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Relationship between serum aminotransferase levels and metabolic disorders in northern China

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Background/aims: *Increasing evidence suggests an association between elevated serum aminotransferase levels and metabolic disorders (metabolic syndrome, hyperlipidemia and diabetes mellitus). However, the significance of relatively low levels of aminotransferases in relation to metabolic disorders has not been fully investigated in the general population. We investigated the association between serum aminotransferase levels and metabolic disorders using data from a survey in Jilin Province, China.* ***Materials and Methods:*** *In 2007, a prospective survey was conducted throughout Jilin, China, covering both urban and rural areas. A total of 3835 people, 18-79 years old, were undergoing real-time ultrasonography, blood tests, and interviews with a structured questionnaire.* ***Results:*** *Serum aminotransferase levels within the normal range were associated with metabolic syndrome independent of age, occupation, cultural and educational level, income, body mass index, waist circumference, smoking, and alcohol intake. Compared with the lowest level (<20 IU/L), the adjusted odds ratios for alanine aminotransferase levels of 20-29, 30-39, 40-49, and >50 IU/L were 1.92, 2.50, 2.97, and 3.52 in men, and 1.38, 1.54, 3.06, and 2.62 in women, respectively. Near-normal serum aminotransferase levels associated with hyperlipidemia, non-alcoholic fatty liver disease, and diabetes mellitus were also found in the study.* ***Conclusions:*** *Normal to near-normal serum aminotransferase levels are associated with metabolic disorders. Serum alanine aminotransferase levels of 21-25 IU/L for men and 17-22 IU/L for women are suggested as cut-off levels that detect metabolic disorders affecting the liver.*

Key words: Aspartate aminotransferase, alanine aminotransferase, metabolic disorders, metabolic syndrome, non-alcoholic fatty liver disease

Kuzey Çin'de serum aminotransferaz düzeyleriyle metabolik bozuklukların ilişkisi

Giriş ve Amaç: *Artmış serum aminotransferaz seviyeleriyle, metabolik hastalıklar (metabolik sendrom, hiperlipidemi ve diabetes mellitus) arasında ilişki olduğuyla ilgili giderek artan kanıtlar vardır. Ancak genel popülasyonda nispeten düşük aminotransferaz düzeylerinin metabolik bozukluklarla ilişkisi tamamen araştırılmamıştır. Çin'in Jilin bölgesinde yapılmış bir araştırmadaki bilgiler kullanılarak, serum aminotransferaz düzeyleriyle metabolik bozukluklar arasındaki ilişkiyi araştırdık.* ***Gereç ve Yöntem:*** *2007'de Çin'in Jilin bölgesinde hem kentsel, hem de kırsal bölgeleri kapsayan prospektif bir çalışma yapıldı. 18 ile 79 yaşları arasında 3835 kişiye gerçek zamanlı ultrasonografi, kan testleri ve özel şekillendirilmiş bir anket uygulandı.* ***Bulgular:*** *Normal sınırlar dahilindeki aminotransferaz düzeyleri, yaş, meslek, kültürel ve eğitimsel düzey, gelir, beden kitle indeksi, bel çevresi, sigara ve alkol kullanma durumlarından bağımsız olarak metabolik sendromla ilişkili idi. En düşük düzeyle (<20 IU/L) karşılaştırıldığında, alanin aminotransferaz seviyeleri için odds oranları 20-29, 30-39, 40-49 ve >50 IU/L için sırasıyla erkeklerde 1.92, 2.50, 2.97, ve 3.52; ve kadınlarda 1.38, 1.54, 3.06 ve 2.62 bulundu. Ayrıca çalışmada normale yakın serum aminotransferaz düzeyleri, hiperlipidemi, non-alkolik yağlı karaciğer hastalığı, diabetes mellitus ile ilişkili bulundu.* ***Sonuç:*** *Normale yakın serum aminotransferaz seviyeleri, metabolik bozukluklarla ilişkilidir. Metabolik bozuklukların karaciğeri etkileyip etkilemediğini saptamak için kullanılacak eşik değerin, erkeklerde 21-25 IU/L, ve kadınlarda 17-22 IU/L olması önerilmektedir.*

