

First-phase insulin secretion is positively correlated with alanine aminotransferase in young adults

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Conflict of interest

None declared

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Abstract

Background. Type 2 diabetes (T2D) is known to be one of the most prevalent diseases, and its prevalence is significantly associated with age and metabolic syndrome (MetS). Few studies have been conducted on liver function, MetS and insulin secretion among young adults.

Objectives. In the present study, we explored the relationship between the liver function enzyme – alanine aminotransferase (ALT) – and first-phase insulin secretion (FPIS) among young adults.

Material and methods. There were 22,971 men and 28,740 women, aged 18–27 years, assigned to subgroups according to the presence of MetS and quartiles of ALT values. Simple correlation was applied to evaluate their relationship. The difference between the slopes of these relationships and FPIS were statistically analyzed with Chris's calculator.

Results. Most values for metabolic parameters, including ALT and FPIS, were determined to be relatively high in individuals with MetS. By contrast, individuals with MetS had lower high-density-lipoprotein cholesterol (HDL-C) counts and FPIS. Similar results were observed in the quartiles of ALT. Significant positive results were also found in the linear model. Depending on the ALT level, the slope change of FPIS still demonstrated a positive correlation between ALT and FPIS. This correlation was stronger for men than for women.

Conclusions. A positive correlation between ALT and FPIS exists among young adults. Moreover, this correlation was stronger for men than for women. Both the cause and the effect require further investigation.

Key words: metabolic syndrome, alanine aminotransferase, first-phase insulin secretion

Introduction

With the increasing prevalence of obesity, metabolic syndrome (MetS) is also coming to prominence as a serious health problem among adolescents and children worldwide.¹ Following obesity, the prevalence of type 2 diabetes (T2D) has been increasing drastically in Taiwan as well as in many other countries. Moreover, among the factors contributing to the leading causes of mortality in Taiwan, T2D has remained among the top 5 for many years.^{2,3} Accordingly, patients, physicians, and health agencies worldwide have identified childhood obesity as a critical health concern. Children with obesity exhibit a higher risk for developing other diseases – some examples of which are coronary artery disease, fatty liver, polycystic ovary syndrome, and hypertension – not only during childhood, but throughout their lives.⁴ It is well-known that fatty liver is closely and bi-directionally related to MetS and T2D. Currently, the general consensus is that fatty liver is the hepatic manifestation of MetS.⁵

Abnormal liver function is often seen in clinical practice. Among the leading causes of abnormal alanine aminotransferase (ALT), nonalcoholic fatty liver disease is the most common, exhibiting a prevalence of 50–90%.⁶ Viral hepatitis is another disease that is endemic in Taiwan. Hepatitis B viral infection has been reported in the literature to have an estimated prevalence of 15–20%.^{7,8} Patients with hepatitis B also have abnormal liver function. Thus, it is necessary to clarify the relationships between abnormal liver function and T2D.

Three major pathophysiological mechanisms are generally considered to be potential causes of glucose intolerance: reduction of insulin activity (or insulin resistance – IR), insulin secretion and glucose effectiveness.⁹ In addition, there are 2 phases of insulin secretion, namely, first-phase insulin secretion (FPIS) and second-phase insulin secretion.^{10,11} Notably, an impairment of insulin secretion is related to a deterioration of liver function.¹² Consequently, clarifying the underlying causes behind T2D and FPIS is crucial for health providers and future treatment strategy. So far, few studies have evaluated the relationship between ALT and FPIS in young adults. The present study was conducted with the underlying aim of exploring the correlation between FPIS and ALT among young adults.

Methods

Study participants

This study employed random sampling to enroll 22,971 men and 28,740 women aged 18–27 years from private clinics and local hospitals in Taiwan. The MJ Health Screening Centers, which are a chain of private clinics in Taiwan, offer their members regularly

scheduled health examinations. They provided data solely for the purpose of research, and approval was obtained for the protocol of this study from the MJ Health Screening Center Institutional Review Board. All participants in this study remained anonymous and provided informed consent. The definition of obesity in this study was a body mass index (BMI) ≥ 25 kg/m². Participants with obesity were excluded if they took any medications that have been demonstrated to affect blood pressure or glucose and lipid levels. The patients were categorized into 2 groups – without MetS (MetS(–) group) and with MetS (MetS(+) group). The presence of MetS was defined according to World Health Organization (WHO) criteria.¹³ Finally, 768 men and 794 women were included in the MetS(+) group. Furthermore, all participants were divided into quartiles based on their ALT levels for advanced analysis.

