VOLUME-7, ISSUE-8, AUGUST-2018 • PRINT ISSN No 2277 - 8160

Original Research Paper

Engineering

GLUTAMIC PYRUVIC TRANSAMINASE IS POSITIVELY CORRELATED WITH INSULIN RESISTANCE IN ELDERLY

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ABSTRACT

Introduction Taiwan is a hyperendemic area of hepatitis. 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 type 2 diabetes (T2D). Custro et al. was the first one to note that hepatitis patients have a four times higher prevalence to have T2D than general population. Deterioration of insulin resistance (IR) was proposed to be responsible for this relationship. In the present study, our goal is to evaluate the relationship between liver function of glutamic pyruvic transaminase (GPT) and IR in the elderlies in both genders.

Methods We randomly enrolled 19,067 men and 20,798 women who were aged over 60 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 In both genders, BMI, WC, BP, FPG, TG, IR, and GPT, but lower HDL-C. All the participants were subdivided into four groups according to the quartiles of GPT results and subjects with a higher GPT were older, and had higher IR. The scatter plot of the correlation between IR and GPT showed positive correlation. We further demonstrate the slopes of the IR in men and women.

Conclusion In the present study, we have showed that GPT is positively related to IR in elderly in both genders. Further longitudinal study to explore the cause-effect relationship between GPT and IR.

KEYWORDS : GPT, IR, diabetes, elderly

Introduction

Taiwan is a hyperendemic area of hepatitis. In the same time, the prevalence of non-alcoholic fatty liver disease was estimated to be around 11.5% [1]. Adding these two most common, the prevalence of abnormal liver function should be high. 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 type 2 diabetes (T2D). Custro et al. was the first one to note that hepatitis patients have a four times higher prevalence to have T2D than general population. Deterioration of insulin resistance (IR) was proposed to be responsible for this relationship [2].

However, other than the IR, there are other perturbations that could cause glucose intolerance, i.e., insulin secretion and glucose effectiveness [3]. It should be pointed out that there are two phases of insulin secretion, the first- and the second-phase [4, 5]. Interestingly, other than the IR, evidences also showed that insulin secretion is also decreased when liver function deteriorated [6]. To our knowledge, there has been no report on the relationship between liver function and and IR.

Due to the decrease of birth rate, Taiwan has already become 'aging society' since Mar 2018. This means that in every seven persons, there is one over 65 years old. It is estimated that, eight years later, we will formally enter the era of 'aged society' [7]. Diabetes is one of the most commonly disease found in the elderlies and its prevalence is obviously related to age [8]. Thus, to understand the underlying pathophysiology for T2D is of major concerns to the health providers and government.

In the present study, we enrolled 36,865 subjects who had no histories of diabetes or taking any medications for diabetes, hypertension and/or dyslipidemia. Our goal is to evaluate the relationship between liver function of glutamic pyruvic transaminase (GPT) and IR in the elderlies in both genders.

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 19,067 men and 20,798 women who were aged over 60 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. There were 6,269 men with metabolic syndrome and 12,798 without, and for women 8,251 and 12,547, respectively. To observe the effect of liver function, the groups were further subdivided into quartiles, according to the 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 IR was calculated by the following equation.

$IR = \log_{10} (1.439 + 0.018 \times sex - 0.003 \times age + 0.029 \times BMI - 0.001$

$0.006 \times DBP + 0.049 \times TG - 0.046 \times HDL\text{-}C - 0.0116 \times FPG) \times 10^{3.333}$

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 IR 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 demographics of our study cohort are shown in Table 1. In men, BMI, WC, BP, FPG, TG, IR, and GPT, but lower HDL-C (Table 1). Similar findings were also noted in women. As mentioned previously, all the participants were subdivided into four groups according to the quartiles of GPT results. It could be noted that, for both genders, subjects with a higher GPT were older, and had higher IR (Table 2). The scatter plot of the correlation is shown in Figure 1. In the figure 2, which demonstrates the slopes of the IR in men and women. As described in the Methods, IR was transformed into a percentage of the maximum value (100%). When compare the IR change slope in both genders, there is no statistic significant between men and women.

Discussion

Due to the decrease of birth rate, Taiwan has already become 'aging society' since Mar 2018. This means that in every seven persons, there is one over 65 years old. It is estimated that, eight years later, we will formally enter the era of 'aged society' [7]. Thus, diseases related to gerontology are major concerns to the health providers and government. Diabetes, [8].

The results of the present study confirmed the findings from those previous studies showing that there is a positive relationship between GPT and IR. It should be noted that our cohort is non-diabetic and no medications for hypertension, diabetes and/or dyslipidemia were used during the study was performed. This was meant to evaluate this relationship without any possible confounding factors. Moreover, the study population number of the present study is quite large which further increases the reliability of our data.