Anahtar kelimeler: Aspartat aminotransferaz, alanin aminotransferaz, metabolik bozukluklar, metabolik sendrom, non-alkolik yağlı karaciğer hastalığı

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is an increasingly recognized condition, the prevalence of which parallels the recent increase in obesity (1-3). NAFLD has also been associated with metabolic disorders, including central obesity, dyslipidemia, hypertension, and hyperglycemia (4-8). In addition, metabolic syndrome (MS), obesity, and insulin resistance are major risk factors in the pathogenesis of NAFLD (9-12). The coexistence of multiple metabolic disorders is associated with a potentially progressive, severe liver disease. The increasing prevalence of obesity, coupled with diabetes, dyslipidemia, hypertension, and ultimately MS puts a very large population at risk of liver failure (13). Patients with metabolic disorders usually have elevated serum aminotransferase activity, and so aminotransferase assays are widely used to monitor liver function in people with metabolic disorders (14). However, many liver diseases are not detected by the currently defined range of normal serum aminotransferase levels (15,16). The significance of serum aminotransferase levels, including those that are in the normal and near-normal range, needs to be reviewed in relation to the metabolic disorders. Three hundred and eighteen non-diabetic patients with NAFLD were investigated for changes in liver enzymes and to analyze the association between liver enzymes and MS in Shanghai, China (16). However, few large studies have been made in the adult population in China. Accordingly, we investigated the independent association between serum aminotransferase levels and metabolic disorders in a representative population in northern China. Individuals with MS, hyperlipidemia or diabetes mellitus (DM) were defined as having metabolic disorders in the present study.

MATERIALS AND METHODS

Design and Study Population

A prospective survey study of aminotransferase levels and the metabolic disorders was carried out in Dehui, Jilin, China in 2007 (population approximately 800,000). Dehui is located 81 km from Changchun, the largest city in the area. The earnings of most inhabitants of Dehui are in the middle income range. The sex and age distribution of inhabitants are similar to those of the province in general. Therefore, Dehui City is representative of other areas in the province in terms of the quality of life and economic and cultural development.

A two-stage, tiered-system sampling method was used. This survey was comprehensive and included geographic, economic, cultural, and other parameters. There are 308 villages and 51 neighborhood committees in Dehui. The first survey covered rural areas and the second covered urban areas. Each stage was divided into two layers. In the first layer, the populations of the villages or neighborhood committees were sorted, and the villages or neighborhood committees were selected by a computer according to the principle of equidistant random samples of the population size. We selected 9 villages and 11 neighborhood committees. In the second layer, the households were marked by the distance from the center of the villages or neighborhood committees, and they were selected according to the principle of equidistant random samples of the distance. Then, 150-200 or 80-100 households were computer-selected in villages or neighborhood committees, respectively. A sample of the general population in the selected households consisting of individuals who were at least 18 years of age and who had lived in the same area for more than 10 years was selected using a systematic random 1-in-3 sampling procedure from the census list, which had been updated on February 1, 2007.

We defined sample sizes of urban and rural groups according to the formula of estimation of sample size: $N=(t/d)^{2}*(1-p)/p$ (t=1.96, p=0.114 and d=0.1)[4]. They were 1800 and 2700 based on the ratio of urban and rural populations of the area, and the total was 4500 (more than the value of N).

In the end, 4298 people responded and agreed to participate in the study, and their serum samples, demographic information, and behavioral factors were collected.

The response rate was high (95.51%, 4298/4500). When we analyzed the relationship between aminotransferase levels and the metabolic disorders, we excluded 75 people who had abnormal autoantibodies, ceruloplasmin, and iron tests (30, 29, and 16 people, respectively). In addition, 151 people who reported consuming at least 40 g of alcohol per day were excluded. We also excluded 45 hepatitis C virus (HCV)-positive people and 192 hepatitis B virus (HBV)-positive people. In the end, 3835 people (1761 men, 2074 women) were eligible for our analyses.