On the day of the study, a senior member of the nursing staff recorded the medical history of all participants, including relevant information regarding any medications currently being taken, and conducted a physical examination. Horizontal measurements were performed at the location of the natural waist to record waist circumference (WC). To calculate BMI, the body weight (in kilograms) of participants was divided by the square of their height (in meters). Standard mercury sphygmomanometers were employed to perform measurements of diastolic blood pressure (DBP) and systolic blood pressure (SBP) measured on the right arm of the participants while they were seated.

Laboratory biochemistry measurement

Blood samples were collected for biochemical analysis after 10 h of fasting. Within 1 h of blood collection, the plasma was extracted, after which it was kept at 30°C until the lipid profile and fasting plasma glucose (FPG) assays were performed. A glucose oxidase approach (YSI 203 glucose analyzer; Yellow Springs Instruments, Yellow Springs, USA) was employed for measuring FPG. Measurements of triglyceride (TG) levels and total cholesterol were conducted using a Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Tokyo, Japan) and a dry, multilayer analytical slide method. Analyses of serum low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) concentrations were performed after dextran sulfate precipitation through an enzymatic cholesterol assay.

Assessment of FPIS

We used the equation derived from our other groups,¹⁴ which are listed below (international units). To demonstrate the reliability of our equations, a short statement is given here. When performing this study, data of 70% of the participants was used to build the equations and

data the remaining 30% was used for external validation. The accuracy of the equations could therefore be tested.

In total, there were 186 subjects enrolled. The FPIS was measured using a frequently sampled intravenous glucose tolerance test. The R-value between the measured and calculated FPIS was 0.671 ($p < 0.001$).¹⁴ The equation is shown below:

$$FPIS = 10^{(1.477 - 0.119 \times FPG + 0.079 \times BMI - 0.523 \times HDL-C)}$$

Statistical analyses

The IBM SPSS v. 19.0 software (IBM Inc., Armonk, USA) was used in the study to conduct all of the statistical analyses. The resulting data is provided as means ± standard deviation (SD). Levene’s test and the Kolmogorov–Smirnov test were applied to all data to assess the homogeneity of variance and normal distribution, respectively. If an abnormal distribution of data was found, then the data was subjected to log transformation before analysis. To identify differences between groups with and without MetS, a t-test was conducted. The study also used one-way analysis of variance (ANOVA) to assess the difference between the mean values of the 4 groups. Bonferroni post hoc analysis was performed for intergroup comparisons. A simple correlation was adopted in order to assess the correlation between 2 independent variables. Concurrently, the slopes of these relationships could also be obtained. We adopted 0% and 100% as the lowest and highest FPIS values, respectively, with values between these 2 extremes being calculated as the corresponding percentage. To compare the slopes between these 2 lines in order to determine whether they differed significantly, we utilized Chris’s calculator.¹⁵

Results

Table 1 presents the demographics of our study cohort. Regardless of gender, the participants in the MetS(+) group exhibited unfavorable results for MetS-related factors, including BMI, WC, SBP, DBP, TG, FPG, HDL-C, and LDL-C. In addition, the participants in the MetS(+) group were determined to have higher levels of both FPIS and ALT, which constituted the most critical factors. As already mentioned, all participants were subdivided on the basis of the quartiles of ALT results into 4 groups. Notably, for both sexes, participants with higher ALT levels had lower HDL-C levels but higher SBP, WC, FPG, DBP, BMI, TG, and LDL-C levels (Table 2). A scatter plot of the correlation of ALT and log transformation of FPIS is presented in Fig. 1. The correlation coefficient (r) values were 0.349 for men and 0.133 for women. The correlations for both genders were statistically significant ($p < 0.001$). Figure 2 presents the different slopes of log transformation of FPIS in men and women. As described in the Methods section, FPIS was transformed into a percentage of the maximum value (100%). Through a comparison of the genders regarding changes to the FPIS slope according to ALT level, we discovered that men had a higher slope than women.

