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A Cross-Sectional Study of the Relationship Between Serum Liver Enzymes Level and the Incidence of Impaired Fasting Glucose in Males and Females

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The aim of this study was to investigate the possible correlation between levels of serum liver enzymes and impaired fasting glucose (IFG) in Chinese adults and to provide a new perspective for the prevention of pre-diabetes.

Material/Methods: Serum liver enzymes of the samples including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ -glutamyl transferase (GGT), as well as plasma glucose, blood lipids, and insulin, were measured. The cumulative incidences of IFG between different quartiles of liver enzymes were compared by the chi-square test. A logistic regression model (binary regression) was used to calculate the odds ratio (OR) of IFG with 95% confidence interval (95% CI).

Results: The total incidence of IFG was 20.3% and the cumulative incidence of IFG was higher in men compared to women. In both sexes, IFG is more prevalent in higher quartiles of liver enzymes. After adjusting for age, BMI, blood pressure, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC), the cumulative incidences of IFG were significantly higher in the highest quartiles of liver enzymes than in the lowest quartiles. A significantly higher cumulative incidence of IFG was found in the highest GGT quartile than in the lowest quartile for woman.

Conclusions: The results of this study suggest that serum liver enzymes are related to the risk of IFG in Chinese adults. We infer that preserving the hepatic function may be an efficient way to prevent the development of IFG, especially in males.

MeSH Keywords: **Blood Glucose • Diabetes Complications • Enzyme Assays**

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Background

The liver is the site of glycogen synthesis, glyconeogenesis, and insulin degradation; thus, the liver plays an important role in the homeostasis of plasma glucose. Change in the plasma levels of hepatic enzymes is an index of hepatobiliary system dysfunction. However, enhanced plasma levels of liver enzymes serum alanine aminotransferase (ALT) [1–3], aspartate aminotransferase (AST) [4], and γ -glutamyltransferase (GGT) [5–8] might also serve as biological markers of type 2 diabetes mellitus (DM). Patients with impaired fasting glucose (IFG) are regarded as being prediabetic, and prevention during this period can decrease the incidence of DM [9]. Several studies showed that IFG might be more prevalent in men than in women, although the reasons for this difference are poorly understood [10,11]. Hence, we investigated the possible relationship between IFG and liver enzymes in both males and females in a large sample to gain insights into sex difference and its implications for pre-diabetes.

Material and Methods

Subjects

This was as a cross-sectional study of 3373 patients from Zhejiang Province who underwent physical examination in the International Health Center, Second Affiliated Hospital, School of Medicine, Zhejiang University from April 2011 to September 2011.

Inclusion criteria were healthy people aged 20–80 years. Subjects who had liver diseases such as fatty liver, chronic viral hepatitis, autoimmune liver diseases, drug-induced liver injury, and genetic liver disease, and those with hypertension, DM, and alcoholism, coronary heart disease, cancer, severe mental disorders, chronic kidney disease, pregnancy, and glucocorticoid therapy were excluded from the study. We also excluded subjects with lack of complete information of medical examination diagnosis.

A total of 2775 healthy subjects were recruited (age range 20–80 years; 1762 men, 1013 women) in this study.

Methods

After fasting for 12 h, patients underwent a physical examination during the hours of 7:30–9:30 AM in the medical center. Anthropometric indices, including height, weight, and body mass index (BMI), were measured and calculated ($BMI = \text{weight (kg)}/\text{height (m)}^2$). The systolic and diastolic blood pressures of the right arm were measured after a 5-min rest in sitting position. Blood pressure was measured using an automated device (Omron 711, USA) and the mean of 2 consecutive blood pressure measurements was recorded. Venous blood

was collected in vacuum BD tubes (BD, USA) and serum was separated (3000 rpm/15 min) within 1 h. Laboratory parameters were measured to complete the analysis within 4 h in the Clinical Laboratory Center, Second Affiliated Hospital, School of Medicine, Zhejiang University.

Laboratory tests, including fasting plasma glucose (FPG), ALT, AST, GGT, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and fasting insulin. FPG were measured by the hexokinase (HK) method, ALT by the IFCC Reference method with P-5-P, AST by the IFCC Reference method with P-5-P, GGT by the modified SZASZ method, TC by the cholesterol oxidase-peroxidase method (CHO-POD), TG by the glycerol phosphate oxidase-peroxidase method, HDL-C by the direct method-surfactant clearance method, LDL-C by the direct method-selected inhibitor method, using a BECKMAN COULTER AU5400 Analyzer, respectively. Fasting insulin were measured by direct chemical luminescence method using with SIEMENS ADVIA CENTAUR XP Analyzer.