Data Collection and Blood Sampling

The selected participants were asked to fast over-

night (≥8 h) and attend a local health center for their scheduled appointments. The selected subjects were visited at home if they could not attend the local health center. An interview using a structured questionnaire was conducted at the time of the participant's visit. The questionnaire included the following questions: (1) How long have you been smoking? (2) Do you drink alcohol (the number and type of drinks per day)? (3) What is your occupation (peasant, laborer, small private businessman or cadre official)? (4) How many years did you study? (5) What is your monthly income? and (6) What is your date of birth, sex, and place of residence? Data on demographics (date of birth, sex, place of residence, ethnicity, family size) and behavioral factors (drinking, smoking, occupation, education level, income) were obtained. The study protocol was approved by the Institutional Review Board of the First Hospital of Jilin University. After written informed consent was obtained, blood samples were taken from each participant for seroprevalence analyses. Sera were stored at -20°C until tested at the First Hospital of Jilin University. Anthropometric measurements including height, weight, and waist and hip circumference were conducted by well-trained examiners on individuals wearing light clothing. Waist circumference was measured to the nearest 0.1 cm at the midpoint between the lower borders of the rib cage and the iliac crest. Abdominal ultrasonography (US) was performed to detect the presence of fatty infiltration in the liver by physicians specializing in diagnostic imaging, all of whom used standard criteria in evaluating the images for hepatic fat (17). Fatty liver was diagnosed by concurrence of three ultrasonographers, who were unaware of the subjects' clinical and biochemical status. The results were supplemented by the liver-spleen density gradient (LSDG) determined with the non-contrast abdominal computed tomography (CT) in the local hospital.

Serological Testing

HBsAg, anti-HCV, glucose, total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride, and liver enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were evaluated by standard methods using kits from Ke Hua (Shanghai, China). ANA, ceruloplasmin and iron studies were also assayed by standard methods with kits from Ke Hua (Shanghai, China). All laboratory analyses were performed at the First Hospital of Jilin University.

Definition of the MS, hyperlipidemia, NAFLD, DM

The diagnosis of MS was based on the new International Diabetes Federation definition, (18) in which central obesity is an essential parameter (body mass index [BMI] ≥25). We used a modified waist circumference cut-off of ≥90 cm in men and ≥80 cm in women. MS was then defined in any individuals who had two or more of the four following criteria: 1) high blood pressure (≥130/85 mmHg) or undergoing treatment for high blood pressure with anti-hypertensive medication, 2) elevated fasting blood glucose (≥5.6 mmol/L) or treatment with anti-diabetic medication, 3) hypertriglyceridemia (≥1.7 mmol/L), and 4) low HDL-cholesterol (men, <1.03 mmol/L; women, <1.29 mmol/L).

Individuals having one or more of the four following criteria were defined as having hyperlipidemia: 1) hypertriglyceridemia (>1.7 mmol/L), 2) HDL-cholesterol (men, <1.04 mmol/L; women, <1.3 mmol/ L), 3) LDL-cholesterol (>4.3 mmol/L), and 4) total cholesterol (>6.0 mmol/L).

Individuals having the following criteria were defined as having NAFLD: 1) consuming <40 g alcohol per week, 2) negative for hepatitis B (HBsAg) and hepatitis C, 3) fatty liver based on US and CT, and 4) no other liver disease.

Individuals having the following criterion were defined as having DM: fasting plasma glucose >7.0 mmol/L.

Statistical Analysis

Statistical analyses were performed using SAS software (version 9.0).

Clinical and biochemical characteristics were compared between men and women using the Wilcoxon scores test or chi-square test.

The sex-specific prevalence of abnormal metabolic conditions and MS was correlated to levels of AST and ALT.

Independent associations between serum aminotransferase levels and MS, hyperlipidemia, NAFLD, and DM were investigated using logistic regression models. The independent variables used were age, BMI, smoking, alcohol intake, waist circumference, occupation (peasant/laborer, small private businessman, cadre officials), cultural and educational level (>8 years of study, or ≤8 years of study), and income level (>800 RMB or ≤800 RMB monthly). Drinkers were classified as

regular alcohol drinkers (individuals whose alcohol consumption was >40 g per week for >4 consecutive years), infrequent drinkers, and non-drinkers. Smokers were defined as individuals who smoked 10 or more cigarettes a day for more than four consecutive years. The thresholds for aminotransferase values were generated by receiver operating characteristics (ROC) analysis. A two-sided $p<0.05$ was considered statistically significant.

