Original Article

Liver Enzymes Concentrations Are Closely Related to Pre-diabetes: Findings of the Shanghai Diabetes Study II (SHDS II)*

GAO Fei[1], PAN Jie Min[1], HOU Xu Hong[1], FANG Qi Chen[1], LU Hui Juan[1], TANG Jun Ling[1], GU Hui Lin[2], PAN Zhi Jian[3], YAO You Hua[4], SHEN Wei Zhen[5], and JIA Wei Ping[1,#]

1. Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Clinical Center for Diabetes, Shanghai Diabetes Institute, Shanghai 200233, China; 2. Huayang Health Center, Shanghai 200042, China; 3. Anting Health Center, Shanghai 201805, China; 4. Linfen Health Center, Shanghai 200435, China; 5. Pengpu Health Center, Shanghai 200072, China

Abstract

Objective To investigate the relationship of liver enzymes with hyperglycemia in a large population in Shanghai and identify the association between liver enzymes and insulin resistance.

Methods A total of 3 756 participants were enrolled. Each participant underwent an oral glucose tolerance test and completed a questionnaire. Anthropometric indices were recorded and serum samples were collected for measurement.

Results Liver enzymes concentrations were independently associated with i-IGT, IFG+IGT, and diabetes. With the increase of ALT and GGT concentrations, ORs for i-IGT, IFG+IGT, and diabetes increased gradually. By comparing patients in the highest quartile of GGT concentrations or ALT concentrations with those in the lowest quartile (Q1), ORs for i-IGT, IFG+IGT, or diabetes was significant after adjustment. Both ALT and GGT concentrations were linearly correlated with HOMA-IR and independently associated with HOMA-IR [ALT OR (95% CI): 2.56 (1.51-4.34) *P*=0.00; GGT OR (95% CI): 2.66 (1.53-4.65) *P*=0.00].

Conclusion Serum ALT and GGT concentrations were closely related to pre-diabetes and diabetes in the Shanghai population and positively associated with insulin resistance.

Key words: Impaired fasting glucose; Impaired glucose tolerance; Diabetes; Alanine-aminotransferase; Gamma-glutamyltransferase; China

Biomed Environ Sci, 2012; 25(1):30-37 doi:10.3967/0895-3988.2012.01.005 ISSN:0895-3988

www.besjournal.com(full text) CN:11-2816/Q

INTRODUCTION

Liver is one of the most important organs that are involved in the development of type 2 diabetes (T2DM). Glycogenesis, glycogenolysis, glyconeogenesis, lipid metabolism, and insulin degradation take place in the liver. In recent decades, it has been proven that hepatic diseases such as non-alcoholic fatty liver disease (NAFLD) are associated with impaired glucose metabolism and the prevalence of diabetes[1-2].

Liver enzymes are routinely used as the clinical examination indices to assess the liver function. Alanine-aminotransferase (ALT) is the most specific marker of acute hepatic dysfunction and gamma-glutamyltransferase (GGT) is considered, though not specific, to be a sensitive indicator of liver damage[3]. Recently, both cross-sectional and

*This research was supported by Shanghai Key Laboratory of Diabetes Mellitus (08DZ2230200) and Major Program of Shanghai Municipality for Basic Research (08dj1400601).

#Correspondence should be addressed to JIA Wei Ping. Tel: 86-21-64369181-58720. Fax: 86-21-64368031. E-mail: wpjia@sjtu.edu.cn

Received: January 30, 2011; Accepted: July 29, 2011

cohort studies have demonstrated that elevated liver enzymes, especially ALT and GGT, are associated with the occurrence of T2DM in different ethnics[1,3-9]. Wannamethee S.G. et al. found that elevated levels of ALT and GGT were independent predictors of type 2 diabetes in British older men[3]. Nakanishi N. et al. showed that the risk for development of T2DM increased in a dose-dependent manner as serum GGT increased in middle-aged Japanese men[9]. However, information on the association of liver enzymes with pre-diabetes, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is relatively rare. A few studies showed that the risk for development of IFG was related with liver enzymes[9-10]. However, IFG in above studies was defined as fasting plasma glucose (FPG) levels greater or equal to 6.1 mmol/L but less than 7.0 mmol/L, without the confirmation of oral glucose tolerance tests (OGTT). Moreover, the relationship of liver enzymes levels with the pathogenesis of type 2 diabetes has not been intensively studied .

