SMGroup

SM Journal of Public Health and Epidemiology

Research Article

Increased Alanine Aminotransferase Predicted Both Prediabetes and Diabetes Development in Chinese Men: A Population-Based Cohort Study

Yuzhen Huang[1,2,3], Yawen Luo[1,2,3], Qin Tang[1,2,3], Yan Tang[1,2,3], Jinling Xie[1,2,3], Chunlei Wu[1,7], Zheng Lu[1,5], Aihua Tan[1,4], Yong Gao[1], Ziting Yao[1,2,3], Yonghua Jiang[1,2,3], Haiying Zhang[1,2,3,6] , Zengnan Mo[1,2,3,5] and Xiaobo Yang[1,2,3,6]*

[1]*Center for Genomic and Personalized Medicine, Guangxi Medical University, Nanning, Guangxi, China*
[2]*Guangxi Key Laboratory of genomic and personalized medicine, Nanning, Guangxi, China*
[3]*Guangxi Collaborative Innovation Center for genomic and personalized medicine, Nanning, Guangxi, China*
[4]*Department of chemotherapy, The Affiliated Tumor Hospital of Guangxi Medical University, Guangxi, China*
[5]*Institute of Urology and Nephrology, First Affiliated Hospital of Guangxi Medical University, Guangxi, China*
[6]*Department of Occupational Health and Environmental Health, School of Public Health, Guangxi Medical University, China*
[7]*Department of Urology, First Affiliated Hospital of Xinxiang Medical College, China*

Article Information

Received date: Aug 02, 2015
Accepted date: Sep 20, 2015
Published date: Nov 03, 2015

***Corresponding author**

Xiaobo Yang, Department of Occupational Health and Environmental Health, Guangxi Medical University, China, Tel: +867715312371; Fax: +867715312371; Email: yxbo21021@163.com

Keywords Alanine aminotransferase (ALT); Impaired Fasting Glucose (IFG); Insulin Resistance (IR); Type 2 Diabetes Mellitus (T2DM); Cohort study

Abstract

Background: Alanine Aminotransferase (ALT) is an enzyme released for the liver pathology. Growing studies have proposed the association between ALT and Type 2 Diabetes Mellitus (T2DM). Current literatures lack data of ALT in newly diagnosed T2DM patients in Chinese population. We therefore, conducted this cohort-study to determine whether elevated serum ALT levels contributed to Insulin Resistance (IR), Impaired Fasting Glucose (IFG), and T2DM simultaneously.

Methods: We combined a cross-sectional and cohort design together in this research. In the cross-sectional study, data was collected from 2423 men at Fangchenggang Area Males Health and Examination Survey (FAMHES). The participants were categorized into three groups, including normal (n=1794), IFG (n=556) and T2DM (n=73) in light of fasting glucose and history of diabetes. Besides, the subjects were divided into non-insulin resistance (Non-IR) (n=1947) and IR (n=403) groups. Moreover, in the longitudinal analysis, 2819 men without T2DM underwent 4-year follow-up examination in the study of observing for the T2DM development.

Results: We observed a significant distinction of ALT between normal, IFG and T2DM groups (38.00(27.00-49.00) U/L, 43.00(30.50-55.50) U/L, and 45.00(32.00-58.00) U/L, respectively, P=0.024). After multiple adjustment, the Odds Ratios (ORs) were substantially higher for IFG [OR=1.73, 95% Confidence Interval (CI) =1.33-2.26)], T2DM [OR=2.05, 95% CI=1.05-3.97] and HOMA-IR [OR=3.12, 95% CI=2.18-4.47] in the highest ALT tertile comparing with those in the lowest tertile. In the longitudinal analysis, 99 individuals had developed T2DM and there were 28 (2.99%), 33 (3.51%) and 38 (4.03%) new cases from the first tertile to the last tertile. Individuals with the highest tertile of ALT were at significantly increased the incidence of T2DM compared with those in the lowest [HR=1.67, 95% CI=1.00-2.75].

Conclusion: Serum ALT concentrations were associated with prediabetes and increased ALT predicted a high risk for T2DM development.

Introduction

Alanine aminotransferase (ALT) is an early, easy, and noninvasive enzyme that can be released for the necrosis of liver cells during the liver damaging [1-3], so the elevation of ALT is used as a surrogate marker of liver pathology in the nowadays clinical examination. In epidemiological studies of the general population, an elevated serum activity of ALT has been suggested as the hallmark of Nonalcoholic Fatty Liver Disease (NAFLD), a subset causations related to it, including obesity, hepatic resistance and type 2 diabetes mellitus (T2DM) [4-6], and more than one half of T2DM patients have or develop NAFLD [7]. Metabolic Syndrome (MS) is a possible link between T2DM and NAFLD, because the occurrence of T2DM is closely resulted from some components of MS [8,9], of which abdominal obesity, dyslipidemia and Insulin Resistance (IR) are related to NAFLD [10].

Cross-sectional studies demonstrated that high levels of hepatic enzymes, including ALT, γ -Glutamyltranspeptidase (GGT) and Aspartate Aminotransferase (AST) were risk factors for T2DM [11-13]. There were several prospective studies proposing that high concentrations of these

enzymes, especially the ALT, may interrelate to the later development of diabetes [14,15]. Because of the simplicity of ALT measurement, elevated serum ALT levels may be used as a future diabetes prediction in the clinical practice.