RESULTS

The clinical characteristics and laboratory data of the 1761 men and 2074 women are shown in Table 1. Compared with women, men had higher ALT, AST levels and metabolic risk factors, except HDL-cholesterol levels, and there was no difference in LDL-cholesterol levels. Smoking and drinking were significantly more common in men than in women.

Serum AST levels were positively associated with all five metabolic abnormalities except glucose in both sexes. On the contrary, serum ALT levels were positively asso-ciated with all five metabolic abnormalities in both sexes except HDL-cholesterol in women (Table 2).

Univariate analysis for the prevalence of MS increased progressively according to the elevated serum ALT levels. The association between elevated ALT levels and the prevalence of MS was attenuated, but was still highly significant in both genders in multivariate analysis. However, elevated AST level was attenuated significantly in both genders ($p>0.05$) except for the 40-49 level in women (Table 3).

In a further analysis, we compared the relative significance of individual liver enzymes by including AST and ALT in the same model. In this model, the prevalence of MS was significantly associated only with elevated ALT levels ($p<0.001$ for both sexes), but not with elevated AST levels (Table 3).

By multivariate analysis, the odds ratios for the prevalence of hyperlipidemia increased progressively according to the increases in serum aminotransferase levels except for ALT in women. Multivariate analysis odds ratios for the prevalence of DM increased progressively according to the increases in serum ALT levels. Univariate analysis odds ratios for the prevalence of NAFLD increased progressively according to increases in serum aminotransferase levels except AST in women (data not shown). The association between ALT level and the prevalence of NAFLD was attenuated, but still highly significant in multivariate analysis (Table 4).

Table 1. Clinical and biochemical characteristics of study participants

Characteristics	Men (n=1761)	Women (n=2074)	*p* value
Median (minimum-maximum)			
Age (yrs)	46.00 (18.00-75.00)	46.00 (18.00-79.00)	>0.05
Body mass index (kg/m²)	24.11 (12.88-54.36)	23.52 (12.11-61.68)	<0.01
Waist circumference (cm)	84.00 (26.00-117.00)	79.00 (27.00-118.00)	<0.01
Systolic blood pressure (mmHg)	130.00 (80.00-230.00)	120.00 (80.00-240.00)	<0.01
Diastolic blood pressure (mmHg)	82.00 (40.00-125.00)	80.00 (40.00-120.00)	<0.01
Glucose (mmol/L)	5.04 (3.26-20.60)	4.76 (3.20-17.10)	<0.01
Total cholesterol (mmol/L)	4.36 (0.22-10.60)	4.24 (0.63-10.71)	<0.01
LDL-cholesterol (mmol/L)	3.00 (0.10-12.40)	2.97 (0.10-9.70)	>0.05
HDL-cholesterol (mmol/L)	1.30 (0.11-5.82)	1.40 (0.00-8.00)	<0.01
Triglyceride (mmol/L)	1.30 (0.20-22.99)	1.19 (0.19-31.89)	<0.01
ALT (IU/L)	21.20 (1.00-211.70)	15.00 (0.60-645.90)	<0.01
AST (IU/L)	22.00 (1.00-188.90)	19.50 (1.00-449.90)	<0.01
Non-smoker, n (%)	752 (42.70)	1629 (78.54)	<0.01
Smoker, n (%)	1009 (57.30)	445 (21.46)	
Non-drinker, n (%)	523 (29.70)	1934 (93.25)	<0.01
Infrequent drinker, n (%)	63 (3.58)	3 (0.14)	
Regular alcohol drinker, n (%)	1175 (66.72)	137 (6.61)	

Wilcoxon test scores for the continuous variables, Cochran-Mantel-Haenszel test for the categorical variables.
ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. HDL: High-density lipoprotein. LDL: Low-density lipoprotein.

