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Relationship between alanine aminotransferase levels and metabolic syndrome in nonalcoholic fatty liver disease

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Abstract: Objective: To investigate the relationship between alanine aminotransferase (ALT) levels and metabolic syndrome (MS) in nonalcoholic fatty liver disease (NAFLD). Methods: A total of 26527 subjects who received medical health checkup in our hospital from January 2005 to July 2007 were enrolled in the study. The diagnosis of fatty liver was based on ultrasound imaging. MS was defined according to the criteria of the Adult Treatment Panel III. ALT, triglyceride (TG), high density lipoprotein cholesterol (HDL-c), fasting plasma glucose (FPG), height, weight, waist circumference (WC), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in each subject to analyze the relationship between MS and ALT activity. Results: (1) The prevalence of NAFLD in men (30.94%) was significantly higher than that in women (15.65%); (2) The incidence of MS in NAFLD (33.83%) was significantly greater than that in non-NAFLD (10.62%); (3) Of the 6470 subjects with NAFLD, in the age-adjusted partial correlation analysis, there were statistically significant correlations between the ALT levels and most metabolic risk factors in each sex (P<0.01), except that ALT levels had no correlation with HDL-c in women. Moreover, in the multiple stepwise regression analysis, SBP lost its significance, and WC, body mass index (BMI), age, DBP, TG and FPG were independently associated with ALT levels in both sexes (P<0.05). HDL-c remained significant and was independently related to ALT levels in men; (4) ALT levels were significantly higher in subjects with MS compared to those without MS (P<0.001). Mean ALT levels increased with the number of MS components in each sex (P<0.05 for trend). Conclusion: We found a strong relationship between ALT levels and MS in NAFLD and revealed that the cluster of MS components might be the predictor for ALT elevations.

Key words: Nonalcoholic fatty liver disease (NAFLD), Alanine aminotransferase (ALT), Metabolic syndrome (MS)
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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common chronic liver disease that has been shown to progress to fibrosis, cirrhosis and liver failure (Saadeh, 2007). The prevalence of NAFLD is reported to be in the 3%~24% range in the general population in various countries, which is increasing in parallel with the increased prevalence of obesity (Clark, 2006; Chitturi *et al*., 2007; Ong and Younossi, 2007). Most individuals with NAFLD are asymptomatic. However, patients with NAFLD are commonly characterized by elevated circulating concentrations of markers of liver injury, including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyltransferase (GGT) (Clark *et al*., 2003). Of these liver enzymes, ALT is most closely related to liver fat accumulation, and is often used in epidemiological studies as a surrogate marker for NAFLD (Schindhelm *et al*., 2006). Elevated plasma ALT levels are associated with obesity and the MS (Marchesini *et al*., 2005; Oh *et al*., 2006), whose central features are abdominal obesity, dyslipidemia, hypertension and hyperglycemia. In addition, some prospective epidemiological studies have demonstrated that high activity of ALT, independent of age, obesity and

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alcohol intake, is associated with the occurrence of type 2 diabetes mellitus and the MS (Hanley *et al*., 2005; Schindhelm *et al*., 2007; Doi *et al*., 2007; Fan *et al*., 2007). However, few studies have been made in a large adult population in China. In this study, we have examined the association between ALT levels and MS in NAFLD in the country.

MATERIALS AND METHODS

Subjects and measurements

The initial study population consisted of 32979 Chinese adults (aged 20~70 years, 19417 men and 13562 women) who visited Health Promotion Center of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China, for a medical health checkup from January 2005 to July 2007. All subjects ate a bland diet during three days before they received their examination. Information on medical history and lifestyle characteristics was obtained from all subjects by questionnaire. We excluded subjects who were taking any medication known to alter the blood pressure, lipid profile, liver enzymes or plasma glucose. A total of 26527 subjects were entered into the final analysis. The ethics committee of Sir Run Run Shaw Hospital approved the study.