To our knowledge, although there were studies which detected the association between ALT and T2DM, few researches investigated the relationship of ALT, prediabetes and diabetes at the same time. Moreover, relatively limit studies have demonstrated the association between ALT and T2DM in China [16-18]. Thus we not only examine the association between ALT and the intermediate process of T2DM (including IFG and IR in this design) but also explored whether rising ALT can predict the occurrence of diabetes integrating a cross-sectional and cohort study together in the FAMHES population.

Materials and Methods

Study population

The Fangchenggang Area Males Health and Examination Survey (FAMHES) was a population-based study which was designed to investigate the effects of environment, genetic factors and their interaction on the development of age-related chronic diseases among 17 to 88 year-old men in China [19].

The subjects with liver diseases, such as viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, cirrhosis and gallbladder diseases were carefully excluded before our population study design. As a result, the cross-sectional study was conducted among 4303 continuous men who participated in a large-scale physical examination in the Medical Examination Centre of First People's Hospital in Fangchenggang from September 2009 to December 2009. All participants provided written informed consents, and the local ethics committee approved the study. In addition, we designed the following exclusion criteria: (1) previously or currently diagnosed type 1 diabetes mellitus, (2) missing serological testing of fasting insulin and glucose, (3) missing serum ALT results. Finally, 2423 men aged from 20 to73 years with complete data of all features of serum ALT concentration, fasting glucose and fasting insulin were enrolled into the analysis.

Based on the cross-sectional study, 1809 participants with fixed department and accommodation were finally selected in 2009 and 1610 men were newly recruited in 2011 in the longitudinal study. The longitudinal analysis was performed by combining these two follow-up periods. The subjects were excluded on the basis of the following criteria: (1) diagnosed as T2DM, (2) missing data in anthropometric measurements and clinical biochemistry assays, (3) loss to follow -up in 2013. Of the subjects, 2819 participants were enrolled in the final longitudinal analysis. Finally, 99 subjects developed T2DM.

Data collection

Data collection was conducted in Fangchenggang First People's Hospital Medical Examination Center. A face-to-face interview was conducted by physicians, who experienced a professional trained before the research. Information on demographic characteristics (age,

Table 1: General demographic characteristics of the study group's population and selected factors.

	Normal	IFG	T2DM	P
N	1794	556	73	
Age‡ (years)	35.00(28.00-42.00)	40.00(32.50-47.50)	47.00(38.50-55.50)	<0.001
ALT ‡ (U/L)	38.00(27.00-49.00)	43.00(30.50-55.50)	45.00(32.00-58.00)	0.024
TP† (g/L)	79.16±4.44	80.02±4.77	80.57±5.44	<0.001
BMI† ($kg\,m^{-2}$)	22.98±3.22	24.22±3.42	24.74±3.87	<0.001
WC† (cm)	79.72±8.85	83.46±9.58	85.47±10.65	<0.001
HDL‡ (mmol/L)	1.35(1.16-1.54)	1.37(1.17-1.58)	1.36(1.06-1.66)	<0.001
CHOL† (mmol/L)	5.58±0.98	6.04±1.08	6.11±1.30	<0.001
TRIG‡ (mmol/L)	1.07(0.63-1.51)	1.31(0.73-1.89)	1.95(0.78-3.12)	<0.001
LDL† (mmol/L)	2.90±0.78	3.17±0.85	3.06±0.81	<0.001
ALB† (g/l)	44.52±2.89	44.29±3.22	43.91±4.01	0.094
Smoking, n (%)				
Now	896(49.94)	273(49.10)	28(38.36)	<0.001
Former	62(3.46)	28(5.04)	10(13.70)	
Never	836(46.60)	255(45.86)	35(47.95)	
Drinking status,				
yes, n(%)	1542(85.93)	470(84.53)	63(86.30)	<0.001
Family history of diabetes,				
yes, n (%)	62(3.46)	25(4.50)	9(12.33)	<0.001

†Unless indicated otherwise, data are presented as mean±standard deviation (SD),
‡Data show the median (25percenile,75percentile) or counts (percent)
The one-way Analysis of Variance (ANOVA) test or the Nonparametric Test was used for categorical variables and Pearson chi-square test was used for continuous variables
IFG: Impaired Fasting Glucose; T2DM: Type 2 Diabetes Mellitus; ALT: Alanine aminotransferase; TP: Total Protein; BMI:Body Mass Index; WC:Waist Circumference; HDL: High-Density Lipoprotein; CHOL: Cholesterol; TRIG:Triglycerides; LDL:Low-Density Lipoprotein; ALB: Albumin.

Table 2: Age-adjusted Spearman partial correlations between log10 (GLU), log10 (HOMA) and some variables.