Diabetes is a challenging public health problem throughout the world and the prevalence has increased at a sharp rate over the past few decades in China. A national investigation which enrolled 46 239 adults, 20 years of age or older from 14 provinces between June 2007 and May 2008, showed that the age-standardized prevalence of diabetes and pre-diabetes were 9.7% and 15.5%, respectively, amounting to 92.4 million adults with diabetes and 148.2 million adults with pre-diabetes[11]. However, only a few investigations have focused considerably the association between liver enzymes and diabetes in the Chinese population. Wen JP, et al. found that increasing serum GGT quartiles were positively associated with the prevalence of type 2 diabetes after adjustment for potential confounders in a Chinese population[12]. Up to now, the relationship of liver enzymes with pre-diabetes, which composes a larger population group than diabetes, has not been well-studied in China.

In the present study, we investigated serum liver enzyme concentrations as well as anthropometric indices, glucose and lipid metabolism references in a large group of the population to clarify the relationship of ALT and GGT concentrations with pre-diabetes and newly diagnosed T2DM in Shanghai, China. Moreover, we tried to probe the association between liver enzymes concentrations and insulin resistance, one of the major pathogenesis of hyperglycemia.

SUBJECTS, MATERIALS AND METHODS

The subjects of this study were enrolled from the Shanghai Diabetes Study II (SHDS II), which was a cross sectional epidemiological survey of diabetes and metabolic syndrome in Shanghai between May 2007 and August 2008 following a multistage stratified design. A detailed description of survey methods and data collection procedures has been published already[13]. A total of 5 372 individuals aged 14 to 79 years participated in the survey. The sampling proportion was based on the age structure of the community. The average response rate was 95.9%. Exclusion criteria were cancer, severe psychiatric disturbance, chronic kidney disease, pregnancy, and glucocorticoid treatment. The present study enrolled the subjects who came from four communities, namelyHuayang, Anting, Linfen, and Pengpu, based on SHDS II. Huayang community represents a high income population, Linfen and Pengpu communities represent the middle income population and Anting community represents the low income population. Informed consent was obtained from each subject before the survey. A total of 3 756 subjects were selected and examined. Individuals who suffered from viral hepatitis, hepatic cirrhosis, cancer, severe disability, or severe psychiatric disturbance were excluded.

Participants arrived at the community service centre at 6 a.m after a 10 hour overnight fasting. Each participant underwent a physical examination including measurement of height, weight, waist circumference, and blood pressure. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured at the horizontal plane between the inferior costal margin and the iliac crest on the mid-axillary line. Blood pressure was the average of three measurements made with a sphygmomanometer at two minute intervals. During the clinic visiting, a standard questionnaire was conducted by trained research staff. Data on the current lifestyle, smoking habit, alcohol intake, physical activity, medical record, diabetes family history (first degree relatives only) were collected for each participant. Alcohol intake was recorded as a three-item categorical variable: no alcohol intake, moderate alcohol intake (<40 g alcohol per day) and heavy alcohol intake (⩾ 40 g alcohol per day).

After a fasting venous blood sample was collected, each participant received a 75-g OGTT. Plasma glucose levels were measured using the

glucose oxidase method. Serum lipid profiles, including total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c), and serum liver enzymes concentrations, including ALT and GGT, were measured by standard commercial methods on a parallel multichannel analyzer (Hitachi 7600-020, Tokyo, Japan). The reference range is 0-65 U/L for ALT and 0-50 U/L for GGT. HbA1c was measured by high performance liquid chromatography (HLC-73G7, Tosoh, Japan). Hepatitis C virus antibody and hepatitis B virus surface antigen were tested by ELISA kits. Serum insulin was detected in the participant from two communities (n=1 240) in duplicates by radioimmunoassay (Beijing North Institute of Biological Technology, China).

After measurement for ALT, GGT, Hepatitis C virus antibody, and hepatitis B virus surface antigen, we excluded the subjects with ALT and/or GGT concentrations of three times higher than the upper limit of the reference range (n=40) and the subjects positive for hepatitis C virus antibody and hepatitis B virus surface antigen (n=192).

Impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes were diagnosed according to the standard criteria by the World Health Organization (WHO) in 1999[14]. i-IFG (isolated-IFG): fasting plasma glucose (FPG) ⩾6.1 mmol/L and <7.0 mmol/L, 2-h postprandial plasma glucose (PG2h)<7.8 mmol/L; i-IGT (isolated-IGT): FPG <6.1 mmol/L, 2hPG⩾7.8 mmol/L and <11.1 mmol/L; IFG+IGT: FPG⩾6.1 mmol/L and <7.0 mmol/L, 2hPG ⩾7.8 mmol/L and <11.1 mmol/L. Diabetes: FPG⩾ 7.0 mmol/L or 2hPG⩾11.1 mmol/L. Diabetes was defined as a self-reported diabetes with a validated history or newly diagnostic diabetes by OGTT. The criteria for hypertension were issued by WHO in 1999 (systolic blood pressure⩾140 mmHg and/or diastolic blood pressure⩾90 mmHg). Obesity and overweight were defined by the guidelines for prevention and control of overweight and obesity in Chinese adults (overweight: 24 kg/m^2⩽BMI< 28 kg/m^2; obesity: BMI⩾28 kg/m^2)[15]. Insulin resistance was assessed by HOMA-IR. Elevated HOMA-IR was defined as the 4th quartile of the HOMA-IR.

Statistical analyses were performed using SAS V8 or SPSS 16.0. ALT, GGT, TC, TG, LDL-c, FPG, and PG2h were logarithmic transformed to obtain approximate normal distribution before statistical analysis. Variables with approximately normal distribution were presented as means±standard deviation while those with skew distribution were shown as geometric means (95% confidence interval [CI]). Continuous variables were compared by analysis of covariance; the covariates were sex, age and BMI. Logistic regression was used to model associations between liver enzymes concentrations and pre-diabetes or newly diagnostic T2DM, taking account of potential confounders. The associations of liver enzymes concentrations with insulin resistance were analyzed by Partial Spearman Correlation and logistic regression analysis. All reported P values were two-tailed and P<0.05 were considered statistically significant.

RESULTS

Clinical Characteristics of Total Participants in the Present Study

The demographic and clinical characteristics of the eligible participants are presented in Table 1. Among the total 3 756 participants, 185 subjects were positive for hepatitis B surface antigen and 6 positive for hepatitis C antibody. One subject was positive for both hepatitis B surface antigen and hepatitis C antibody. The sero-positive rate for hepatitis B surface antigen and hepatitis C antibody was 4.95% and 1.86‰, respectively.

Table1. Characteristics of the Participants in Four Shanghai Communities

	Male (n=1 365)	**Female (n=2 391)**
Age (years)	52.04 (12.52)	51.24 (11.70)
BMI (kg/m^2)	24.23 (3.37)	23.77 (3.58)
Waist (cm)	83.94 (9.49)	77.74 (9.47)
SBP (mmHg)	125.35 (16.19)	121.62 (16.72)
DBP (mmHg)	80.59 (10.31)	76.51 (9.58)
TC (mmol/L)	4.63 (4.58-4.67)	4.78 (4.75-4.82)
TG (mmol/L)	1.53 (1.48-1.58)	1.31 (1.28-1.34)
HDL-c (mmol/L)	1.22 (0.29)	1.41 (0.30)
LDL-c (mmol/L)	2.90 (2.86-2.94)	2.91 (2.88-2.94)
FPG (mmol/L)	5.47 (5.40-5.54)	5.36 (5.31-5.40)
PG2h (mmol/L)	6.62 (6.47-6.78)	6.48 (6.39-6.58)
HbA1c (%)	5.95 (1.14)	5.77 (0.90)
FIN (uIU/mL)#	7.11 (6.66-7.59)	7.67 (7.30-8.07)
IN2h(uIU/mL)#	19.65 (18.07-21.38)	25.54 (23.98-27.20)
ALT (U/L)	22.14 (21.51-22.79)	17.51 (17.11-17.91)
GGT (U/L)	28.27 (27.37-29.21)	19.05 (18.61-19.51)
Positive for HBsAg, n (%)	66 (4.84)	120 (5.02)
Positive for anti-HCV, n (‰)	3 (2.20)	4 (1.67)

(Continued)