IFG [10] was defined as 5.6 mmol/L to 6.9 mmol/L fasting plasma glucose (FPG) according to the American Diabetes Association (ADA). Insulin resistance index (HOMA-IR) and insulin secretion index (HOMA- β) were calculated based on the HOMA model: $HOMA-IR = (FPG \times FINS)/22.5$; $HOMA-\beta = 20 \times FINS/(FPG-3.5)$.

Statistical analysis

The statistical analysis was performed using PASW Statistics 18.0. The TG, ALT, AST and GGT measurements generally show skewed distribution, so we analyzed these parameters after log transformation. Categorical variables were compared by the χ^2 test, and continuous variables by the T test. Logistic regression analysis was performed to evaluate the relationship between serum liver enzymes level and the incidence of impaired fasting glucose. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of the study subjects

Of 2775 subjects studied, 20.3% (562/2775) were found to have IFG. The incidence of IFG in males was 23.6% (415/1762), which was significantly higher ($\chi^2=32.6$, $P < 0.001$) than 14.5% (147/1013) in females. Other parameters that showed sex differences are presented in Table 1. The average age of the 2 groups did not show any significant difference. The mean value of systolic and diastolic blood pressures, FPG, BMI, TC, LDL-C, TG, AST, and ALT were higher in males compared to females, except for HDL-C levels, which were lower in males.

Table 1. Characteristics of subjects by sex.

	Men (n=1762)	Women (n=1013)	t	P
Age (yrs)	44.5±8.9	44.2±10.0	0.7	>0.05
Systolic blood pressure (mm Hg)	129.7±13.5	120.1±13.6	18.1	<0.001
Diastolic blood pressure (mm Hg)	80.9±11.3	72.8±10.6	18.7	<0.001
Fasting plasma glucose (mmol/L)	5.28±0.53	5.14±0.48	6.9	<0.001
BMI (kg/m ²)	24.9±3.0	22.5±2.7	21.3	<0.001
Total cholesterol (mmol/L)	5.01±0.95	4.87±0.93	4.0	<0.001
HDL-C (mmol/L)	1.35±0.30	1.56±0.33	-16.9	<0.001
LDL-C (mmol/L)	3.21±0.79	2.88±0.75	10.6	<0.001
Triglycerides (mmol/L)*	1.74 (0.72~6.03)	1.19 (0.56~3.33)	19.6	<0.001
ALT (U/L)*	25 (10~94)	15 (7~49)	25.6	<0.001
AST (U/L)*	23 (15~52)	19 (13~38)	17.5	<0.001
GGT (U/L)*	35 (13~197)	14 (8~68)	36.0	<0.001

HDL-C – high-density lipoprotein-cholesterol; LDL-C – low-density lipoprotein-cholesterol; ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – γ -glutamyltransferase.

HOMA-IR and HOMA- β and liver enzymes

We compared the relationship among HOMA-IR and HOMA- β in subjects of each sex with different levels of liver enzymes. These results (Table 2) revealed that there are significant differences ($P<0.01$) among the subgroups, except for the HOMA-IR and HOMA- β , in which there were different levels of AST in females.

Quartiles of each liver enzyme and incidence analysis of impaired fasting glucose

Subjects of each sex are divided into 3 groups according to the differences in the levels of liver enzymes, and then into quartiles of the normal range of each according to their serum concentrations. Comparison of the results of different subgroups showed that the frequency of IFG increased with elevation in liver enzymes, as depicted in Figure 1. For example, in males the incidence of IFG was higher in those with ALT of the fourth quartile than that of the first quartile, while that of the second, third, and fourth quartile were higher than the first one in females. On the other hand, the third and fourth quartiles of AST showed a higher incidence of IFG compared to the first quartile in males; while in females, the highest quartile AST group had a higher incidence of IFG compared to the lowest quartile. With regard to GGT in males, the third and fourth quartile had higher incidence of IFG compared to the first quartile; while in females, the odds of the IFG increased in the second, third, and fourth quartile subgroups.