Variable	Log10(GLU)		Log10(HOMA)	
	R	P	R	P
Log(ALT)	0.089	<0.001	0.345	<0.001
TP	0.164	<0.001	0.080	<0.001
ALB	0.097	<0.001	-0.048	0.019
CHOL	0.131	<0.001	0.168	<0.001
Log10(TRIG)	0.236	<0.001	0.414	<0.001
Log(HDL)	0.057	0.005	-0.241	<0.001
LDL	0.075	<0.001	0.204	<0.001

GLU: fasting Glucose; HOMA: Homeostasis Model Assessment Algorithm (glucose (mm/liter) insulin (mlU/liter)/22.5); ALT: Alanine Aminotransferase; TP: Total Protein; ALB: Albumin; CHOL: Cholesterol; TRIG: Triglycerides; HDL: High-Density Lipoprotein ; LDL: Low-Density Lipoprotein.

education, occupation, etc), lifestyle characteristics (smoking, alcohol consumption, etc), health status, and medical history were collected using a standardized questionnaire. Drinking and smoking behaviors were assessed on the basis of self-administered life questionnaire. Smoking habit was defined as never, current (daily smoking>6 months), and former (stoped smoking>6months). Drinkers were defined as person who had one or more alcoholic drinks, including beer, wine and hard liquor, per week [20]. Family history of diabetes was positive if the participants' parents or siblings had a history of diabetes. The trained persons used a standardized protocol to conduct the anthropometric measures. Subjects were weighted no shoes to the nearest 0.1kg. Standing heights were measured by using a vertical telescopic stadiometer with a horizon headboard on the top to the nearest 0.1 cm. Waist circumference (WC) was measured in the middle of lower rib margin to the iliac. Body mass index (BMI) was then calculated as weight (in kilograms)/height (in square meters).

Laboratory measurements

Overnight fasting venous blood samples were obtained between 8 a.m. and 10 a.m. All of these blood specimens were divided into 2 parts. One part was centrifugated to separate the serum

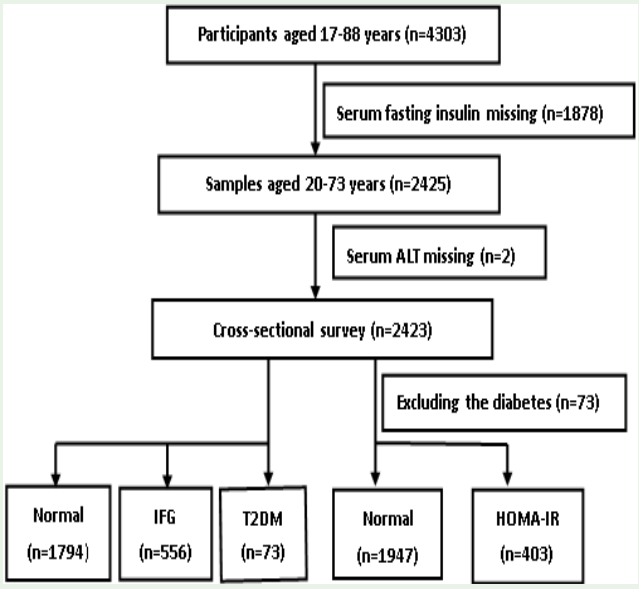

Figure 1: Procedures for selection of the participants in the cross-section study. ALT, alanine aminotransferase; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus; Non-IR, non-insulin resistance; IR, insulin resistance.

Table 3: Odds Ratios (ORs) and 95% CI for ALT with IFG and T2DM according to the tertile of ALT: a multivariate analysis.

		Model1	P	Model2	P	Model3	P
IFG	T1	1		1		1	
	T2	1.65(1.29-2.10)	<0.001	1.57(1.22-2.02)	<0.001	1.47 (1.14-1.90)	0.003
	T3	2.06(1.62-2.62)	<0.001	2.16(1.68-2.76)	<0.001	1.73 (1.33-2.26)	0.002
T2DM	T1	1		1		1	
	T2	1.33(0.71-2.48)	0.337	1.29 (0.68-2.43)	0.438	1.31 (0.66-2.56)	0.433
	T3	2.14(1.20-3.83)	0.01	2.52(1.39-4.57)	0.032	2.05 (1.05-3.97)	0.035

Model 1 was unadjusted;
Model 2 was adjusted for age;
Model 3 was further adjusted for age, CHOL, LDL, HDL, TRIG, TP, ALB; smoking status, drinking status and family history.
IFG: Impaired Fasting Glucose; T2DM: Type 2 Diabetes Mellitus; CHOL: Cholesterol; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; TRIG: Triglycerides; TP: Total Protein; ALB: Albumin.

for immediate measurement. Triglycerides (TG), High-Density Lipoprotein (HDL), ALT, fasting blood glucose, albumin (ALB) and Low Density Lipoprotein (LDL) were measured on a Dimension-RxL Chemistry Analyzer (Dade Behring, Newark, Delaware) in the Department of Clinical Laboratory at the Fangchenggang First People's Hospital. Besides, the Total Protein (TP) was obtained from serum by measuring on an automatic analyzer (Dade Behring, USA). Another part of specimens were transported frozen to the testing center of the First Affiliated Hospital of Guangxi Medical University in Nanning in about 2 hours, centrifuged within 15 to 2 minutes, and stored at 280uC until analysis. The fasting level of serum insulin was measured using electrochemiluminescence immunoassay on COBAS 6000 system E601 (Elecsys Module) immunoassay analyzer (Roche Diagnostics, GmbH, Mannheim, Germany) with the same batch of reagents.