	Male (*n*=1 365)	Female (*n*=2 391)
T2DM, *n* (%)	222 (16.26)	260 (10.87)
IGR, *n* (%)	204 (14.95)	362 (15.14)
i-IFG, *n* (%)	56 (4.10)	96 (4.02)
i-IGT, *n* (%)	122 (8.94)	203 (8.49)
IFG+IGT, *n* (%)	26 (1.90)	63 (2.63)
Hypertension, *n* (%)	545 (39.92)	686 (28.69)
Overweight, *n* (%)	528 (38.68)	771 (32.25)
Obese, *n* (%)	176 (12.89)	253 (10.58)
Regular physical activity*, *n* (%)	408 (29.89)	749 (31.33)
Current smoker, *n* (%)	791 (57.95)	41 (1.71)
T2DM family history, *n* (%)	244 (17.88)	440 (18.40)
Alcohol intake, *n* (%)	408 (29.89)	44 (1.84)

Note. *Regular physical activity: regular physical activity at least once a week. #*n*=510 in male; *n*=730 in female. Abbreviations: SD, standard deviation; BMI, body mass index; SBP, systolic pressure; DBP, diastolic pressure; GM, geometric mean; CI, confidence interval; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein-cholesterol;LDL-c,low-density lipoprotein-cholesterol; FPG, fasting plasma glucose; PG2h, 2-h postprandial plasma glucose; HbA1c, glycosylated hemoglobin-1c; FIN, fasting insulin; IN2h, 2-h postprandial insulin; ALT, alanine-aminotransferase; GGT, gamma-glutamyltransferase; IGR, impaired glucose regulation; i-IFG, isolated impaired fasting glucose; i-IGT, isolated impaired glucose tolerance; T2DM, type 2 diabetes; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus.

The prevalence of different glucose regulation status was 4.05% for i-IFG, 8.65% for i-IGT, 2.37% for IFG+IGT and 12.83% for T2DM. There were 34.58% of overweight participants and 11.42% of obese participants. The prevalence of hypertension in the current population was 32.77%. The rates of regular physical activity and current smoking were 30.80% and 22.15%, respectively. Alcohol intake rate was 12.03% and the rates of moderate and heavy alcohol intake were 7.69% and 4.34%, respectively. 18.21% of the participants had T2DM family history.

The Relationship of Serum Liver Enzymes Concentrations with Pre-diabetes

From the total 3 756 participants, we excluded the subjects with ALT and/or GGT concentrations of three times higher than the upper limit of the reference range (*n*=40) and the subjects positive for hepatitis C virus antibody and hepatitis B virus surface antigen (*n*=192). We also excluded the subjects with a validated history of diabetes mellitus (*n*=234), and the remaining 3 293 subjects were included in the following analyses.

We found that with the increase of ALT and GGT concentrations, plasma FPG, PG2h, and HbA1c levels (Figure 1) were raised gradually in both male and female subjects. After adjustment for age and BMI, in male subjects, only serum PG2h level showed significant linear test for trend among the four quartiles of ALT (*P*=0.00). However, among the quartiles of GGT, these three indexes all showed significant linear test for trend (FPG *P*=0.02; PG2h *P*<0.0001; HbA1c *P*=0.00). In females, these three indexes were all significantly raised with the increase of both ALT and GGT (ALT: FPG *P*=0.00; PG2h *P*<0.0001; HbA1c *P*=0.01; GGT: FPG *P*<0.0001; PG2h *P*<0.0001; HbA1c *P*<0.0001).

Logistic analysis showed that serum ALT concentrations were independently associated with i-IGT and IFG+IGT after the adjustment for the potential confounders which were correlated with glucose metabolism, such as lipid profiles, blood pressure, BMI, waist circumference, etc (Table 2). Trends across quartiles of ALT or GGT for i-IGT were statistically significant (*P* for trend <0.05) in both genders whereas trends across quartiles of both liver enzymes for i-IFG or IFG+IGT were not statistically significant. With the increase of liver enzymes levels, the ORs for i-IGT were raised gradually. In male, the OR for i-IGT comparing patients in the highest quartile of the serum GGT concentrations with those in the lowest quartile was statistically significant after adjustment for age, community, physical activity, smoking habit, alcohol intake, T2DM family history, BMI, waist circumference, lipid profiles, blood pressures [OR (95% CI) 3.19 (1.48-6.85)], but the OR for i-IGT of ALT concentrations (the highest quartile versus the lowest quartile) was otherwise. In female, the ORs for i-IGT of ALT concentrations (the highest quartile versus the lowest quartile) was statistically significant after adjustment [OR (95% CI) 2.35 (1.30-4.26)], but the OR for i-IGT of GGT concentrations (the highest quartile versus the lowest quartile) was otherwise.