Discussion

In the current study, our data demonstrated that there is a positive relationship between ALT and FPIS in Chinese young adults. This is the first study, to our knowledge, to present these results for a group of relative healthy, non-obese subjects without any possible confounding effects

Table 1. General characteristics of subjects without and with metabolic syndrome (MetS) according to gender

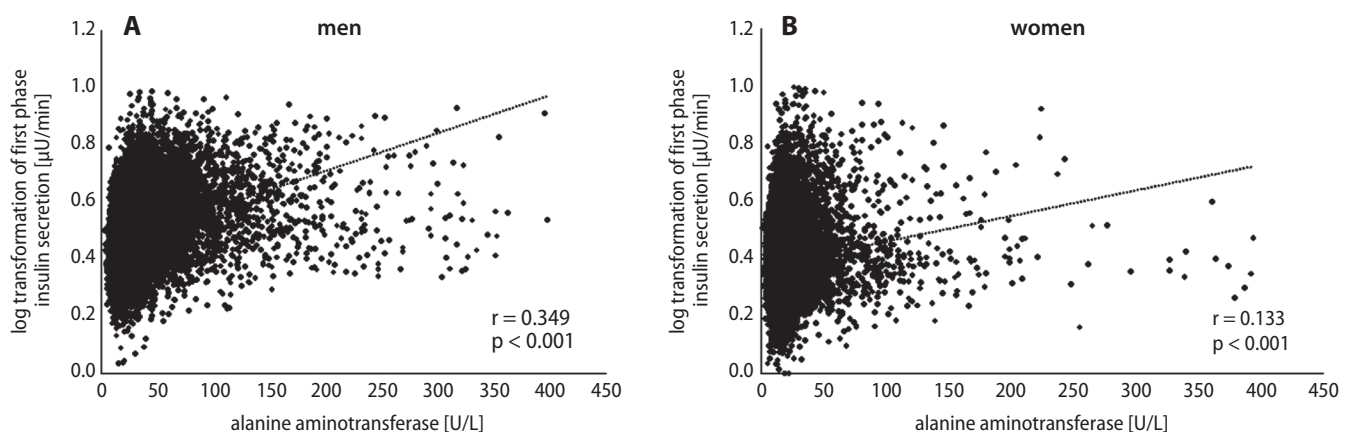
| Parameter | Group | | | | | |
|--------------------------|---------------|---------------|---------|--------------|---------------|---------|
| | Men | | | Women | | |
| | MetS(-) | MetS(+) | p-value | MetS(-) | MetS(+) | p-value |
| N | 21,236 | 1735 | | 28,225 | 515 | |
| Age [years] | 24.21 ±2.55 | 24.58 ±2.54 | <0.001 | 24.23 ±2.42 | 24.17 ±2.61 | 0.596 |
| BMI [kg/m ²] | 22.4 ±3.3 | 28.7 ±4.4 | <0.001 | 20.1 ±2.8 | 28.9 ±5.3 | <0.001 |
| WC [cm] | 76.3 ±8.1 | 92.0 ±10.4 | <0.001 | 65.8 ±6.2 | 84.5 ±10.9 | <0.001 |
| SBP [mm Hg] | 118.3 ±12.4 | 133.3 ±12.8 | <0.001 | 106.6 ±11.1 | 125.6 ±14.1 | <0.001 |
| DBP [mm Hg] | 68.2 ±8.8 | 77.1 ±10.3 | <0.001 | 62.8 ±8.1 | 73.4 ±10.7 | <0.001 |
| FPG [mg/dL] | 93.51 ±7.38 | 101.57 ±17.98 | <0.001 | 89.82 ±7.25 | 101.90 ±23.31 | <0.001 |
| TG [mg/dL] | 86.30 ±42.12 | 172.61 ±72.12 | <0.001 | 67.92 ±29.26 | 146.50 ±66.58 | <0.001 |
| HDL-C [mg/dL] | 51.81 ±11.54 | 39.58 ±8.20 | <0.001 | 62.75 ±14.10 | 43.32 ±7.74 | <0.001 |
| LDL-C [mg/dL] | 105.02 ±28.37 | 117.97 ±32.58 | <0.001 | 97.80 ±26.50 | 112.08 ±30.39 | <0.001 |
| ALT [U/L] | 27.8 ±25.8 | 57.6 ±46.0 | <0.001 | 16.0 ±14.7 | 34.3 ±32.6 | <0.001 |
| Log_FPIS [μU/min] | 1.928 ±0.327 | 2.534 ±0.374 | <0.001 | 1.624 ±0.322 | 2.496 ±0.452 | <0.001 |