Liver plays a vital role in glucose regulation. It could affect the glucose metabolism through several mechanisms. For example, liver is a major site for insulin clearance [9, 10]. In the same time, it is also an end organ to express the results of IR. The ability of suppress glucose production and increase glycogenesis would be diminished in subjects with IR [10]. Thus, as early as in 1988, Ohlson et al. first published a longitudinal study showing that subjects with the highest quintile of GPT had a 3.9 times higher chance to have diabetes in a 13.5 years follow up [11]. Other than this study done in Caucasian, the similar relationship was also reported in Chinese. By using homeostasis model assessment (HOMA), Hsiao et al. also showed that GPT level was positively related to IR in a group of pre-diabetic subjects [6]. It is interesting to note that these subjects were relatively milder in glucose dysregulation, which further validates the previous study. Also, this study could be interpreted as that it might be a universal association in different ethnic group.

Non-alcoholic fatty liver disease (NAFLD) is one of the most important causes for elevated GPT [12]. Kotornen A et al were one of the first groups to report that increased liver fat, impaired IR and hepatic IR are the main characteristics of T2D. They used euglycemic insulin clamp technique to measure hepatic glucose production, glucose uptake and serum free fatty acid which made the results of their study more reliable. However, they only enrolled relatively small number of subjects (n = 68) and they were all diabetic patients [13]. Follow this pioneer study, Yatsuya et al successfully showed that intrahepatic fat is correlated with HOMA after age, sex and other confounding factors were adjusted [14]. They used 3-T magnetic resonance imager to quantify liver fat. The partial correlation coefficient was as high as 0.44 ($p = 0.02$). In that study, there was only 33 subjects were enrolled. The two important information could be derived from this study. First, the relationship between liver fat and IR could also be found in Asians. Second, the same association is also proved in non-diabetic subjects.

There are three possible underlying mechanisms postulated to be responsible for this phenomenon. First, subjects with increased liver fat have higher gluconeogenesis [15] and the increased ambient blood glucose level will cause deterioration of IR. This effect is called glucotoxicity [16]. Other than this, impaired insulin clearance is also reported which may further enhances this correlation [17, 18]. Finally, it is found that in NAFLD subjects, increased mitochondrial oxidation of fatty acid was observed [15], which could lead to 50% higher rates of lipolysis. Like the glucose level, the elevated free fatty acid also contributes to higher IR [19].

There are limitations in this study. This is a cross-sectional study. Although we have a large n number, still it is less persuasive than a longitudinal study. Secondly, one could argue that our equation is not as accurate as other sophisticated technique such as intravenous glucose tolerance test or clamp study. However, by using those methods, the study cohort is limited to the labor-consuming and expensive nature. To realize the relationship between GPT and IR in a large cohort, surrogate like our equation is the only possible method.

In conclusion, in the present study, we have showed that GPT is positively related to IR in elderly in both genders. Further longitudinal study to explore the cause-effect relationship between GPT and IR.

Acknowledgement

[redacted].

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	12798	6269	
Age	66±5.8	66±5.9	<0.001
Body mass index (kg/m2)	23.0±2.7	25.9±2.8	<0.001
Waist circumference (cm)	82.0±7.7	91.4±7.7	<0.001
Systolic blood pressure (mmHg)	129±19	142±18	<0.001
Diastolic blood pressure (mmHg)	75±11	81±11	<0.001
Fasting plasma glucose (mg/dl)	104.2±26.1	120.1±36.9	<0.001
Triglyceride (mg/dl)	104.1±47.5	179.5±75.5	<0.001
Log Triglyceride (mg/dl)	1.980±0.178	2.215±0.189	<0.001
HDL-C (mg/dl)	53.41±13.50	42.08±10.72	<0.001
LDL-C (mg/dl)	124.8±32.1	125.4±33.5	<0.001
GPT(U/L)	26.55±21.10	32.04±24.89	<0.001
IR (10-4 · min-1 · pmol-1 · L-1)	3.670±0.024	3.699±0.022	<0.001

Female			
n	12547	8251	
Age	64±5.0	66±5.8	＜0.001
Body mass index (kg/m2)	23.0±3.0	26.0±3.3	＜0.001
Waist circumference (cm)	75.3±7.2	83.9±7.9	＜0.001
Systolic blood pressure (mmHg)	130.2±20.0	144.1±18.6	＜0.001
Diastolic blood pressure (mmHg)	73.4±11.3	79.6±11.1	＜0.001
Fasting plasma glucose (mg/dl)	100.8±21.6	119.1±37.8	＜0.001
Triglyceride (mg/dl)	104.5±45.1	172.6±71.6	＜0.001
Log Triglyceride (mg/dl)	1.985±0.170	2.200±0.184	＜0.001
HDL-C (mg/dl)	63.9±14.7	49.8±12.0	＜0.001
LDL-C (mg/dl)	128.7±33.2	131.2±35.0	＜0.001
GPT(U/L)	24.34±21.74	28.55±22.98	＜0.001
IR (10-4 · min-1 · pmol-1 · L-1)	3.671±0.024	3.699±0.023	＜0.001