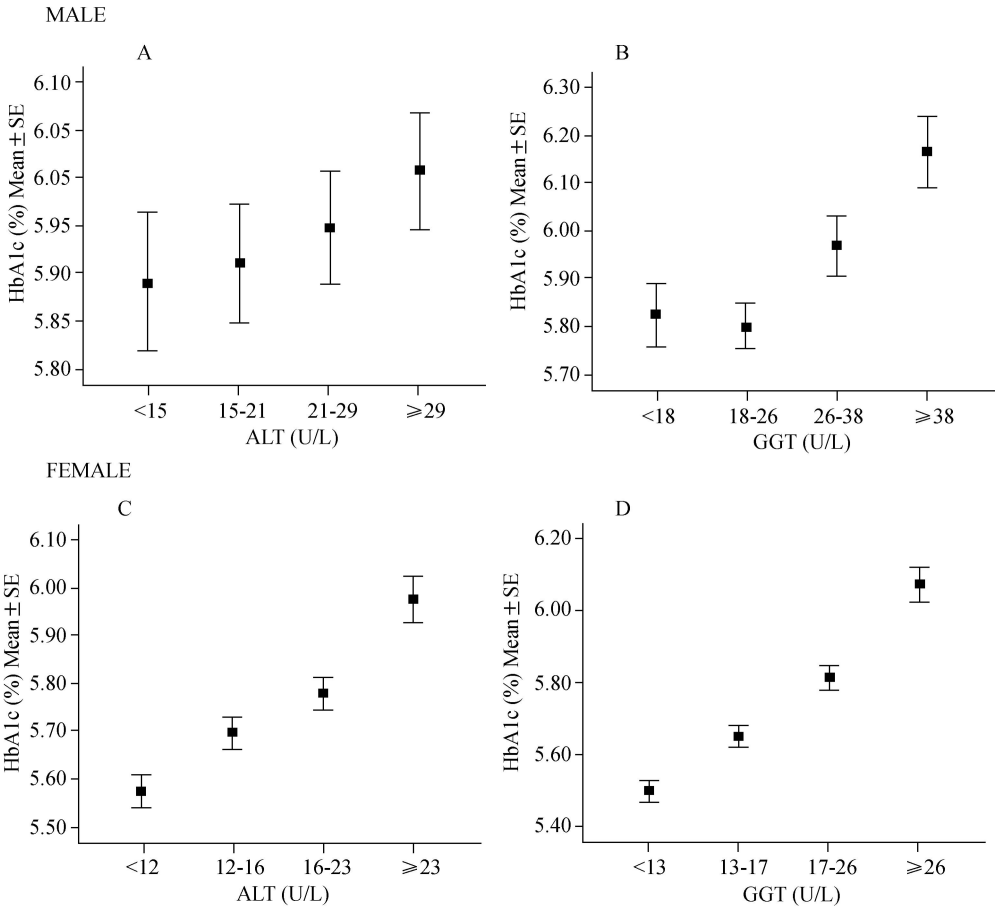

Figure 1. The plasma HbA1c concentrations stratified by liver enzymes quartiles in male (A,B) and female (C,D). Male *n*=1 278; Female *n*=2 249. Except Figure A, HbA1c concentrations significantly increased cross the quartiles of liver enzymes concentrations after adjustment for age and BMI.

The Relationship of Serum Liver Enzymes Concentrations with Diabetes

Logistic analysis showed that both serum ALT concentrations and GGT concentrations were independently associated with newly diagnostic diabetes after adjustment for the potential variables (Table 2). Trends across quartiles of ALT and GGT for newly diagnostic T2DM were statistically significant (*P* for trend <0.05) in both genders. With the increase of liver enzymes levels, the ORs for newly diagnostic T2DM were raised gradually. After adjustment for age, community, physical activity, smoking habit, alcohol intake, T2DM family history, BMI, waist circumference, lipid profiles, blood pressures, the ORs for newly diagnostic T2DM remained statistically significant in both genders by comparing patients in the highest quartile of the serum ALT and GGT concentrations with those in the lowest quartile [ALT OR(95% CI): 2.31 (1.03-5.14) in male, 2.47 (1.21-5.07) in female; GGT OR (95% CI): 2.96 (1.30-6.73) in male, 3.23 (1.53-6.83) in female].