Data presented as means ± standard deviation (SD); BMI – body mass index; WC – waist circumference; SBP – systolic blood pressure; DBP – diastolic blood pressure; FPG – fasting plasma glucose; TG – triglyceride; HDL-C – high-density-lipoprotein cholesterol; LDL-C – low-density-lipoprotein cholesterol; ALT – alanine aminotransferase; Log FPIS – log transformation of first-phase insulin secretion.

Table 2. Categorization of alanine aminotransferase levels from low to high

| Parameter | ALT1 | | ALT2 | | ALT3 | | ALT4 | | p-value |
|--------------------------|--------------|------------------|--------------|------------------|--------------|------------------|--------------|------------------|---------|
| Men | | | | | | | | | |
| n | 5,414 | | 6,230 | | 5,759 | | 5,531 | | |
| ALT [U/L] | 11.6 ±2.0 | ^{2,3,4} | 17.8 ±2.0 | ^{1,3,4} | 27.0 ±3.7 | ^{1,2,4} | 65.0 ±41.4 | ^{1,2,3} | <0.001 |
| Age [years] | 24.63 ±2.38 | ^{2,3,4} | 24.55 ±2.45 | ^{1,3,4} | 24.15 ±2.57 | ^{1,2} | 25.63 ±2.69 | ^{1,2} | <0.001 |
| BMI [kg/m ²] | 20.8 ±2.4 | ^{2,3,4} | 21.9 ±2.8 | ^{1,3,4} | 23.2 ±3.3 | ^{1,2,4} | 25.6 ±4.4 | ^{1,2,3} | <0.001 |
| WC [cm] | 72.22 ±6.36 | ^{2,3,4} | 75.20 ±7.25 | ^{1,3,4} | 78.42 ±9.30 | ^{1,2,4} | 84.08 ±10.59 | ^{1,2,3} | <0.001 |
| SBP [mm Hg] | 117 ±12 | ^{2,3,4} | 118 ±13 | ^{1,3,4} | 120 ±13 | ^{1,2,4} | 120 ±13 | ^{1,2,3} | <0.001 |
| DBP [mm Hg] | 67 ±9 | ^{2,3,4} | 68 ±9 | ^{1,3,4} | 69 ±9 | ^{1,2,4} | 71 ±10 | ^{1,2,3} | <0.001 |
| FPG [mg/dL] | 93 ±7 | ^{2,3,4} | 94 ±10 | ^{1,4} | 94 ±8 | ^{1,4} | 95 ±9 | ^{1,2,3} | <0.001 |
| TG [mg/dL] | 74 ±31 | ^{2,3,4} | 81 ±39 | ^{1,3,4} | 96 ±48 | ^{1,2,4} | 121 ±65 | none | <0.001 |