The logistic regression analyses

Logistic regression analyses showed that increased levels of hepatic enzymes might be a significant predictor of IFG. We evolved a model of logistic regression wherein subjects with normal glucose tolerance (NGT) are valued as 0, and those with IFG as 1, and considering quartiles of the levels of different liver enzymes as independent variables, and fasting plasma glucose as the dependent variable. The results, presented in Table 3, suggest that after the adjustment for age, data of the male subjects showed that the risk of having IFG in the highest quartile of AST, ALT, and GGT was significantly greater than those in the lowest quartile (OR for ALT: 2.29, 95% CI: 1.67~3.12; OR for AST: 1.93, 95% CI: 1.43~2.60; OR for GGT: 3.19, 95% CI: 2.31~4.40). Similar statistical analysis performed in the females revealed that there was a significant correlation between the levels of liver enzymes and the incidence of IFG for the GGT group (OR for GGT: 3.63, 95% CI: 2.01~6.56), but not for ALT and AST enzymes. Further logistic regression analysis (after adjusting for variables such as blood pressure, blood lipids, and BMI) showed that the correlation between the liver enzymes and IFG was still significant (Males: OR for ALT: 1.52, 95% CI: 1.07~2.15; OR for AST: 1.51, 95% CI: 1.09~2.08; OR for GGT: 2.38, 95% CI: 1.66~3.41; Females: OR for GGT: 2.93, 95% CI: 1.58~5.43).

Discussion

Pre-diabetes is a state in which carbohydrate metabolism is mildly abnormal, the plasma glucose is slightly above the

Table 2. Homa-IR and Homa-β for the trend of Impaired fasting glucose according to quartiles of each liver enzyme.

		n	HOMA-IR	Pfor trend	HOMA-β	Pfor trend
ALT						
Men	~18	502	1.5±0.9		79.2±44.8	
	19~25	396	1.9±0.9		95.4±52.9	
	26~37	441	2.1±1.0		110.5±54.9	
	38~	423	2.9±1.7	<0.001	136.9±76.9	<0.001
Women	~11	267	1.5±0.7		82.3±39.8	
	12~15	287	1.7±0.9		101.1±73.7	
	16~20	209	1.9±1.0		98.9±47.5	
	21~	250	2.0±1.1	<0.001	106.0±54.4	<0.001
AST						
Men	~20	557	1.8±1.0		92.7±53.1	
	21~23	332	1.9±1.1		96.0±49.4	
	24~29	472	2.2±1.2		111.2±66.6	
	30~	401	2.6±1.7	<0.001	120.1±71.8	<0.001
Women	~17	342	1.8±1.0		98.1±50.6	
	18~19	194	1.7±0.9		102.4±83.7	
	20~23	259	1.7±0.9		91.1±44.4	
	24~	218	1.8±1.0	0.233	97.0±48.6	0.198
GGT						
Men	~22	488	1.6±0.9		84.2±44.4	
	23~34	393	2.0±1.0		104.3±61.7	
	35~57	451	2.3±1.3		113.4±61.3	
	58~	430	2.6±1.6	<0.001	118.4±73.0	<0.001
Women	~11	270	1.4±0.6		85.0±37.5	
	12~14	242	1.7±0.8		93.6±45.9	
	15~20	272	1.9±1.0		105.1±76.1	
	21~	229	2.1±1.1	<0.001	104.9±56.6	<0.001

Homa-IR = (FINS × FPG)/22.5 Homa-β = (20 × FINS)/(FPG – 3.5). ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – γ-glutamyltransferase.

normal range, and other criteria indicating the presence of diabetes mellitus are absent. The American Diabetes Association (ADA) considers that prediabetes is a high-risk factor for the development of DM [12,13]. There are 2 forms of pre-diabetes: impaired fasting glucose (IFG) and impaired glucose intolerance. A worldwide epidemiological study showed that the incidence of both prediabetes and type 2 diabetes mellitus are increasing rapidly [14]. A report from the American National

Health and Nutrition Examination Survey (NHANES) showed that 79 000 000 persons were in the prediabetic state by 2010 [15]. A large study performed in China revealed that the incidence of IFG among those who were 40–75 years old with hypertension is 14.1% [16]. As per the statistics presented by ADA, it was opined that 70% of prediabetic patients eventually develop DM, and this rate was found to be more than 90% in China [17]. A prospective study in 2007 reported that