The Association of Serum Liver Concentrations with Insulin Resistance

Serum insulin levels were measured in subjects from two communities, who had not been treated by insulin previously (*n*=1 240). With the increase of ALT and GGT concentrations, serum fasting insulin (FIN), 2-h postprandial insulin (IN2h) concentrations were raised gradually. After adjustment for sex, age and BMI, both FIN and IN2h concentrations were significantly increased across the quartiles of ALT and GGT concentrations (ALT: FIN *P*<0.0001; IN2h *P*<0.0001; GGT: FIN *P*=0.00; IN2h *P*<0.0001).

Insulin resistance was evaluated by HOMA-IR. After adjustment for sex, age, and BMI, serum liver enzymes were linearly correlated with HOMA-IR (ALT: r=0.12 *P*<0.0001; GGT: r=0.12 *P*<0.0001). Furthermore, logistic regression analysis revealed that ALT and GGT concentrations were both

independently associated with elevated HOMA-IR after adjustment for potential variables that might affect insulin sensitivity, such as sex, age, physical activity, smoking habit, alcohol intake, diabetic family history, BMI, waist circumference, lipid profiles and blood pressure [ALT OR (95% CI): 2.58 (1.52-4.38) *P*=0.00; GGT OR (95% CI): 2.63 (1.51-4.59) *P*=0.00].

Table 2. Liver Enzymes and Other Metabolic Risk Factors and Risks to Pre-diabetes and Newly Diagnosed Type 2 Diabetes

		OR	95% CI
i-IFG	BMI	1.07	1.03-1.12
	SBP	1.02	1.01-1.03
	DM family history	1.70	1.12-2.56
i-IGT	ALT*	2.81	1.54-5.15
	Waist Circumference	1.03	1.01-1.05
	TG*	4.45	2.52-7.85
	SBP	1.02	1.01-1.02
	DM family history	1.43	1.03-1.98
	Alcohol intake	0.83	0.70-0.99
IFG+IGT	ALT*	3.27	1.09-9.84
	Waist circumference	1.04	1.01-1.07
	TG*	3.63	1.28-10.33
T2DM	ALT*	2.77	1.29-5.96
	GGT*	3.41	1.67-6.98
	LDL-c*	5.13	1.35-19.52
	Waist circumference	1.03	1.01-1.05
	TG*	3.51	1.78-6.90
	SBP	1.02	1.01-1.03
	DM family history	1.74	1.21-2.49

Note. Independent variables: ALT, GGT, Age, Sex, Regular physical activity, Current smoking, DM family history, Alcohol intake, BMI, Waist circumference, HDL-c, LDL-c, TG, SBP. Dependent variables: i-IFG, i-IGT, IFG+IGT, Newly diagnostic T2DM. *:logarithmic transformed. Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; SBP, systolic pressure; HDL-c, high-density lipoprotein-cholesterol; LDL-c, low-density lipoprotein-holesterol; TG, triglyceride; ALT, alanine-minotransferase; GGT, gamma-glutamyltransferase.

DISCUSSION

In the present study, we investigated the relationship of serum liver enzyme concentrations with pre-diabetes and diabetes in a large population in Shanghai, China. It was found that serum ALT and/or GGT concentrations were independently related to i-IGT, IFG+IGT and newly diagnosed T2DM. With the increase of serum ALT and GGT concentrations, fasting plasma glucose, 2 h plasma glucose and HbA1c concentrations increased gradually and the ORs for pre-diabetes and newly diagnosed T2DM was also raised. Liver enzymes concentrations were linearly correlated with HOMA-IR and independently associated with this insulin resistance index.