Definition of IFG, T2DM and HOMA-IR

According to the fasting glucose and self-reporting, the participants were divided into three groups: normal group (the fasting glucose<5.6mmol/liter), impaired fasting glucose (IFG, 5.6 mmol/liter≤the fasting glucose≤6.9mmol/liter) and diabetes group (the fasting glucose≥7mmol/liter or intake of anti-diabetic agents, receiving insulin treatment, doctor-diagnosed diabetes) [21]. IR was assessed through the homeostasis model assessment algorithm (HOMA) by the established formulas: glucose (mm/liter) × insulin (mlU/liter)/22.5. When the value of HOMA was higher than 2.7, we define it as insulin resistance [22].

Statistical analysis

All statistical analysis was performed using SPSS for Windows 16.0 (SPSS Inc, Chicago, IL, USA). Statistical tests were 2-sided and a P <0.05 was considered statistically significant. The current analysis was restricted to 2423 subjects with complete data all features of the ALT, fasting glucose and fasting insulin. In the general characteristics, continuous variables were expressed as mean±standard (SD) or median (interquartile range) and categorical variables were expressed as number (n) and percentage (%). The statistical differences among groups were tested with one-way Analysis of Variance (ANOVA), but the age, ALT and TRIG values showed a markedly skewed distribution,

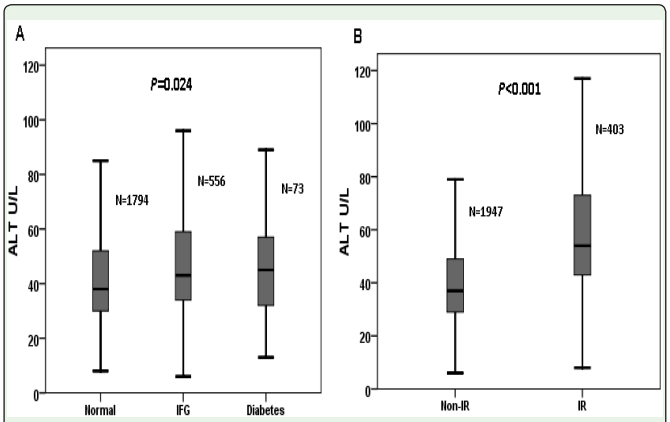

Figure 2: Distribution of ALT levels according to the components, the bars represent median, 25th, and 75th percentile of ALT. ALT, alanine aminotransferase; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus; Non-IR, non-insulin resistance; IR, insulin resistance.

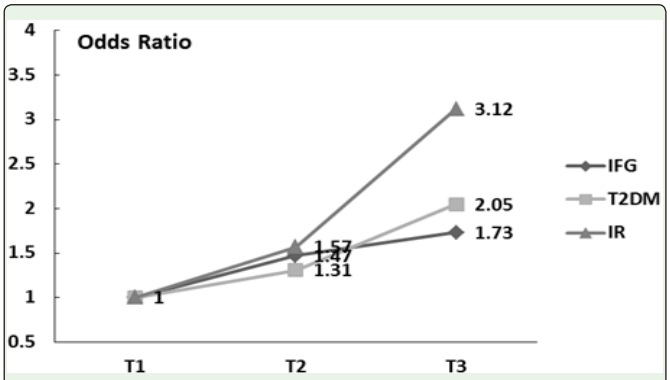

Figure 4: The line chart for the Odds of IFG, IR, T2DM By ALT Tertiles. ORs were adjusted for age, CHOL, LDL, HDL, TRIG, TP, ALB; smoking status, drinking status and family history with the first tertile being the referent group. IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus; CHOL, cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TRIG, triglycerides; TP, total protein; ALB, albumin.

so the parameters were compared among the different groups by using the Nonparametric Test. Pearson chi-square test was used to assess the proportion of the clinical characteristics among the groups. Age adjusted Spearman partial correlation coefficients were calculated between continuous variables, and the age, ALT and TRIG values were logarithmically transformed (log10) to perform approximate normality. The association between ALT, IFG and T2DM was analyzed with multinomial logistic regression, and the relationship between ALT and IR was performed by the binary regression. The binary regression and the multinomial logistic regression were conducted in unadjusted, age adjusted and multivariate adjusted models (adjusting for the other liver enzymes and variables relating to T2DM), respectively. In addition, in the longitudinal analysis, the cox-regression was used to calculate the value of Hazard Risk (HR).

Results

General characteristics in cross-sectional survey

Figure 1 showed the flowchart for participants' selection in the cross-sectional analysis. After exclusions, 2423 men aged 20-73 years-old and eligible for the annual examination in 2009 with complete covariate data were recruited. According to the fasting glucose and history of diabetes, the subjects were categorized into normal (n= 1794), IFG (n=556) and T2DM (n= 73). Besides, the participants were divided into Non-IR (n=1947) and IR (n=403) on the basis of homeostasis model assessment algorithm.