Table 2. Prevalence (%) of metabolic abnormalities associated with serum aminotransferase levels

Metabolic Abnormalities	Alanine aminotransferase, IU/L					*p* for trend	Aspartate aminotransferase, IU/L					*p* for trend
	<20	20-29	30-39	40-49	≥50		<20	20-29	30-39	40-49	≥50	
Men												
Hypertension-positive	37.32	45.70	54.62	53.70	57.33	0.01	39.50	45.54	50.25	50.79	63.64	0.01
Central obesity	18.60	34.00	44.96	54.63	63.33	0.01	27.12	31.87	38.58	44.44	63.64	0.01
Triglyceride ≥1.7 (mmol/L)	20.44	35.54	49.58	56.48	64.67	0.01	25.39	33.82	47.72	61.90	70.45	0.01
HDL-cholesterol <1.3 mmol/L	53.57	57.84	54.62	62.96	64.67	0.01	58.62	56.04	51.78	50.79	56.82	0.11
Glucose >5.6 (mmol/L)	19.95	23.40	26.47	32.41	32.00	0.01	23.82	22.71	22.34	25.40	36.36	0.35
Women												
Hypertension-positive	31.64	43.97	43.54	51.52	56.72	0.01	31.49	38.26	47.96	63.27	51.52	0.01
Central obesity	34.25	50.94	68.52	74.24	67.16	0.01	36.39	43.43	52.04	83.67	63.64	0.01
Triglyceride ≥1.7 (mmol/L)	22.19	33.78	43.52	46.97	55.22	0.01	23.32	28.91	33.67	65.31	42.42	0.01
HDL-cholesterol <1.3 (mmol/L)	46.23	42.90	44.44	48.48	53.73	0.57	49.55	41.29	37.76	48.98	51.52	0.03
Glucose >5.6 (mmol/L)	11.99	17.16	13.89	18.18	14.93	0.04	13.07	12.63	16.33	20.41	18.18	0.16

HDL: High-density lipoprotein.

Table 3. Independent associations between serum aminotransferase levels and the metabolic syndrome

Aminotransferase levels	Number (n)	Metabolic Syndrome, n (%)	Odds Ratio (95% CI) for Metabolic Syndrome		
			Univariate	Multivariate adjusted*	Multivariate adjusted†
Men					
ALT <20 (IU/L)	812	84 (10.34)	1	1	1
20-29	453	115 (25.39)	2.95 (2.16-4.02)	1.79 (1.15-2.80)	1.92 (1.20-3.06)
30-39	238	77 (32.35)	4.14 (2.91-5.90)	1.80 (1.17-3.04)	2.50 (1.14-3.53)
40-49	108	47 (43.52)	6.68 (4.29-10.39)	1.81 (1.21-3.59)	2.97 (1.27-4.01)
>50	150	80 (53.33)	9.90 (6.69-14.66)	3.31 (1.87-5.87)	3.52 (1.96-6.32)
Total	1761	403 (22.88)			
AST <20 (IU/L)	638	112 (17.55)	1	1	1
20-29	819	189 (23.08)	1.41 (1.09-1.83)	1.13 (0.77-1.65)	0.99 (0.66-1.49)
30-39	197	56 (28.43)	1.87 (1.29-2.70)	1.20 (0.68-2.13)	1.13 (0.64-2.00)
40-49	63	23 (36.51)	2.70 (1.56-4.69)	1.78 (0.76-4.17)	1.75 (0.75-4.08)
>50	44	23 (52.27)	5.14 (2.75-9.62)	2.32 (0.93-5.76)	2.33 (0.95-5.76)
Total	1761	403 (22.88)			
Women					
ALT <20 (IU/L)	1460	225 (15.41)	1	1	1
20-29	373	108 (28.95)	2.24 (1.72-2.92)	1.40 (1.25-1.95)	1.38 (1.27-1.95)
30-39	108	43 (39.81)	3.63 (2.41-5.48)	1.46 (1.19-2.35)	1.54 (1.26-2.35)
40-49	66	36 (54.55)	6.59 (3.98-10.91)	3.09 (1.62-5.89)	3.06 (1.60-5.86)
>50	67	33 (49.25)	5.33 (3.23-8.78)	2.63 (1.36-5.11)	2.62 (1.35-5.09)
Total	2074	445 (21.46)			
AST <20 (IU/L)	1102	188 (17.06)	1	1	1
20-29	792	180 (22.73)	1.43 (1.14-1.80)	1.18 (0.89-1.58)	1.08 (0.80-1.47)
30-39	98	28 (28.57)	1.95 (1.22-3.10)	1.15 (0.64-2.07)	0.99 (0.54-1.82)
40-49	49	34 (69.99)	11.02 (5.88-20.64)	6.19 (2.82-13.56)	5.65 (2.57-2.42)
>50	33	15 (45.45)	4.05 (2.01-8.18)	2.11 (1.80-5.62)	2.01 (1.76-5.34)
Total	2074	445 (21.46)			