Trained medical personnel took anthropometric measures: weight, height and waist circumference (WC). Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Blood pressures were measured according to the guidelines by Revision Committee of the Chinese Guidelines on Prevention and Treatment of Hypertension (2004). Blood samples were drawn after 12 h of fasting and were subsequently measured at the certified laboratory in our hospital. Plasma concentrations of glucose, total cholesterol, triglyceride (TG), high density lipoprotein cholesterol (HDL-c) and ALT were measured with an autoanalyzer. Hepatitis B surface antigen (HBsAg) and antibody to hepatitis C virus (HCV-Ab) were tested by using the direct sandwich enzyme-linked immunosorbent assay (ELISA) method. Abdominal ultrasonography was performed to detect the presence of fatty infiltration in the liver by physicians specializing in image diagnostic, all of whom used standard criteria in evaluating the images for hepatic fat (Sanyal, 2002).

Diagnosis criteria

We defined NAFLD according to the guidelines issued by Fatty Liver and Alcoholic Liver Disease Study Group of the Chinese Liver Disease Association (2006), which was based on the combination of medical history, clinical symptoms, laboratory and ultrasonography findings. Subjects who had been known as having liver disease and alcohol intake >140 g/week for men and >70 g/week for women were excluded. Regarding liver disease, subjects positive for HBsAg or HCV-Ab and those who reported a history of known liver disease, including viral, genetic, autoimmune, and drug-induced liver disease, were also excluded (Brunt, 2005). In this study, no subject underwent liver biopsy.

The diagnosis of fatty liver was used according to the standard criteria accepted by the American Gastroenterology Association (Clark and Diehl, 2003): liver and kidney echo discrepancy, presence of an increased liver echogenicity (bright), echo penetration into the deep portion of the liver, and vessel blurring and narrowing of the lumen of hepatic veins in the absence of findings suggestive of other chronic liver diseases (Sanyal, 2002).

MS was diagnosed by the Adult Treatment Panel III (ATP III) definition. Participants having ≥3 of the following 5 criteria were defined as having MS: (1) a WC >102 cm for males or >88 cm for females, (2) serum TG levels ≥150 mg/dl, (3) serum HDL-c levels <40 mg/dl for males or <50 mg/dl for females, (4) systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg, and (5) a fasting plasma glucose (FPG) ≥110 mg/dl (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002).

Statistical analysis

The statistical analysis was conducted using SPSS version 13.0 statistical software. All reported *P*-values were two-sided, and $P \leq 0.05$ was considered statistically significant. Descriptive data are expressed as mean±*SD*. Comparisons between the quantitative data were done by Student's *t*-tests and categorical variables were done by χ^2 tests.

Age-adjusted partial correlation analysis was performed in NAFLD to determine the relationship

between ALT levels and the MS components in men and women separately. To further examine the association between ALT levels and the MS components, we performed the following analyses. Multiple stepwise regression analysis with the ALT levels as the dependent variables and components of MS and age as the independent variables was used to identify significant predictors for ALT levels in each sex. Subjects with different numbers of MS components were grouped into 6 subgroups graded by Nos. 0~5. Means of ALT concentrations were then calculated for each subgroup by means of a multiple linear regression model, with adjustment for age in both sexes. After subjects were grouped into those with and without MS, the means of ALT concentrations were calculated by means of a multiple general linear regression model.

RESULTS

The 26527 subjects (15162 men and 11365 women) were entered into the final analysis. Mean age and BMI were 47.41 years (*SD* 10.13, range 20 to 70 years) and 23.22 kg/m^2 (*SD* 2.59, range 15.38 to 39.81 kg/m^2), respectively. The baseline characteristics and prevalence of the NAFLD of the 26527 subjects are summarized in Table 1. Mean age and mean BMI were the same for both sexes. ALT, WC, SBP, DBP, FPG and TG levels in men were significantly higher and HDL-c levels in men were lower than those in women (P<0.001). Compared with women, men had a higher prevalence of NAFLD (P<0.001).