The general characteristics of 2423 participants were showed in Table 1. The median age of normal, IFG and T2DM group was respect to 35 (interquartile range (IQR): 28.00-42.00), 40 (IQR: 32.50-47.50) and 47 (IQR: 38.50-55.50), P<0.001.The serum ALT levels of T2DM and IFG groups were obviously higher than that of the normal group (median and IQR: 45.00 (32.00-58.00) vs. 43.00(30.50-55.50) *vs.* 38.00 (27.00-49.00) U/L, P=0.024).A significant rising ALT trend between Non-IR and IR was observed in Figure 2 (median and IQR: 37.00 (29.00-49.00) *vs.* 54.00 (43.00-75.00) U/L, respectively, P<0.001). Besides, compared to subjects who were normal, subjects of IFG and T2DM had higher TP, BMI, WC, CHOL, TRIG and LDL, (all P<0.001).

Partial correlation coefficients

Table 2 provided the age-adjusted spearman partial correlation coefficients between log10 (GLU), log10 (HOMA-IR) and other

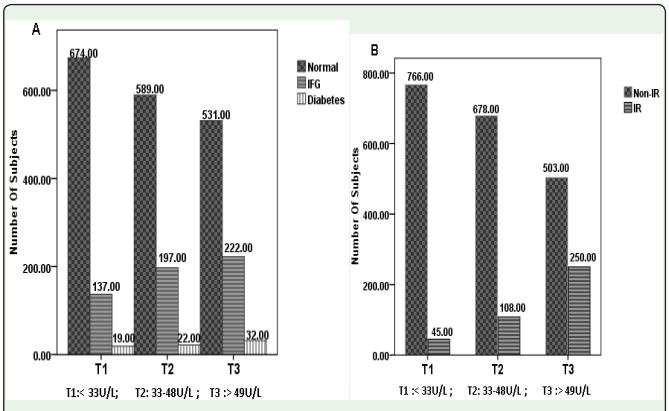

Figure 3: The participants distributed in each ALT tertile. T1=the first tertile; T2=the second tertile; T3=the last tertile. ALT, alanine aminotransferase; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus; Non-IR, non-insulin resistance; IR, insulin resistance.

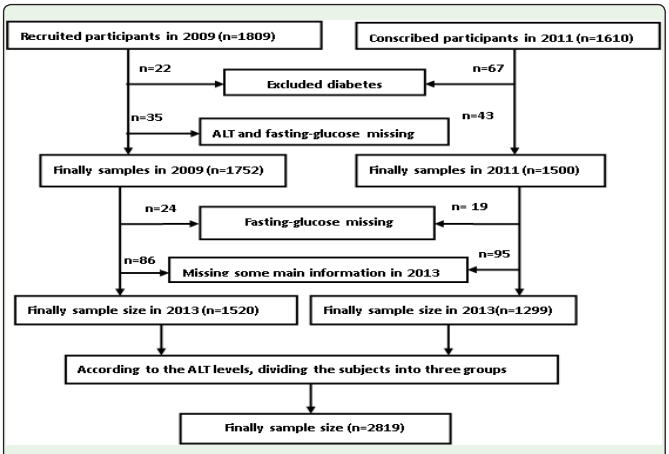

Figure 5: Flow chart of recruitment in the prospective study. ALT, alanine aminotransferase.

Table 4: Odds Ratios (ORs) and 95% CI for ALT with HOMA-IR according to the tertile of ALT: a binary logistic regression model.

		Model1	P	Model2	P	Model3	P
HOMA-IR	T1	1		1		1	
	T2	2.71(1.89-3.90)	<0.001	2.67(1.86-3.85)	<0.001	1.57(1.08-2.28)	0.018
	T3	8.46(6.04-11.85)	<0.001	8.49(6.06-11.89)	<0.001	3.12(2.18-4.47)	<0.001

Model 1was unadjusted;
Model 2 was adjusted for age;
Model 3 was further adjusted for age, CHOL, LDL, HDL, TRIG, TP, ALB, smoking status, drinking status and family history
HOMA-IR, Homeostasis Model Assessment Algorithm of Insulin; CHOL: Cholesterol; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; TRIG: Triglycerides; TP: Total Protein; ALB: Albumin.

Table 5: Hazards Ratios (HRs) and 95% CI for the incidence of the diabetes according to tertile groups of serum ALT.

	Total Number	New diabetes	HR	Confidence Interval(CI)	P
ALT T1	936	28(2.99%)	1		
ALT T2	939	33(3.51%)	1.24	(0.73-1.09)	0.427
ALT T3	944	38(4.03%)	1.67	(1.00-2.75)	0.052

The HRs were adjusted for age, CHOL, LDL, HDL, TRIG ,TP, ALB, smoking status, drinking status and family history; CI: Confidence Interval; CHOL: Cholesterol; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; TRIG: Triglycerides; TP: Total Protein; ALB: Albumin.

variables. Log10 (ALT) was positively correlated to log10 (GLU) (r=0.089, P<0.001) after adjusting for age. We also observed a strong positive correlation between log10 (ALT) and log10 (HOMA-IR), (r=0.345, P<0.001). Moreover, the significant correlations between log10 (GLU), log10 (HOMA-IR) and other variables relating to T2DM were also presented, (P<0,001).