* Adjusted for age, BMI, occupation, cultural and educational level, income level, smoking, alcohol intake, and waist circumference.
† Adjusted for age, BMI, occupation, cultural and educational level, income level, smoking, alcohol intake, waist circumference, and (ALT or AST).
ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. BMI: Body mass index.

Table 4. Independent associations between serum aminotransferase levels and hyperlipidemia, DM and NAFLD

Aminotransferase Level	Number (n)	Odds Ratio (95% CI) for DM		Odds Ratio (95% CI) for NAFLD		Odds Ratio (95% CI) for Hyperlipidemia	
		DM, n (%)	Multivariate Adjusted*	NAFLD, n (%)	Multivariate Adjusted*	Hyperlipidemia, n (%)	Multivariate Adjusted*
Men							
ALT <20 (IU/L)	812	29 (3.57)	1	50 (6.16)	1	259 (31.90)	1
20-29	453	32 (7.06)	1.69 (0.99-2.89)	54 (11.92)	1.35 (0.87-2.09)	209 (46.14)	1.35 (1.15-1.74)
30-39	238	16 (6.72)	1.44 (0.75-2.79)	34 (14.29)	1.50 (1.29-2.51)	137 (57.56)	1.92 (1.39-2.64)
40-49	108	8 (7.41)	1.41 (0.60-3.31)	34 (31.48)	3.26 (1.84-5.77)	72 (66.67)	2.53 (1.59-4.02)
>50	150	17 (11.33)	2.29 (1.16-4.54)	51 (34.00)	3.66 (2.19-6.11)	113 (75.33)	3.44 (2.24-5.29)
Total	1761	102 (5.79)		223 (12.66)		790 (44.86)	
Women							
ALT <20 (IU/L)	1460	51 (3.49)	1	194 (13.29)	1	655 (44.86)	1
20-29	373	20 (5.36)	1.36 (1.19-2.34)	100 (26.81)	1.58 (1.13-2.21)	210 (56.30)	1.24 (0.97-1.59)
30-39	108	5 (4.63)	1.28 (1.16-2.85)	45 (41.67)	1.89 (1.11-3.20)	62 (57.41)	0.94 (0.61-1.45)
40-49	66	10 (15.15)	3.86 (1.81-8.26)	31 (46.97)	2.44 (1.30-4.58)	44 (66.67)	1.37 (0.79 2.39)
>50	67	8 (11.94)	2.72 (1.17-6.33)	32 (47.76)	3.23 (1.70-6.14)	46 (68.66)	1.70 (0.97-2.99)
Total	2074	94 (4.53)		402 (19.38)		1017 (49.04)	

* Adjusted for age, BMI, occupation, cultural and educational level, income level, smoking, alcohol intake, and waist circumference.
ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. DM: Diabetes mellitus. NAFLD: Non-alcoholic fatty liver disease. BMI: Body mass index. The odds ratio between AST and metabolic disorders was not shown because the associations in the results were weaker, especially after multivariate adjustment.

A positive association between elevated ALT levels and the prevalence of MS, hyperlipidemia, DM, and NAFLD was observed even within the normal range of aminotransferase levels (Tables 2, 4). The associations between AST and the prevalence of hyperlipidemia, DM and NAFLD are not shown because the associations in the results were weaker, especially after multivariate adjustment.

We assessed the association between elevated ALT and AST level and the prevalence of MS in non-drinkers and drinkers separately. The positive association between serum ALT and AST levels and the prevalence of MS were not affected by alcohol intake. The most positive association between serum AST levels and the prevalence of MS was found for levels of 40-49 IU compared with <20 IU in the non-drinker group, but not in the drinker group (Table 5).