| HDL-C [mg/dL] | 52.3 ±11.3 | ^{3,4} | 52.2 ±11.5 | ^{3,4} | 50.8 ±12.1 | ^{1,2,4} | 48.1 ±11.6 | ^{1,2,3} | <0.001 |
| LDL-C [mg/dL] | 96.4 ±25.7 | ^{2,3,4} | 101.9 ±27.0 | ^{1,3,4} | 108.9 ±28.1 | ^{1,2,4} | 117.1 ±30.6 | ^{1,2,3} | <0.001 |
| Log_FPIS [μU/min] | 1.796 ±0.265 | ^{2,3,4} | 1.885 ±0.300 | ^{1,3,4} | 2.006 ±0.345 | ^{1,2,4} | 2.215 ±0.409 | ^{1,2,3} | <0.001 |
| Women | | | | | | | | | |
| n | 7,762 | | 8,070 | | 6,046 | | 6,853 | | |
| ALT [U/L] | 8.7 ±1.4 | ^{2,3,4} | 11.9 ±0.8 | ^{1,3,4} | 15.2 ±1.1 | ^{1,2,4} | 31.2 ±26.0 | ^{1,2,3} | <0.001 |
| Age [years] | 24.34 ±2.37 | ^{2,3,4} | 24.34 ±2.38 | ¹ | 24.22 ±2.43 | ¹ | 23.99 ±2.52 | ¹ | <0.001 |
| BMI [kg/m ²] | 19.7 ±2.3 | ^{2,3,4} | 19.9 ±2.5 | ^{1,3,4} | 20.3 ±2.9 | ^{1,2,4} | 21.4 ±4.1 | ^{1,2,3} | <0.001 |
| WC [cm] | 65.0 ±5.3 | ^{2,3,4} | 65.5 ±5.7 | ^{1,3,4} | 66.2 ±6.4 | ^{1,2,4} | 68.4 ±8.8 | ^{1,2,3} | <0.001 |
| SBP [mm Hg] | 106 ±11 | ^{3,4} | 107 ±11 | ⁴ | 107 ±11 | ^{1,4} | 108 ±12 | ^{1,2,3} | <0.001 |
| DBP [mm Hg] | 63 ±8 | ⁴ | 63 ±8 | ⁴ | 63 ±8 | none | 64 ±9 | ^{1,2} | <0.001 |
| FPG [mg/dL] | 90 ±7 | ⁴ | 90 ±7 | ⁴ | 90 ±7 | ⁴ | 91 ±11 | ^{1,2,3} | <0.001 |
| TG [mg/dL] | 65 ±26 | ^{3,4} | 66 ±28 | ^{3,4} | 69 ±32 | ^{1,2,4} | 78 ±40 | ^{1,2,3} | <0.001 |
| HDL-C [mg/dL] | 61 ±13 | ^{2,3} | 63 ±14 | ^{1,4} | 64 ±15 | ^{1,4} | 62 ±15 | ^{2,3} | <0.001 |
| LDL-C [mg/dL] | 95 ±25 | ^{2,3,4} | 97 ±27 | ^{1,4} | 98 ±26 | ^{1,4} | 102 ±28 | ^{1,2,3} | <0.001 |
| Log_FPIS [μU/min] | 1.607 ±0.276 | ⁴ | 1.604 ±0.302 | ⁴ | 1.625 ±0.343 | ⁴ | 1.732 ±0.435 | ^{1,2,3} | <0.001 |