Associations of IFG, IR and T2DM with ALT

Figure 3 showed the number of the participants distributing in each tertile. It presented an unanalogous trends from the first tertile to the last tertile in the normal (T1 to T3: n=674,589 and 531), IFG (T1 to T3: n=137,197 and 222) and T2DM (T1 to T3: n=19, 22 and 32) groups. Besides, from the first tertile to the last tertile, the subjects with Non-IR decreased by degree (T1 to T3: n=766,678 and 503), whereas the IR group increased obviously (T1 to T3: n=45,108 and 250).

As showed in Table 3, increasing ORs for IFG and T2DM groups were observed from 1st to 3rd ALT tertiles by multivariate logistic regression. With the first tertile (T1) as reference, subjects in the highest tertile (T3) had an odd ratios (OR) of 2.06 for IFG [95%CI: 1.62-2.62, P<0.001], 2.14 for T2DM [95% CI: 1.20-3.83, P=0.01], respectively in the unadjusted model. Compared with the subjects in T1, those in the T3 had an OR of 1.73 [95% CI: 1.33-2.26, P=0.002] for IFG and 2.05 [95% CI=1.05-3.97, P=0.035] for T2DM after adjusting for age, TRIG, CHOL, LDL, HDL, TP, ALB, smoking status, drinking status and family history (model 3). Moreover, increasing ORs for IR were observed from T1 to T3 by binary logistic regression. The ORs of IR with respect to T2, T3 were 1.57 [95% CI: 1.08-2.28, P=0.018], 3.12 [95% CI: 2.18-4.47, P<0.001] after further gradually multifariously adjusting (P<0.001) (Table 4). In the line chart for the regression analysis among those in the tertiles of ALT after confounders adjusting (Figure 4), the odds of IFG, IR and T2DM were increased gradually from T1 to T3.

Longitudinal analysis

Figure 5 showed the recruitment in the longitudinal study. Excluding 22 subjects who were T2DM, 1752 participants were included in the cohort study in 2009. After 4 years follow-up, excepting for the participants who lacked some important information or loss to follow-up, the finally samples in the longitudinal study in 2013 were 1520. Similarly, 1500 subjects without T2DM were newly enrolled in 2011 and 1299 men were available in the last research in 2013. We investigated by combining with the two periods follow-up examination. After the follow-up periods, 2720 (96.49%) participants still had normal fasting blood glucose, while 99 (3.51%) participants developed T2DM.

Table 5 presented the HRs and 95% CI for the T2DM incidence and the new cases scattering in each tertile. The incidence of T2DM increased gradually from T1 to T3 (2.99%, 3.51% and 4.03%). Compared with the T1 (referent), the HR of T2DM was 1.24 [95% CI=0.73-1.09, P=0.427] in T2 and 1.67 [95% CI: =1.00-2.75, P=0.052] in T3 after multiple adjustment.

Discussion

To best of our knowledge, this was a large cohort study to investigate the associations between ALT, IFG, IR and the T2DM at the same time in Chinese men population. IFG were united in wedlock with IR to explore the relationship between ALT and prediabetes. Both IFG and IR were significantly bound up with ALT and increased ALT predicted a bordline significant risk for diabetes development.

In the age-adjusted spearman partial correlations, both IFG and IR had positive correlations with ALT, of which the correlation between ALT and IR was pronounced. Significant interrelation between ALT and risk for IFG and IR were observed in the regression analysis. Similarly, In the Thailand's and Chinese population study, they also found that the participants who were IFG had significant higher baseline ALT levels than the normal person [18,23]. Another study recommended that the serum ALT concentrations were prospectively connected with a decline in hepatic insulin sensitivity [24], which was closely correlated to glucose tolerance. In animal model, the hyperinsulinemia leading to the IR by means of repressing the liver gluconeogenesis, characterized by down-regulating the mRNA for IRS-2 and stimulating production of SREBP-1c resulting in activating fatty acid synthesis [25], which might be the reason that the elevated serum ALT levels were interrelated with IFG and IR in our results.

We further examined the nexus between serum ALT concentrations and T2DM incident in the longitudinal study. Serum ALT levels were positively associated with a risk of T2DM in men even after adjusting for potential confounders. What's more, we demonstrated

that the elevation of serum ALT concentrations predicted the T2DM occurrence. In accordance with a study in Florence [26], we also detected that the diabetic group had a higher ALT than the normal group and the serum ALT was positively associated with T2DM. In the late 1980s, after follow-up in a cohort of 766 Swedish subjects, the investigators reported that baseline ALT was a predictor of the incidence of T2DM with a significant risk for men's participants [27]. In addition, our present study was in line with the growing studies which proposed the association between ALT and the risk of incident T2DM [28-30]. However, a study proposed that the ALT level was no longer significantly associated with type 2 diabetes when gamma-glutamyltransferase (γ -GT) activity was taking into account [31]. In China, there was a literature reported that serum levels of GGT were more closely correlated to the onset of T2MD than the level of ALT or AST [16]. The measurements of our present study did not include γ -GT, so we could not control its potential influence in this analysis.

