.

CONCLUSION

Our data suggest that there is a negative relationship between GPT and GE in young Chinese adult. Moreover, men with tighter correlation than women. Whether it is the cause or the effect remains further study to explore and clarify.

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CONFLICT OF INTEREST STATEMENT

All authors had no conflict of interest.

Table 1 Study subjects with and without metabolic syndrome

	MetS (-)	MetS (+)	p
Male			
n	21236	1735	
Age	24±2.6	24±2.5	<0.001
Body mass index (kg/m^2)	22.4±3.3	28.7±4.4	<0.001
Waist circumference (cm)	76.3±8.1	92.0±10.4	<0.001
Systolic blood pressure (mmHg)	118.3 ±12.4	133.3±12.8	<0.001
Diastolic blood pressure (mmHg)	68.2 ±8.8	77.1±10.3	<0.001
Fasting plasma glucose (mg/dl)	93.51±7.38	101.57±17.98	<0.001
Triglyceride (mg/dl)	86.30±42.12	172.61±72.12	<0.001
Log Triglyceride (mg/dl)	1.894±0.185	2.197±0.195	<0.001
HDL-C (mg/dl)	51.81±11.54	39.58±8.20	<0.001
LDL-C (mg/dl)	105.02±28.37	117.97±32.58	<0.001
Hemoglobin ($10^3/\mu L$)	15.52±0.98	15.79±0.98	<0.001
White blood cell count ($10^3/\mu L$)	6.377±1.560	7.330±1.735	<0.001
Platelet count ($10^3/\mu L$)	240.2±49.4	260.5±54.5	<0.001
Log_γ-Glutamyl transpeptidase	1.238±0.227	1.503±0.273	<0.001
Uric acid (mg/dl)	6.904±1.356	8.000±1.633	<0.001
Creatinine (mg/dl)	1.072±0.133	1.068±0.142	0.235
Cholesterol (mg/dl)	174.1±31.1	192.0±36.0	<0.001
GPT(U/L)	27.8±25.8	57.6 ±46.0	<0.001
GE ($10^{-2} \cdot dL \cdot min^{-1} \cdot kg^{-1}$)	0.021±0.001	0.018±0.002	<0.001
Female			
n	28225	515	
Age	24±2.4	24±2.6	0.596
Body mass index (kg/m^2)	20.1±2.8	28.9±5.3	<0.001
Waist circumference (cm)	65.8±6.2	84.5±10.9	<0.001

Systolic blood pressure (mmHg)	106.6±11.1	125.6±14.1	<0.001
Diastolic blood pressure (mmHg)	62.8±8.1	73.4±10.7	<0.001
Fasting plasma glucose (mg/dl)	89.82±7.25	101.90±23.31	<0.001
Triglyceride (mg/dl)	67.92±29.26	146.50±66.58	<0.001
Log Triglyceride (mg/dl)	1.800±0.162	2.119±0.208	<0.001
HDL-C (mg/dl)	62.75±14.10	43.32±7.74	<0.001
LDL-C (mg/dl)	97.80±26.50	112.08±30.39	<0.001
Hemoglobin (10^3/μL)	13.26±0.94	13.59±0.96	<0.001
White blood cell count (10^3/μL)	6.213±1.575	7.853±1.838	<0.001
Platelate count (10^3/μL)	253.4±54.6	302.5±66.3	<0.001
Log_γ-Glutamyl transpeptidase	1.037±0.190	1.286±0.246	<0.001
Uric acid (mg/dl)	4.970±1.062	6.325±1.588	<0.001
Creatinine (mg/dl)	0.793±0.116	0.794±0.138	0.858
Cholesterol (mg/dl)	174.1±29.9	184.96±34.5	<0.001
GPT(U/L)	16.0±14.7	34.3 ±32.6	<0.001
GE (10^{-2} ·dL ·min^{-1} ·kg^{-1})	0.022±0.001	0.019±0.002	<0.001