Each participant in our study underwent oral glucose tolerance test (OGTT). Thus, pre-diabetes was diagnosed with OGTT confirmation. We did not find significant relationship between i-IFG and liver enzymes in either gender. However, in the study from Kim D.J. et al., it was shown that ORs of GGT for IFG were statistically significant[10]. Moreover, Nakanishi N. et al. found that risk for development of IFG increased in a dose-dependent manner as serum GGT increased in middle-aged Japanese men[9]. It was noticed that the diagnostic criteria of IFG in their studies were fasting plasma glucose ⩾ 6.1 mmol/L and <7.0 mmol/L, but OGTT was not performed. Thus, a number of subjects in the IFG group might be IFG+IGT indeed, which could be the confounder of the study. Otherwise, the number of subjects with i-IFG in our investigation was relatively small and this might make the relationship of IFG with liver enzymes underestimated.

Some findings of our study were consistent with previously reported studies[3-8,10,16]. For examples, Hanley A.J.G. et al. found that ALT concentration independently predicted T2DM from a prospective study in an American population[4]. Kim D.J. et al. revealed that serum GGT concentrations were closely associated with the presence of diabetes from a cross-sectional survey in a large Korean population[10]. The study from Nannipieri M. et al. showed that GGT was an independent predictor of IGT in the Mexico City Diabetes Study[5]. Furthermore, the logistic regression analysis showed that the threshold values of serum ALT and GGT concentrations that pointed out significantly increased frequencies of hyperglycemia were much lower than the traditional cut-off points for elevated liver enzymes, and these outcomes were in line with other studies, indicating that the risk to pre-diabetes or T2DM was increased when the liver enzymes were still within the normal reference ranges[3,9-10,17].

There were some differences between our findings and the finding s from other studies. We found that both ALT and GGT concentrations were closely associated with pre-diabetes and newly

diagnosed T2DM. However, studies based on French and Mexican populations showed no relationship between ALT and IGT or diabetes[1,5], whereas studies based on Pima Indian and Filipino-American population showed that ALT, rather than GGT, was related with diabetes[18-19]. This inter-study disparity could reflect the ethnic differences in the studied populations, the methodological differences or the differences in the design of projects.

The mechanisms for the association between liver enzymes and hyperglycemia are not clear. In the present study, independent relationships were found between liver enzymes and elevated HOMA-IR, an index that estimates body general insulin resistance status. Therefore, we deduced that liver enzyme concentrations might reflect the insulin resistance status to some extent. Previous studies showed that elevated liver enzymes were likely to reflect non-alcoholic fatty liver disease (NAFLD) which is now known to be characterized by insulin resistance and high diabetes prevalence[4,20-22]. Some researchers considered that raised liver markers reflected insulin resistance localized to the liver due to the factor as revealed by some investigators that associations between liver enzymes concentrations and diabetes risk were independent of directly measured insulin sensitivity or insulin resistance (HOMA-IR)[3-4]. Moreover, it was directly proven that high ALT was associated with decreased hepatic insulin sensitivity[18]. In the present study, by only measuring the insulin concentration in part of the subjects, we identified an independent relationship between liver enzymes and insulin resistance. Unfortunately, we could not measure the hepatic insulin resistance in the study. Hyperinsulinemic-uglycemic glucose clamp technique is a must for further analysis.

There were several other limitations in the present study. The study was a cross-sectional one, which could not allow us to determine temporal relationships between liver enzymes concentrations and hyperglycemia. Another limitation was that we did not exclude the subjects who were alcoholic drinkers. However, in the statistical analysis, the alcohol intake was adjusted as a co-variant which could be excluded as confounding factor. Otherwise, according to the others studies, the association between liver enzymes and T2DM were largely unchanged after the exclusion of ex- and moderate/heavy drinkers[4].

In conclusion, this study has identified that serum ALT and GGT were closely related to the pre-diabetes and T2DM in the Shanghai population in China even after adjustment for a broad spectrum of type 2 diabetes risk factors. These two liver enzymes were also independently associated with insulin resistance index. Elevated hepatic enzymes might be helpful to identify persons who are likely to have insulin resistance and who are at particularly high risk to diabetes. The present study has also supported that NAFLD plays an important role in the pathogenesis of diabetes.

ACKNOWLEDGEMENTS

We thank the participants who took part in the studies described in this report.