Data is presented as means ± standard deviation (SD); ¹ p < 0.05 vs ALT1; ² p < 0.05 vs ALT2; ³ p < 0.05 vs ALT3; ⁴ p < 0.05 vs ALT4; BMI – body mass index; WC – waist circumference; SBP – systolic blood pressure; DBP – diastolic blood pressure; FPG – fasting plasma glucose; TG – triglyceride; HDL-C – high-density-lipoprotein cholesterol; LDL-C – low-density-lipoprotein cholesterol; ALT – alanine aminotransferase; Log FPIS – log transformation of first-phase insulin secretion.

**Fig. 1.** Scatter plot of log-transformed first-phase insulin secretion and alanine aminotransferase levels in (A) men and (B) women

from drugs used for treating hypertension, dyslipidemia or T2D.

Few studies have evaluated the correlation between ALT and FPIS. Therefore, the relative issue is still debated.

By using the homeostasis model assessment, Hsiao et al. reported that both insulin secretion and sensitivity exhibited simultaneously significant impairment with increased ALT levels in 284 Chinese adults.¹² Their findings contrast

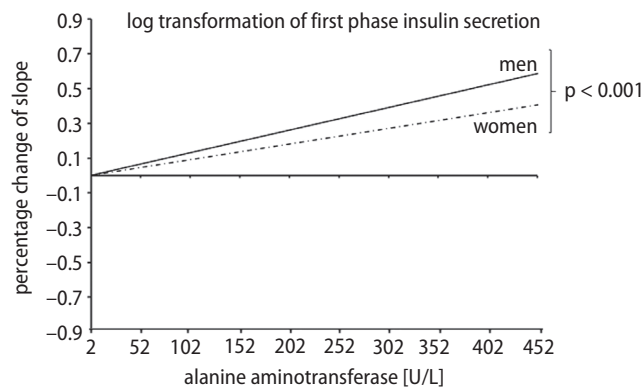


Fig. 2. Comparison of the genders regarding slope changes of first-phase insulin according to ALT levels

with ours. However, their study population was smaller than ours and they evaluated only participants who had FPG levels ranging from 100 mg/dL to 109 mg/dL. In order to explain the discrepancy between these 2 different results, we hypothesize that obesity may be the link between ALT and FPIS. We can observe that individuals with obesity have higher ALT levels as well as elevated insulin secretion. Therefore, it could be postulated that people with higher ALT levels exhibit increased insulin secretion.

It is well-known that insulin secretion consists of 2 phases: FPIS and SPIS.^{10,11} After intravenous glucose infusion, glucose concentration increases rapidly. A biphasic response of insulin secretion is then observed, which comprises a sharp increase that reaches a peak. This stage is followed by a nadir between peaks and subsequently a slower increasing phase. Although the existence of FPIS is still under debate, a great deal of evidence supports it. For instance, Steiner et al. demonstrated that FPIS and SPIS play different roles in insulin secretion.¹⁶ Using a sophisticated method that employed a pancreatic clamp, they discovered that FPIS is crucial for suppressing the acute response of glucose stimulation. Even though this paper was published 30 years ago, it still constitutes a milestone in this topic. Furthermore, Kepner et al. suggested that the cascade involved in SPIS is different from that in FPIS.¹⁷ In SPIS, Cool-1/ β PPIX operates as an exchange factor for guanine nucleotide to regulate insulin secretion, which is not the case in FPIS.

In our study, we discovered that participants with obesity had higher levels of insulin secretion. Kreisberg et al. might be the first group to report this observation.¹⁸ In 1968, Karam et al. further expounded on this relationship.¹⁹ They discovered that after glucose challenge, a more considerable acute insulin increase was noted in obese patients compared with healthy individuals.²⁰ Because studies have indicated no impairment of insulin clearance, they concluded that this increase in insulin response must be due to higher levels of insulin secretion. Many studies conducted since then have also shown that individuals with obesity have superior cell function due to a greater cell mass compared with individuals without obesity.^{21–23}

Recently, our group also validated this result by enrolling individuals with the same age and BMI. Our data suggested that BMI is positively related to FPIS in both men and women (R-value: 0.966 and 0.926, respectively). It should be noted that this is the only reference, to our knowledge, that is directly related to the role of FPIS alone.²⁴

The ALT levels are higher in obese individuals. This finding is the final component needed to clarify the link between BMI and FPIS. Abnormal liver function has an estimated prevalence of 10–21%.²⁵ Among the causes of abnormal ALT, the most common is nonalcoholic fatty liver disease, which accounts for 50–90% of cases.⁶ Fatty liver disease can cause either simple steatosis without inflammation or nonalcoholic steatohepatitis.²⁶ The second most common cause, particularly in Taiwan, is viral hepatitis; this is because Taiwan is one of the most endemic areas for hepatitis.⁸ Research has determined that there is a strong association between obesity and nonalcoholic fatty liver disease, with approx. 80% of obese individuals reported as having nonalcoholic fatty liver disease.^{27,28} Moreover, viral hepatitis C was reported to have a correlation with obesity.²⁹ Such research validates the finding that ALT levels are higher among individuals with obesity.

This study has some limitations worth noting. Firstly, because this is a cross-sectional study, recall and selection bias are inherent limitations. Further research may be required in order to overcome these limitations. Secondly, it may be disputed that our equation is not an accurate method for quantifying FPIS. However, this method has been validated and published with an R-value of 0.6–0.7. Therefore, we still believe that the present study elucidates the relationships between ALT and FPIS by enrolling a large study sample.

Conclusions

In conclusion, our study revealed that there is a positive relationship between FPIS and ALT in Chinese young adults.

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