Table 1 Baseline characteristics and prevalence of the NAFLD by sex (n=26527)

Characteristics	Male	Female	P
n	15162	11365	
Age (years)	47.52±11.34	47.31±10.97	0.084
WC (cm)	84.01±9.06	79.62±8.83	<0.001
BMI (kg/m^2)	23.13±2.52	23.47±2.68	0.722
TG (mg/dl)	121.91±99.23	102.23±89.16	<0.001
HDL-c (mg/dl)	48.45±13.28	52.34±10.59	<0.001
FPG (mg/dl)	100.83±26.85	97.28±23.72	<0.010
SBP (mmHg)	127.64±16.47	122.98±19.22	<0.001
DBP (mmHg)	81.12±10.36	74.62±9.98	<0.001
ALT (U/L)	30.92±22.78	22.64±15.66	<0.001
NAFLD (%)	30.94	15.65	<0.001

Of the 26527 subjects, 6470 subjects were diagnosed as having NAFLD. After matching based on the sex, age and BMI confounding factors, of the 20057 subjects without NAFLD, 7140 subjects were chosen as controls. As shown in Table 2, the incidence of MS in NAFLD was 33.83%, which was significantly higher than that in non-NAFLD controls (χ^2=1067.91, P<0.001). In NAFLD, plasma ALT levels in men [(41.22±24.47) U/L] were higher than those in women [(30.89±19.87) U/L]. Using a bivariate correlation analysis among ALT levels and age, we found that the ALT levels were significantly correlated with age in both sexes (r=−0.234 in men and r=0.085 in women, P<0.05). Among the subjects younger than 50 years old, the mean of ALT levels in men was significantly higher than that in women (P<0.01), but in subjects older than 50 years the case was just the opposite (P<0.05) (Fig.1).

Table 2 Incidence of metabolic syndrome in NAFLD and non-NAFLD

Characteristics	MS	Non-MS	Total	Incidence (%)
NAFLD	2189	4281	6470	33.83
Non-NAFLD	787	6353	7140	10.62

χ^2=1067.91; P<0.001

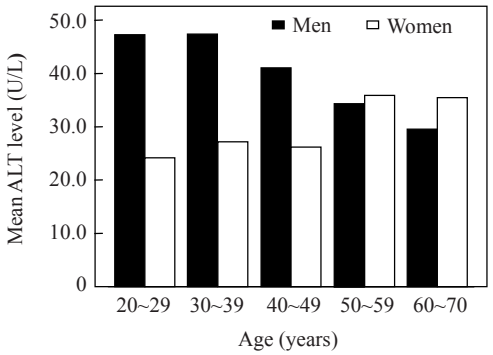

Fig.1 Mean ALT levels stratified by age group and sex

Of the 6470 subjects with NAFLD, using an age-adjusted partial correlation analysis, we found that there were statistically significant correlations between the ALT levels and most metabolic risk factors in each sex (P<0.01), except that ALT levels had no correlation with HDL-c in women (Table 3). Moreover, multiple stepwise regression analysis was performed with the ALT levels as the dependent variables, and with the values of all MS components

and age as the independent variables in each sex (Table 4). SBP lost its significance and WC, BMI, age, DBP, TG and FPG were independently associated with ALT levels in both sexes (P<0.05). HDL-c remained significant and was independently related to ALT levels in men.