MetS(-) = Without metabolic syndrome; MetS (+) = With metabolic syndrome; HDL-C = High-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol; GPT = Glutamic-pyruvic transaminase; GE = Glucose effectiveness.
Data shown are mean ± SD

Table 2 Grouping of alanine aminotransferase from low to high

	GPT 1	GPT 2	GPT 3	GPT 4	p
Male					
n	5414	6230	5759	5531	
Age	24±2[234]	24±2[134]	25±2[12]	25±2[12]	<0.001
Body mass index (kg/m^2)	20.8±2.4[234]	21.9±2.8[134]	23.2±3.3[124]	25.6±4.4[123]	<0.001
Waist circumference (cm)	72.22±6.36[234]	75.20±7.25[134]	78.42±9.30[124]	84.08±10.59[123]	<0.001
Systolic blood pressure (mmHg)	117±12[234]	118±13[134]	120±13[124]	120±13[123]	<0.001
Diastolic blood pressure (mmHg)	67±9[234]	68±9[134]	69±9[124]	71±10[123]	<0.001
Fasting plasma glucose (mg/dl)	93±7[234]	94±10[14]	94±8[14]	95±9[123]	<0.001
Triglyceride (mg/dl)	74 ±31[234]	81±39[134]	96±48[124]	121± 65	<0.001
Log Triglyceride (mg/dl)	1.836±0.161[234]	1.871±0.182[134]	1.935±0.193[124]	2.030±0.216[123]	<0.001
HDL-C (mg/dl)	52.3±11.3[34]	52.2±11.5[34]	50.8±12.1[124]	48.1±11.6[123]	<0.001
LDL-C (mg/dl)	96.4±25.7[234]	101.9±27.0[134]	108.9±28.1[124]	117.1±30.6[123]	<0.001
Hemoglobin (10^3/μL)	15.3±1.0[234]	15.5±1.0[134]	15.6±1.0[124]	15.7±1.0[123]	<0.001
White blood cell count (10^3/μL)	6.2±1.6[34]	6.3±1.5[34]	6.5±1.6[124]	6.8±1.7[123]	<0.001
Platelet count (10^3/μL)	236±47[34]	238±48[34]	243±51[124]	250±52[123]	<0.001
Log_γ-Glutamyl transpeptidase	1.094±0.145[234]	1.181±0.156[134]	1.282±0.194[124]	1.479±0.263[123]	<0.001
Uric acid (mg/dl)	6.7±1.3[234]	6.8±1.3[134]	7.0±1.4[124]	7.5±1.6[123]	<0.001
Creatinine (mg/dl)	1.075±0.13	1.073±0.13	1.074±0.14	1.066±0.13	0.001
Cholesterol (mg/dl)	163±28	170±29	179±30	190±34	<0.001
GPT(U/L)	11.6±2.0[234]	17.8±2.0[134]	27.0±3.7[124]	65.0±41.4[123]	<0.001
GE (10^{-2} ·dL ·min^{-1} ·kg^{-1})	0.0214 ±0.0011[234]	0.0211±0.0013[134]	0.0206±0.0016[124]	0.0198±0.0021[123]	<0.001
Female					
n	7762	8070	6046	6853	
Age	24±3[234]	24±2[1]	24±2[1]	24±2[1]	<0.001
Body mass index (kg/m^2)	19.7±2.3[234]	19.9±2.5[134]	20.3±2.9[124]	21.4±4.1[123]	<0.001
Waist circumference (cm)	65.0±5.3[234]	65.5±5.7[134]	66.2±6.4[124]	68.4±8.8[123]	<0.001
Systolic blood pressure (mmHg)	106±11[34]	107±11[4]	107±11[14]	108±12[123]	<0.001
Diastolic blood pressure (mmHg)	63±8[4]	63±8[4]	63±8	64±9[12]	<0.001
Fasting plasma glucose (mg/dl)	90±7[4]	90±7[4]	90±7[4]	91±11[123]	<0.001
Triglyceride (mg/dl)	65±26[34]	66±28[34]	69±32[124]	78±40[123]	<0.001
Log Triglyceride (mg/dl)	1.79±0.15[34]	1.79±0.16[4]	1.80±0.17[14]	1.85±0.19[123]	<0.001
HDL-C (mg/dl)	61±13[23]	63±14[14]	64±15[14]	62±15[23]	<0.001
LDL-C (mg/dl)	95±25[234]	97±27[14]	98±26[14]	102±28[123]	<0.001
Hemoglobin (10^3/μL)	13.1±0.9[234]	13.3±0.9[14]	13.3±0.9[14]	13.4±0.9[123]	<0.001
White blood cell count (10^3/μL)	6.2±1.5[34]	6.2±1.5[4]	6.3±1.6[14]	6.4±1.7[123]	<0.001
Platelet count (10^3/μL)	252±53[4]	252±53[4]	255±56[4]	259±59[123]	<0.001
Log_γ-Glutamyl transpeptidase	0.954 ±0.144[234]	1.006 ±0.149[134]	1.057 ±0.163[124]	1.166 ±0.239[123]	<0.001
Uric acid (mg/dl)	4.9±1.02[34]	4.9±1.03[4]	5.0±1.05[14]	5.2±1.22[123]	<0.001
Creatinine (mg/dl)	0.792 ±0.113	0.797 ±0.113[4]	0.796 ±0.123[4]	0.786 ±0.118[23]	<0.001
Cholesterol (mg/dl)	170±28[234]	174±30[134]	176±29[124]	179±32[123]	<0.001
GPT(U/L)	8.7±1.4[234]	11.9±0.8[134]	15.2±1.1[124]	31.2±26.0[123]	<0.001
GE (10^{-2} ·dL ·min^{-1} ·kg^{-1})	0.022±0.001[34]	0.022±0.001[34]	0.022±0.001[124]	0.021±0.001[123]	<0.001