Table 6 shows the thresholds for ALT values from ROC analyses of various diseases ($p<0.05$). The p values for thresholds of AST for various diseases were more than 0.05. AST values were not shown.

DISCUSSION

We found a positive association between serum aminotransferase levels and metabolic disorders in the Chinese population. Recent epidemiologic studies have also reported an association between aminotransferase elevations and metabolic disorders such as MS, hyperlipidemia, and DM (19). This association has been observed in various populations, including obese people, post-menopausal women, elderly men, patients with NAFLD, and even adolescents (2,16,20). Similar findings have already been reported in other countries such as Korea, Singapore and Japan (21). Another more important finding of this study is that the association was observed even in normal to near-normal aminotransferase levels, in a level-related manner. Aminotransferase levels of 40-49 were very significantly related in women, and need further investigation. The reason for the stronger association of ALT 40-49 with the prevalence of MS than ALT >50 is not clear, but may be related to the fact that the progression of liver damage in NAFLD is generally slow, and the levels of ALT are most commonly only mildly elevated. Similar findings also were reported in some Korean populations (22).

We found that the association of ALT with the prevalence of MS persisted even after adjustment for waist circumference. This is in a way over-adjustment, because waist circumference is part of the definition of the MS, but provides additional insight by indicating that it is not simply the well-known association of obesity or abdominal obesity that mediates the association.

Table 5. Association between serum aminotransferase levels and metabolic syndrome by alcohol drinking status

Risk factor	Drinker			Non-drinker		
	Number (n)	Metabolic syndrome n (%)	Odds Ratio (95% CI)	Number (n)	Metabolic syndrome n(%)	Odds Ratio (95% CI)
Alanine aminotransferase						
ALT <20 IU/L)	652	75 (11.50)	1	1620	234 (14.44)	1
20-29	348	90 (25.86)	2.02 (1.24-3.29)	103	133 (27.82)	1.40 (1.02-1.91)
30-39	189	64 (33.86)	1.95 (1.11-3.43)	99	56 (35.67)	1.44 (1.28-2.33)
40-49	75	35 (46.67)	2.81 (1.30-6.07)	157	48 (48.48)	2.31 (1.32-4.05)
>50	114	59 (51.75)	3.49 (1.89-6.43)	478	54 (52.43)	3.02 (1.71-5.34)
Aspartate aminotransferase						
AST <20(IU/L)	507	92 (18.15)	1	1233	208 (16.87)	1
20-29	613	137 (22.35)	1.11 (0.73-1.70)	998	232 (23.25)	1.20 (0.91-1.57)
30-39	165	51 (30.91)	1.40 (0.77-2.53)	130	33 (25.38)	1.02 (0.58-1.79)
40-49	53	21 (39.62)	1.88 (1.62-4.31)	59	36 (61.02)	5.64 (2.66-11.95)
>50	40	22 (55.00)	3.78 (1.45-9.87)	37	16 (43.24)	1.28 (1.10-3.23)

Odds ratios with 95% confidence intervals are adjusted for age, body mass index, occupation, cultural and educational level, income level, waist circumference, smoking status, and sex. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase.

NAFLD has been associated with metabolic disorders, including central obesity, dyslipidemia, hypertension, and hyperglycemia, the major risk factors for the development of NAFLD (23). Because the number of MS components has increased, the prevalence and odds ratio for having increased ALT activity were also significantly increased (24). In the present study, metabolic disorder components (triglycerides, LDL, total cholesterol, etc.) and NAFLD were correlated with increased ALT activity. Unexplained elevations in ALT levels have been suggested to signify the presence of NAFLD in adults. Individuals with the metabolic disorders (MS, hyperlipidemia and DM) have a significantly higher prevalence of unexplained elevations in ALT levels (24). Therefore, this also supports the notion that NAFLD is part of the spectrum of metabolic disorders.