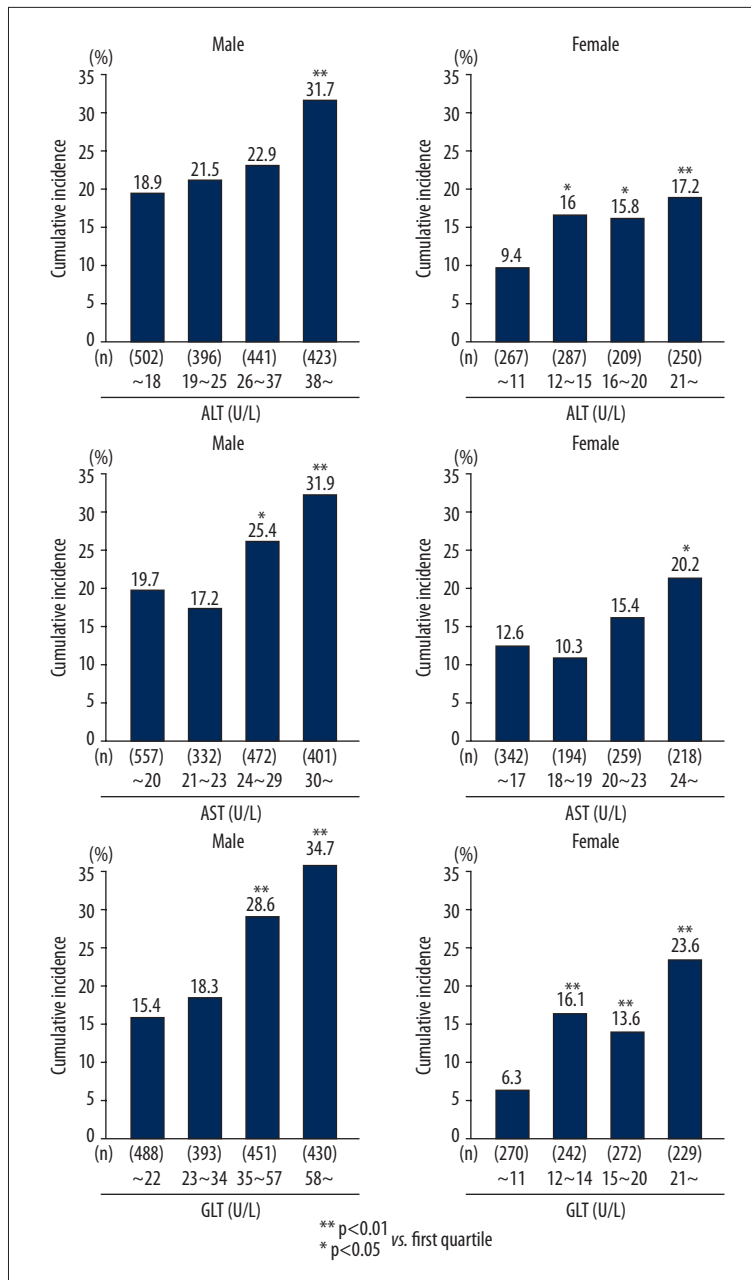


Figure 1. The cumulative incidences of impaired fasting glucose according to quartiles of each liver enzyme, ALT – alanine aminotransferase, AST – aspartate aminotransferase, GGT – γ -glutamyltransferase.

6–9% of those with IFG developed DM, and 15–19% of those with both IFG with IGT eventually develop DM [18], although this rate of conversion from prediabetes to DM varies depending on race [19,20]. Since pre-diabetes is reversible, modification of the life-style factors and medication could revert plasma glucose to normal and thus significantly lower morbidity due to DM [9,21–24]. It is estimated that in China, 148 million people have prediabetes. Hence, it is important to detect factors that could predispose to the development of pre-diabetes and accordingly develop preventive strategies. The liver plays a significant role in the metabolism of glycogen, lipids, and protein and is responsible for the carbohydrate metabolism,

including gluconeogenesis, glycogenesis, and the breakdown of the insulin. Thus, liver dysfunction could influence plasma glucose regulation. Several studies revealed liver enzymes are not only markers of liver function, but also could serve as a predictive index of DM [1–8]. The reported correlation between fasting glucose and fasting insulin levels [25,26] suggest that elevated blood glucose is associated with insulin resistance. Therefore, levels of liver enzymes could be interpreted to detect a dysfunction of insulin secretion and breakdown [27]. The results of the present study indicate that such as association between the levels of liver enzymes and plasma glucose does indeed exist.