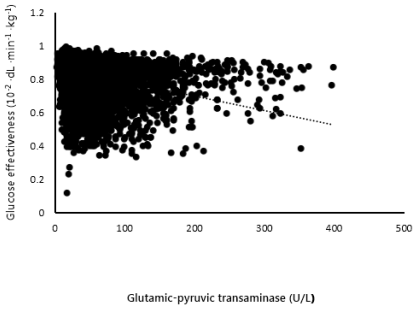
MetS(-) = Without metabolic syndrome; MetS (+) = With metabolic syndrome; HDL-C = High-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol; GPT = Glutamic-pyruvic transaminase; GE = Glucose effectiveness.
Data shown are mean ± SD

Table 3 Correlation between glucose effectiveness and gutamic-pyruvic transaminase

	r	P
Male	-0.304	＜0.001
Female	-0.153	＜0.001

Figure 1 Scatter plot of glucose effectiveness and glutamic-pyruvic transaminase.

Male



Female

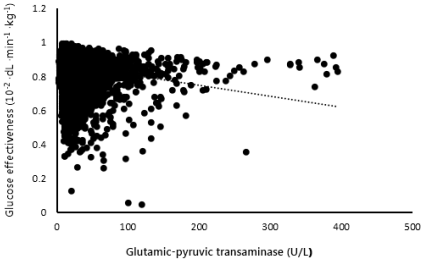
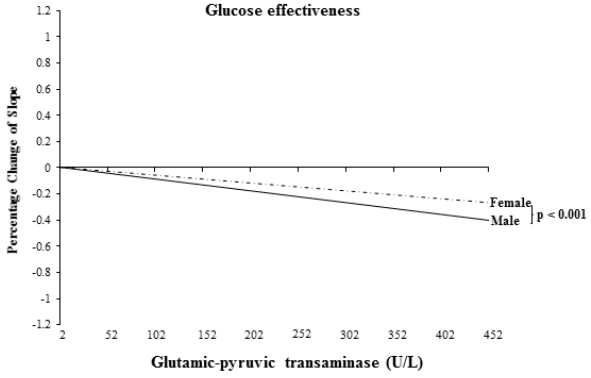


Figure 2 Slope change if glucose effectiveness and glutamic-pyruvic transaminase.



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