In routine clinical practices, the simplicity and availability of ALT measurement suggested that this enzyme activity could be included in future diabetes prediction algorithms [32]. In the present study, the increased serum ALT levels were closely related to IFG and HOMA-IR, and were risk factors for T2DM development. Perhaps the serum ALT levels can be used as one of the indices to screen the people who are in a certain condition of the high risk state of prediabetes or diabetes, and to investigate that which areas are in a high risk of diabetes in epidemiological research. However, more future investigations in China should be conducted to explore the feasibility and reliability of using liver enzymes to detect diabetes for the influence of other diseases.

Nevertheless, several potential limitations of this study should be considered. Firstly, after 4-year followed up in our prospective study, we found that only 99 (3.51%) subjects had developed T2DM, which were relatively lower than other studies in China [33,34].This might be due to the young people accounting for the majority of all participants, of which 1487 (61.37%) subjects younger than 40 years old. Another explanation might be that diabetes was slow development during the early period of abnormal glucose metabolism [23], so a longer time of follow-up study should be conducted. Secondly, our present study performed only in Chinese men. Finally, we had only tested the ALT levels in the liver enzymes and thus more liver enzymes should be measured in the future research.

Conclusion

Our analysis provided clear evidence of an independently elevated serum ALT concentrations predisposing to IFG, IR and T2DM at the same time. Thus, elevated levels of ALT were associated with an increased incidence of diabetes in men. This association remained significant after multifariously adjustments.

Acknowledgement

The work described in this article is supported by grants from the National Natural Science Foundation of China (Grant No. 81472962, 81460159, 81260130), Guangxi Science Fund for Distinguished Young Scholars (2012GXNSFFA060009) and the Guangxi Natural Science Foundation (2014GXNSFBA118150). Guangxi science and technology development project (1355007-1); and Program for New Century Excellent Talents in University (NCET-12-0653).The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Zengnan Mo and Xiaobo Yang had full access to all of the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis and the decision to submit for publication. Aihua Tan wrote the protocol and reviewed the manuscript. Yuzhen Huang reviewed the protocol, gathered data, performed data analysis and wrote the manuscript. Yawen Luo, Qin Tang, Yan Tang and Jinling Xie reviewed the protocol and reviewed the manuscript. Yong Gao, Zheng Lu and Chunlei Wu gathered data and reviewed the manuscript. Ziting Yao and Yonghua Jiang reviewed the manuscript. Haiying Zhang reviewed the protocol, gathered data and reviewed the manuscript. All authors have approved the final version of the manuscript. We thank all the participants who volunteered to take part in this study, all members of the FAMHES cohort research team, the nurses and administrators in Fangchenggang First People's Hospital, Fangchenggang, China. We also like to thank the editors and proofreaders who review our essay.

References

1. Clark JM, Brancati FL, Dieh AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol. 2003; 98: 960-967.
2. Yu AS, Keeffe EB. Elevated AST or ALT to nonalcoholic fatty liver disease: accurate predictor of disease prevalence? Am J Gastroenterol. 2003; 98: 955-956.
3. Pearce SG, Thosani NC, Pan JJ. Noninvasive biomarkers for the diagnosis of steatohepatitis and advanced fibrosis in NAFLD. Biomark Res. 2013; 1: 7.
4. Polyzos SA, Kountouras J, Zavos C. Nonalcoholic fatty liver disease: the pathogenetic roles of insulin resistance and adipocytokines. Curr Mol Med. 2009; 9: 299-314.
5. Socha P, Wierzbicka A, Neuhoff-Murawska J, Włodarek D, Podleśny J, Socha J. Nonalcoholic fatty liver disease as a feature of the metabolic syndrome. Rocz Panstw Zakl Hig. 2007; 58: 129-137.
6. Targher G. Non-alcoholic fatty liver disease, the metabolic syndrome and the risk of cardiovascular disease: the plot thickens. Diabet Med. 2007; 24: 1-6.
7. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology. 2003; 37: 917-923.
8. Mor A, Svensson E, Rungby J, Ulrichsen SP, Berencsi K. Modifiable clinical and lifestyle factors are associated with elevated alanine aminotransferase levels in newly diagnosed type 2 diabetes patients: results from the nationwide DD2 study. Diabetes Metab Res Rev. 2014; 30: 707-715.
9. Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/ American Heart Association conference on scientific issues related to definition. Circulation. 2004; 109: 433-438.
10. Schindhelm RK, Dekker JM, Nijpels G, Stehouwer CD, Bouter LM. Alanine aminotransferase and the 6-year risk of the metabolic syndrome in Caucasian men and women: the Hoorn Study. Diabet Med. 2007; 24: 430-435.
11. Schindhelm RK, Diamant M, Bakker SJ, van Dijk RA, Scheffer PG, Teerlink T, et al. Liver alanine aminotransferase, insulin resistance and endothelial dysfunction in normotriglyceridaemic subjects with type 2 diabetes mellitus. Eur J Clin Invest. 2005; 35: 369-374.
12. Oh SY, Cho YK, Kang MS, Yoo TW, Park JH. The association between increased alanine aminotransferase activity and metabolic factors in nonalcoholic fatty liver disease. Metabolism. 2006; 55: 1604-1609.
13. Al-Jameil N, Khan FA, Arjumand S, Khan MF, Tabassum H. Associated liver enzymes with hyperlipidemic profile in type 2 diabetes patients. Int J Clin Exp Pathol. 2014; 7: 4345-4349.