REFERENCE

1. André P, Balkau B, Born C, et al. Hepatic markers and development of type 2 diabetes in middle aged men and women: a three-year follow-up study: the D.E.S.I.R. study. Diabetes Metab, 2005; 31, 542-50.
2. Baig NA, Herrine SK, Rubin R. Liver disease and diabetes mellitus. Clin Lab Med, 2001; 21, 193-207.
3. Wannamethee SG, Lennon L, Shaper AG, et al. Hepatic enzymes, the metabolic syndrome, and the risk of type 2 diabetes in older men. Diabetes Care, 2005; 28, 2913-8.
4. Hanley AJG, Williams K, Festa A, et al. Elevations in markers of liver injury and risk of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes, 2004; 53, 2623-32.
5. Nannipieri M, Gonzales C, Baldi S, Posadas R, et al. Liver enzymes, the metabolic syndrome, and incident diabetes: the Mexico City diabetes study. Diabetes Care, 2005; 28, 1757-62.
6. Lee DH, Silventoinen K, Jacobs DR, JR, et al. Gamma-Glutamyltransferase, Obesity, and the Risk of Type 2 Diabetes: Observational Cohort Study among 20 158 Middle-Aged Men and Women. J Clin Endocrinol Metab, 2004; 89, 5410-4.
7. André P, Balkau B, Born C, et al. Three-year increase of gamma-glutamyltransferase level and development of type 2 diabetes in middle-aged men and women: the D.E.S.I.R. cohort. Diabetologia, 2006; 49, 2599-603.
8. Lee DH, Ha MH, Kim JH, et al. Gamma-glutamyltransferase and diabetes-a 4 year follow-up study. Diabetologia, 2003; 46, 359-64.
9. Nakanishi N, Nishina K, LI W, et al. Serum γ-glutamyltransferase and development of impaired fasting glucose or type 2 diabetes in middle-aged Japanese men. J Intern Med, 2003; 254, 287-95.
10. Kim DJ, Noh JH, Cho NH, et al. Serum γ-glutamyltransferase within its normal concentration range is related to the presence of diabetes and cardiovascular risk factors. Diabet Med, 2005; 22, 1134-40.
11. Yang W, Lu J, Weng J, et al. Prevalence of Diabetes among Men and Women in China. N Engl J Med, 2010; 362, 1090-101.
12. Wen J, Liang Y, Wang F, et al. C-reactive protein, gamma-glutamyltransferase and type 2 diabetes in a Chinese population. Clinica Chimica Acta, 2010; 411, 198-203.
13. Bao Y, Ma X, Li H, et al. Glycated haemoglobin A1c for diagnosing diabetes in Chinese population: cross sectional epidemiological survey. BMJ, 2010; 340, c2249.

14.Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med, 1998; 15, 539-53.
15.Chen C, Lu FC. Department of disease control ministry of health, PR China. The guidelines for prevention and control of overweight and obesity in Chinese adults. Biomed Environ Sci, 2004; 17 Supplement, 1-36.
16.Lee DH, Jacobs DR Jr, Gross M, et al. Gamma-Glutamyltransferase Is a Predictor of Incident Diabetes and Hypertension: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. Clinical Chemistry, 2003; 49, 1358-66.
17.Perry IJ, Wannamethee SG, Shaper AG. Prospective study of serum gamma-glutamyltransferase and risk of NIDDM. Diabetes Care, 1998; 21, 732-7.
18.Vozarova B, Stefan N, Lindsay RS, et al. High Alanine Aminotransferase Is Associated With Decreased Hepatic Insulin Sensitivity and Predicts the Development of Type 2 Diabetes. Diabetes, 2002; 51, 1889-95.
19.Wong CA, Araneta MRG, Barrett-Connor E, et al. Probable NAFLD, by ALT levels, and diabetes among Filipino-American Women. Diabetes Res Clin Pract, 2008; 79, 133-40.
20.Mulhall BP, Ong JP, Younossi ZM. Non-alcoholic fatty liver disease: an overview. J Gastroenterol Hepatol, 2002; 17, 1136-43.
21.Angulo P, Lindor KD. Non-alcoholic fatty liver disease. J Gastroenterol Hepatol, 2002; 17 (Suppl.), S186-90.
22.Chitturi S, Farrell GC, George J. Non-alcoholic steatohepatitis in the Asia-Pacific region: future shock? J Gastroenterol Hepatol, 2004; 19, 368-74.