The prevalence of NAFLD is mainly associated with the male sex, obesity and waist circumference, but it may vary significantly among different population groups (22). Recent studies have added evidence that insulin resistance, a key component of the MS and DM, may contribute to the development of NAFLD (24). Central obesity may be an underlying cause of insulin resistance, and can also contribute to the development of NAFLD (2). Compared with adipose tissue in other sites, visceral adipose tissue is more resistant to insulin, and the associated relative hyperinsulinemia promotes lipogenesis in the liver, which contributes to NAFLD (25).

Table 6. Thresholds for ALT values from ROC analyses

	Threshold value (IU/L)	
	Men	Women
Diabetes mellitus	23.45	21.90
Hyperlipidemia	21.50	14.90
Metabolic syndrome	25.30	16.85
Non-alcoholic fatty liver disease	23.80	16.85

Those with diabetes mellitus, hyperlipidemia, metabolic syndrome, or non-alcoholic fatty liver disease were defined as the disease group and the others were the control group in each ROC analyses.

ALT: Alanine aminotransferase. ROC: Receiver operating characteristics.

Asians have been shown to have more subcutaneous fat, and have a different fat distribution compared to Caucasians. The relationship between BMI and body fat percentages in different population groups has been shown to vary (23,24). Thus, the significance of central obesity in connection with liver dysfunction and metabolic disorders may differ by ethnicity. The connection in the present study was similar to that found in another previous study (22).

Some conditions such as alcohol consumption, viral hepatitis or hemochromatosis, which can increase aminotransferase activity, may also be associated with the MS. The association between metabolic risk factors and ALT elevation was shown to be similar in subjects with and without identifiable causes of chronic liver disease (alcohol use) (26). The association was also seen in the non-

drinker or drinker regression model in the present study. Some systemic diseases and medications may also elevate serum aminotransferase levels. Accordingly, we performed further analysis after excluding 524 people who were receiving hormone replacement therapy or medications for hypertension, DM, liver disease, or renal disease during the three months before the examination. We still found a strong association between serum aminotransferase levels and MS, even in the normal to near-normal range of aminotransferases. For MS patients with levels <20 IU/L, the adjusted odds ratios for ALT levels of 20-29, 30-39, 40-49, and >50 IU/L were 1.82, 2.08, 1.88, and 2.72 in men and 1.37, 1.34, 3.07, and 2.46 in women, respectively ($p<0.05$ for all). In addition, patients with hyperlipidemia and DM had the same trend.

In the present study, serum ALT levels were more closely associated with MS than AST levels. In addition, only ALT levels were significantly associated with MS when both enzymes were simultaneously investigated in a single model. This finding is in agreement with previous studies, and can be explained by a higher specificity of ALT for liver disease (22). The cut-off level of aminotransferase that discriminates between healthy and diseased livers has not been clearly defined. Several previous studies have demonstrated that serum aminotransferase levels, even within the normal range, may be associated with morbidity and mortality (27). In liver disease, elevated serum aminotransferase levels have a more positive association with non-alcoholic steatohepatitis than other frequent causes of hepatitis (alcoholic hepatitis, chronic hepatitis B and C) and some rare causes (autoimmune hepatitis) (26).

From the multivariate analysis of patients with metabolic disorders, the linear association between serum aminotransferase levels (especially ALT at 20-29 level compared to the lowest level [<20 IU/L]) suggests that people with high normal aminotransferase levels may need further investigation for the presence of metabolic disorders such as MS. Considering the increasing prevalence of metabolic disorders and their association with liver dysfunction, the significance of the serum aminotransferase assay needs to be re-evaluated. Therefore, we evaluated thresholds for aminotransferase values by ROC analysis. Serum ALT levels of 21-25 IU/L for men and 17-22 IU/L for women are suggested as cut-off levels that detect metabolic disorders affecting the liver.

In a recent study from Korea, calculated thresholds for ALT values were 35 IU/L for men and 26 IU/L for women (28). Relatively high threshold levels of normal serum aminotransferases were also found in our study. Therefore, adjustment of the normal limit of serum aminotransferases should be considered for monitoring liver function, especially in people with metabolic disorders.

One of the limitations in the present study is that the diagnosis of fatty liver was based on US imaging and CT, and not confirmed by liver biopsy, the gold standard for the assessment of liver histology and a key test to diagnose NAFLD.

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