14. Loureiro C, Martínez-Aguayo A, Campino C, Carvajal C, Fardella C. [Hepatic steatosis as diabetes type 2 predictor]. Nutr Hosp. 2014; 29: 350-358.

15. Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Hepatic enzymes, the metabolic syndrome, and the risk of type 2 diabetes in older men. Diabetes Care. 2005; 28: 2913-2918.

16. Ma X, Wang Q, Qin G, Zhao Y, Zhang Y. [The correlation study of liver enzymes level and risk of type 2 diabetes]. Zhonghua Nei Ke Za Zhi. 2014; 53: 198-201.

17. Zhou J, Mo Y, Li H, Ran X, Yang W. Alanine aminotransferase is associated with an adverse nocturnal blood glucose profile in individuals with normal glucose regulation. PLoS One. 2013; 8: e56072.

18. Qin G, Lu L, Xiao Y, Zhu Y, Pan W, Xu X, et al. A cross-sectional study of the relationship between serum liver enzymes level and the incidence of impaired fasting glucose in males and females. Med Sci Monit. 2014; 20: 1319-1325.

19. Gao Y, Wang M, Zhang H, Tan A, Yang X. Are metabolic syndrome and its components associated with lower urinary tract symptoms? Results from a Chinese male population survey. Urology. 2012; 79: 194-201.

20. Shiels MS, Rohrmann S, Menke A, Selvin E, Crespo CJ. Association of cigarette smoking, alcohol consumption, and physical activity with sex steroid hormone levels in US men. Cancer Causes Control. 2009; 20: 877-886.

21. Kerner W, Brückel J. German Diabetes Association. Definition, classification and diagnosis of diabetes mellitus. Exp Clin Endocrinol Diabetes. 2014; 122: 384-386.

22. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28: 412-419.

23. Jiamjarasrangsi W, Sangwatanaroj S, Lohsoonthorn V, Lertmaharit S. Increased alanine aminotransferase level and future risk of type 2 diabetes and impaired fasting glucose among the employees in a university hospital in Thailand. Diabetes Metab. 2008; 34: 283-289.

24. Vozarova B, Stefan N, Lindsay RS, Saremi A, Pratley RE. High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. Diabetes. 2002; 51: 1889-1895.

25. Shimomura I, Matsuda M, Hammer RE, Bashmakov Y, Brown MS. Decreased IRS-2 and increased SREBP-1c lead to mixed insulin resistance and sensitivity in livers of lipodystrophic and ob/ob mice. Mol Cell. 2000; 6: 77-86.

26. Monami M, Bardini G, Lamanna C, Pala L, Cresci B. Liver enzymes and risk of diabetes and cardiovascular disease: results of the Firenze Bagno a Ripoli (FIBAR) study. Metabolism. 2008; 57: 387-392.

27. Ohlson LO, Larsson B, Björntorp P, Eriksson H, Svärdsudd K. Risk factors for type 2 (non-insulin-dependent) diabetes mellitus. Thirteen and one-half years of follow-up of the participants in a study of Swedish men born in 1913. Diabetologia. 1988; 31: 798-805.

28. Hanley AJ, Williams K, Festa A, Wagenknecht LE, D'Agostino RB. Elevations in markers of liver injury and risk of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes. 2004; 53: 2623-2632.

29. Goessling W, Massaro JM, Vasan RS, D'Agostino RB, Ellison RC. Aminotransferase levels and 20-year risk of metabolic syndrome, diabetes, and cardiovascular disease. Gastroenterology. 2008; 135: 1935-1944.

30. Kunutsor SK, Apekey TA, Walley J. Liver aminotransferases and risk of incident type 2 diabetes: a systematic review and meta-analysis. Am J Epidemiol. 2013; 178: 159-171.

31. André P, Balkau B, Born C, Royer B, Wilpart E. 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 (Data from an Epidemiological Study on the Insulin Resistance syndrome). Diabetes Metab. 2005; 31: 542-550.

32. Sattar N, Scherbakova O, Ford I, O'Reilly DS, Stanley A, Forrest E, et al. Elevated alanine aminotransferase predicts new-onset type 2 diabetes independently of classical risk factors, metabolic syndrome, and C-reactive protein in the west of Scotland coronary prevention study. Diabetes. 2004; 53: 2855-2860.

33. Dong Y, Gao W, Nan H, Yu H, Li F. Prevalence of Type 2 diabetes in urban and rural Chinese populations in Qingdao, China. Diabet Med. 2005; 22: 1427-1433.

34. Xu L, Jiang CQ, Schooling CM, Zhang WS, Cheng KK, Lam TH. Prediction of 4-year incident diabetes in older Chinese: Recalibration of the Framingham diabetes score on Guangzhou Biobank Cohort Study. Prev Med. 2014; 69: 63-68.