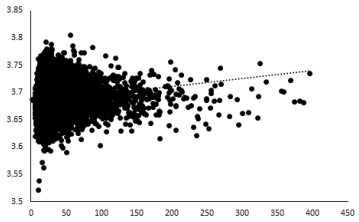
MetS(-) = Without metabolic syndrome; MetS (+) = With metabolic syndrome; HDL-C = High-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol; GPT = Glutamic-pyruvic transaminase; IR = Insulin resistance.
Data shown are mean ± SD

Table 2 Grouping of alanine aminotransferase from low to high

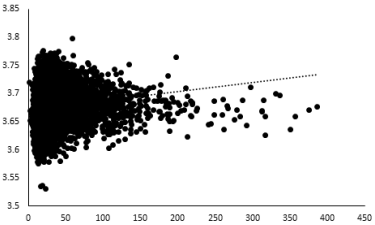
	GPT 1	GPT 2	GPT 3	GPT 4	p
Male					
n	4997	4479	4951	4631	
Age	68±6.5234	66±5.7134	65±5.412	65±5.312	＜0.001
Body mass index (kg/m2)	23±3234	24±3134	24±3124	25±3123	＜0.001
Waist circumference (cm)	82.2±8.7234	84.3±8.5134	86.0±8.5124	87.8±8.9123	＜0.001
Systolic blood pressure (mmHg)	132±214	133±204	134±19	134±1912	＜0.001
Diastolic blood pressure (mmHg)	76±12234	77±12134	78±1112	79±1112	＜0.001
Fasting plasma glucose (mg/dl)	106.9±30.64	108.2±30.74	109.2±2914	113.4±33.0123	＜0.001
Triglyceride (mg/dl)	113.4±58.2234	122.2±62.1124	133.8±69.6134	146.8±76.8123	＜0.001
Log Triglyceride (mg/dl)	2.007±0.199234	2.039±0.203124	2.074±0.213134	2.111±0.221123	＜0.001
HDL-C (mg/dl)	50.7±13.84	50.5±13.64	49.9±13.54	47.5±13.7123	＜0.001
LDL-C (mg/dl)	122.4±31.423	122.7±31.61	126.9±33.014	124.0±34.03	＜0.001
GPT(U/L)	14.2±2.49234	20.0±1.40134	26.4±2.49124	53.9±33.8123	＜0.001
IR (10-4 ·min-1 ·pmol-1 ·L-1)	3.668±0.026234	3.677±0.026134	3.684±0.026124	3.689±0.027123	＜0.001
Female					
n	5063	5713	4743	5268	
Age	66±6234	65±51	65±51	65±51	＜0.001
Body mass index (kg/m2)	23±3234	24±3134	25±3124	25±3123	＜0.001
Waist circumference (cm)	76.7±8.2234	77.8±8.2134	79.3±8.5124	81.1±8.7123	＜0.001
Systolic blood pressure (mmHg)	135±214	135±214	136±20	137±2012	＜0.001
Diastolic blood pressure (mmHg)	75±1234	75±1234	76±1212	77±1112	＜0.001
Fasting plasma glucose (mg/dl)	104±2734	106±2734	109±30124	114±36123	＜0.001
Triglyceride (mg/dl)	121±61234	126±63134	135±67124	144±71123	＜0.001
Log Triglyceride (mg/dl)	2.04±0.20234	2.05±0.20134	2.08±0.21124	2.11±0.21123	＜0.001
HDL-C (mg/dl)	59.1±15.44	59.6±15.54	58.5±15.44	56.0±14.8123	＜0.001
LDL-C (mg/dl)	128.5±33.6	130.5±32.9	130.9±34.1	129.0±35.4	0.001
GPT(U/L)	12.8±2.0234	17.9±1.4134	23.5±2.0124	49.7±34.0123	＜0.001
IR (10-4 ·min-1 ·pmol-1 ·L-1)	3.674±0.027234	3.679±0.026134	3.685±0.027124	3.690±0.027123	＜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; IR = Insulin resistance.
Data shown are mean ± SD

Figure 1 Scatter plot of insulin resistance and glutamic-pyruvic transaminase.
Male

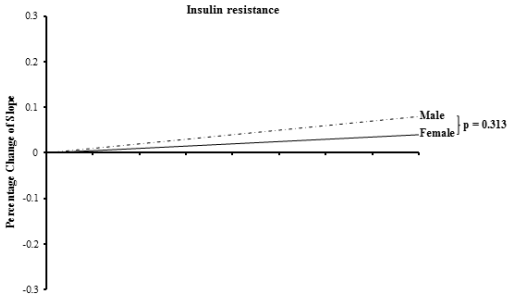


Glutamic-pyruvic transaminase (U/L)
Female



Glutamic-pyruvic transaminase (U/L)

Figure 2 Slope change if insulin resistance and glutamic-pyruvic transaminase.



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