Table 3 Pearson's correlation coefficients (r) between ALT levels and MS components in NAFLD after adjustment for age

Characteristics	Male		Female	
	r	P	r	P
BMI	0.396	<0.01	0.269	<0.01
WC	0.332	<0.01	0.301	<0.01
TG	0.106	<0.01	0.112	<0.01
HDL-c	−0.112	<0.01	−0.062	0.061
FPG	0.102	<0.01	0.149	<0.01
SBP	0.119	<0.01	0.198	<0.01
DBP	0.154	<0.01	0.220	<0.01

Table 4 Standardized regression coefficients (beta) from the multiple linear regression analysis of ALT level in relation to the indicated variables in NAFLD

Indicated variables	Male		Female	
	Beta	P	Beta	P
Age	−0.226	<0.01	0.068	<0.05
BMI	0.112	<0.01	0.120	<0.01
WC	0.203	<0.01	0.215	<0.01
TG	0.091	<0.01	0.107	<0.05
HDL-c	−0.073	<0.01	0.009	0.783
FPG	0.096	<0.01	0.102	<0.01
SBP	0.007	0.254	0.028	0.364
DBP	0.052	<0.01	0.106	<0.01

In 6470 subjects with NAFLD, the number of those with 0, 1, 2 and ≥3 MS components were 726 (11.22%), 1902 (29.40%), 1653 (25.55%) and 2189 (33.83%), respectively. The mean ALT value in subjects with MS was 45.75 U/L (SD 27.84), which was significantly higher than that in subjects without MS (mean 36.36 U/L, SD 21.43, P<0.001). Fig.2 shows mean ALT levels according to the number of MS components in each sex. The greater the number of MS components presented, the higher the ALT values were (P<0.05).

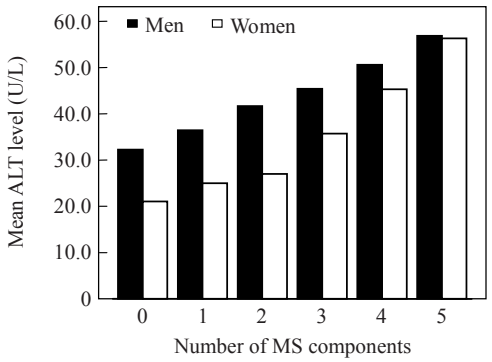

Fig.2 Mean ALT levels according to the number of metabolic syndrome (MS) components by sex

DISCUSSION

NAFLD is being increasingly recognized as one of the major causes of chronic liver disease in Western countries and also in the developing countries (Clark, 2006; Chitturi *et al*., 2007; Ong and Younossi, 2007). Recently, NAFLD is considered to be the hepatic component of MS (Tarantino *et al*., 2007). In addition, some studies have demonstrated that ALT is associated with risks of type 2 diabetes mellitus and MS (Schindhelm *et al*., 2007; Doi *et al*., 2007). However, very little progress has been made in a large adult population in China. The purpose of our study was to investigate the association between ALT levels and MS in NAFLD.

In China, previous studies reported that the prevalence of the MS is 6.6% to 13.8% in the general population (Gu *et al*., 2005; Yao *et al*., 2007). In the present study, we found that, according to the ATP III definition, MS was more common among subjects with NAFLD (33.83%), based on liver ultrasonography, compared with subjects without NAFLD (10.62%). Similar findings have also been reported in previous studies (Clark, 2006; Oh *et al*., 2006). Our result supports that NAFLD is associated with the MS.

ALT is an indicator of liver injury and often used as a surrogate marker for NAFLD (Schindhelm *et al*., 2006). However, the exact pathogenesis of raised ALT in NAFLD remains unclear. Current understanding of the progression of NAFLD involves a "2-hit" hypothesis. The first hit involves accumulation of excess fat in the hepatic parenchyma. This step has been linked to insulin resistance associated with