Table 3. Age- and multivariate-adjusted ORs and 95% CIs for the development of Impaired fasting glucose according to quartiles of each liver enzyme.

		Range	IFG (%)	NGT (%)	Model 1 OR (95%CI)	Pfor trend	Model 2 OR (95%CI)	Pfor trend
ALT								
Men	~18	95	(18.9)	407	(81.1)	1	1	
	19~25	85	(21.5)	311	(78.5)	1.14 (0.82~1.59)	0.98 (0.70~1.39)	
	26~37	101	(22.9)	340	(77.1)	1.33 (0.97~1.83)	1.04 (0.74~1.46)	
	38~	134	(31.7)	289	(68.3)	2.29 (1.67~3.12)	<0.001	1.52 (1.07~2.15)
Women	~11	25	(9.4)	242	(90.6)	1	1	
	12~15	46	(16.0)	241	(84.0)	1.66 (0.98~2.81)	1.55 (0.91~2.66)	
	16~20	33	(15.8)	176	(84.2)	1.47 (0.84~2.59)	1.21 (0.67~2.18)	
	21~	43	(17.2)	207	(82.8)	1.56 (0.91~2.68)	0.275	1.23 (0.70~2.18)
AST								
Men	~20	110	(19.7)	447	(81.3)	1	1	
	21~23	57	(17.2)	275	(82.8)	0.83 (0.58~1.18)	0.84 (0.59~1.21)	
	24~29	120	(25.4)	352	(74.6)	1.38 (1.03~1.86)	1.24 (0.92~1.69)	
	30~	128	(31.9)	273	(68.1)	1.93 (1.43~2.60)	<0.001	1.51 (1.09~2.08)
Women	~17	43	(12.6)	299	(87.4)	1	1	
	18~19	20	(10.3)	174	(89.7)	0.73 (0.42~1.29)	0.72 (0.40~1.29)	
	20~23	40	(15.4)	219	(84.6)	0.99 (0.61~1.61)	0.95 (0.58~1.56)	
	24~	44	(20.2)	174	(79.8)	1.26 (0.77~2.06)	0.342	1.15 (0.70~1.92)
GGT								
Men	~22	75	(15.4)	413	(84.6)	1	1	
	23~34	72	(18.3)	321	(81.7)	1.31 (0.91~1.87)	1.14 (0.79~1.65)	
	35~57	129	(28.6)	322	(71.4)	2.03 (1.47~2.82)	1.58 (1.11~2.24)	
	58~	149	(34.7)	281	(65.3)	3.19 (2.31~4.40)	<0.001	2.38 (1.66~3.41)
Women	~11	17	(6.3)	253	(93.7)	1	1	
	12~14	39	(16.1)	203	(83.9)	2.63 (1.44~4.80)	2.52 (1.36~4.66)	
	15~20	37	(13.6)	235	(86.4)	1.98 (1.08~3.65)	1.81 (0.97~3.39)	
	21~	54	(23.6)	175	(76.4)	3.63 (2.01~6.56)	<0.001	2.93 (1.58~5.43)

OR – odds ratio; CI – confidence interval; ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – γ -glutamyltransferase. Model 1 – adjustment was made for age. Model 2 – adjustment was made for age, BMI, blood pressure and lipid.

Conclusions

A number of studies have also revealed that IFG could be related to sex, age, and BMI. The risk of IFG increases with age

[15,28]. Subjects with high BMI are likely to be obese, with fat deposition in various organs, including the liver, have hyperlipidemia, and suffer from impaired insulin sensitivity that could eventually lead to β islet cell dysfunction and

consequent elevation of plasma glucose [29,30]. This seems to be more likely in males. The much weaker correlation between levels of liver enzymes and IFG in females could be attributed to the stimulatory action of estrogen on insulin secretion [31]. In conclusion, our study shows that IFG can be related to the levels of hepatic enzymes; hence, efforts made

to improve liver function to normal could prevent diabetes, especially in males.

Statement

All the authors declare that they have no conflict of interest.

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