MS, modulated mainly by adipocytokines and dysfunction of cellular TG synthesis and transport. On the basis of the first hit event, oxidation stress as a second hit event caused by reactive oxygen species (ROS) induces necroinflammation in the fatty liver (Adams *et al*., 2005; Bugianesi *et al*., 2005; Utzschneider and Kahn, 2006). Vozarova *et al*.(2002) reported that serum ALT concentrations were related to hepatic insulin resistance and suggested that a raised ALT reflects fatty changes in the liver. Oh *et al*.(2006) investigated the association between increased ALT activity and the metabolic factors in NAFLD, in which MS was defined by the new International Diabetes Federation (IDF) definition. They found that central obesity, raised TG, reduced HDL-c and raised FPG are MS components that contributed to increased ALT activity. Schindhelm *et al*.(2007) also reported that ALT was associated with risk of the MS in a general population of middle-aged Caucasian men and women after 6.4 years follow-up. In this study, among NAFLD subjects, we found that there were statistically significant correlations (P<0.001) between the ALT levels and most metabolic risk factors. By multiple stepwise regression analysis we also observed that TG, FPG, BMI, WC, DBP and deceased HDL-c, which were components of MS, were associated with ALT levels in NAFLD subjects. Furthermore, mean ALT levels increased according to the number of MS components and ALT values in subjects with MS were significantly higher compared to those without MS. These might be explained that in NAFLD, the elevation of ALT levels might be the expression of excess deposition of fat in the liver as the result of various metabolic conditions and reflect ongoing inflammation which impairs insulin signaling both in the liver and in the entire body (Schindhelm *et al*., 2005; Machado and Cortez-Pinto, 2006; Tarantino *et al*., 2007). Therefore, our results demonstrate a strong relationship between ALT levels and MS in NAFLD. NAFLD may be regarded as the hepatic manifestation of the MS. It is also implicated that the cluster of MS components might be the predictor of ALT elevations in subjects with NAFLD.

Although NAFLD is found to be closely related to metabolic disorders, it is interesting to be noted that a significant number of subjects with NAFLD (11.22%) have no features of MS defined by ATP III in our study. One contributing factor may be that the definition of central obesity using WC in ATP III criteria for the MS may not be appropriate for Asians, which may underestimate the subjects at risk in this study. It has been recognized that obesity-related metabolic disorders commence at much lower levels of BMI in Asians. Studies on body fat have shown that Asians have higher percentage adiposity at a lower BMI than Caucasians (Fan and Peng, 2007). In previous studies, at lower BMI and WC, increased risk of having obesity-related cardiovascular risk factors was found in Asians (Lin *et al*., 2002; Thomas *et al*., 2004; Wildman *et al*., 2004). Given the importance of MS in the diagnosis of NAFLD and the discrepancies in various criteria for MS, further work is needed to explore different criteria in all the subjects to determine which criterion best defines the MS in Asians. Another possible factor is that the possibility of residual confounding effects still exists in subjects with NAFLD because we obtained medical history and lifestyle characteristics with a simple questionnaire so that we were not able to exclude the possible presence of other rare causes of liver disease.

Our results show that the incidence of NAFLD in men (30.94%) was much higher than that in women (15.65%), and that in NAFLD men had higher ALT levels compared with women, except for the population of 50 years old or older. These results are consistent with those of previous studies and indicate that NAFLD is more prevalent in males (Schwimmer *et al*., 2005; Arun *et al*., 2006; Zelber-Sagi *et al*., 2006). The pathogenic mechanism may be that men generally have greater abdominal visceral fat mass, which seems to be an important risk factor for NAFLD, even in patients with a normal BMI (Garcia-Monzón *et al*., 2000). Compared with adipose tissue in other sites, visceral adipose tissue is more resistant to insulin, exhibits greater lipolysis, and produces more free fatty acids (Kabir *et al*., 2005). Moreover, we observed the peak levels of ALT in women older than 50 years, which might be due to the menopausal status and lack of physical exercise in this period of time. It may, therefore, suggest that the prevention of NAFLD is more important for men and postmenopausal women.

In conclusion, we found a strong relationship between ALT levels and MS in patients with NAFLD and revealed that mean ALT levels increased with the number of MS components. These findings suggest

that the cluster of MS components might be the predictor for ALT elevations in NAFLD. One of the limitations in the present study is that the diagnosis of fatty liver was based on ultrasound imaging, which was not confirmed by liver biopsy, the gold standard for the assessment of liver histology and a key test to diagnose NAFLD (Brunt, 2005).

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