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Factors underlying the association of body mass index with serum ALT in Chinese hypertensive adults without known hepatic diseases*

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Abstract: Objective: High body mass index (BMI) is considered as the most important risk factor for elevated serum alanine aminotransferase (ALT) concentration. This study examined an array of factors, including waist circumference (WC) and folate deficiency, which may mediate the association of BMI with serum ALT concentration in Chinese hypertensive adults without known hepatic diseases. Methods: A multicenter, cross-sectional study was carried out. A total of 378 patients with mild or moderate hypertension and without known hepatic diseases were recruited from five hospitals in Harbin, Shanghai, Beijing, Xi'an, and Nanjing. Results: Of the 360 hypertensive patients with complete data in our final analysis, 13.6% had high ALT concentrations (>40 IU/L). Factors including BMI, WC, triglyceride level, and folate concentration were associated with ALT concentration in univariate analysis. Consistently higher prevalence rates of elevated ALT were observed in subjects with lower folate concentrations (≥12 vs. <12 nmol/L, 9.9% vs. 17.8%, P=0.03), with higher BMI (≥28 vs. <28 kg/m^2, 21.5% vs. 11.4%, P=0.02) or higher WC (≥90 vs. <90 cm, 18.5% vs. 10.0%, P=0.02). However, in multivariate analysis, the association between BMI and ALT concentration disappeared (P=0.802 in males and 0.369 in females), while WC in females (P<0.001) and folate concentration (P=0.036 in males and 0.044 in females) remained as significant predictors for ALT concentration. Conclusions: This multicenter study demonstrated that WC and low folate concentration were important factors underlying the association between BMI and ALT concentrations in Chinese hypertensive adults without known hepatic diseases.

Key words: Alanine aminotransferase (ALT), Body mass index (BMI), Waist circumference (WC), Folate
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1 Introduction

Serum alanine aminotransferase (ALT) activity has been considered as a reliable and sensitive marker of a variety of hepatic disorders. Emerging data also suggest that ALT may well predict a range of health

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outcomes. Kim *et al.* (2004) analyzed the association between ALT concentration and mortality in a large, prospective cohort in Korea. They found a continuous and positive association between ALT concentration and all-cause mortality, or mortality from liver diseases, cancers, and cardiovascular diseases in men with adjustment for almost all the traditional risk factors. Furthermore, ALT (both in normal and elevated ranges) was independently associated with the long-term development of multiple metabolic disorders and cardiovascular diseases (Schindhelm *et al.*, 2007; Goessling *et al.*, 2008; Yun *et al.*, 2009).

The cause of abnormal ALT concentration is incompletely understood. High body mass index (BMI) is considered as the most important risk factor for elevated ALT concentration (Salvaggio *et al.*, 1991; Sull *et al.*, 2009; Kim and Jo, 2010). However, waist circumference (WC) is correlated with central fat, which provides a greater supply of potentially hepatotoxic fatty acids to the liver, and may be a stronger predictor for elevated ALT concentrations than BMI (Ruhl and Everhart, 2003). Furthermore, folate deficiency may possibly accelerate or promote hepatic injury by increasing hepatic homocysteine (Hcy) and *S*-adenosylhomocysteine concentrations, decreasing hepatic *S*-adenosylmethionine and glutathione concentrations, increasing lipid peroxidation, or promoting insulin resistance (Björck *et al.*, 2006; Purohit *et al.*, 2007).

We hypothesized that folate deficiency and WC may at least partly mediate the association between BMI and serum ALT concentration in populations without folic acid fortification. To our knowledge, no similar studies have been published, particularly in Chinese hypertensive populations. A better understanding of factors that modulate the ALT concentration in subjects without known hepatic diseases will help us to perform more aggressive monitoring, lifestyle interventions, or medications in target populations.

2 Materials and methods

This was a multicenter, cross-sectional study conducted in China. The details regarding "Participants", "Data collection procedures", and "Laboratory methods" have been previously described (Qin *et al.*, 2012a; 2012b; 2012c). Briefly, a total of 378 hypertensive patients aged 18–75 years old, with seated systolic blood pressure (SBP) between 140 and 180 mmHg and/or seated diastolic blood pressure (DBP) between 90 and 110 mmHg, were recruited from one hospital in each of five cities (Harbin, Shanghai, Beijing, Xi'an, and Nanjing) located in different regions, from September to December, 2005. Participants were excluded if they were pregnant or had serious self-reported diseases, including cardiovascular diseases such as myocardial infarction, hepatic diseases such as hepatitis and hepatocirrhosis, chronic kidney diseases, tumor, type 1 diabetes, or uncontrolled type 2 diabetes (fasting plasma glucose >11.1 mmol/L). This study was approved by the Ethics Committee of Peking University First Hospital in Beijing, China. Participants signed informed consents before their enrollment.

Demographic and baseline clinical information was obtained according to standard operating procedures. Because of the positively skewed distributions of the ALT, Hcy and folate concentrations, the natural logarithms of these variables were used in all statistical analyses as continuous variables. Means or medians were calculated for population characteristics by gender. The differences in population characteristics between males and females were compared via Student's *t*-tests. With adjustment for age, sex, and study centers, we separately examined the relationships between ln-transformed ALT concentration [ln(ALT)] and SBP, DBP, WC, total cholesterol (TC) level, high-density lipoprotein cholesterol (HDL-C) level, triglyceride (TG) level, and the ln-transformed folate concentration [ln(folate)]. Partial R-squares were provided for each explanatory factor. A multivariable regression model was also used to evaluate the association between the ln(ALT) and major explanatory factors. SAS software version 6.12 (SAS Institute, USA) was used for the analysis.

3 Results

A total of 378 hypertensive patients were enrolled, of whom only 360 with complete data for BMI, WC, and folate concentration were included in our final analysis. Compared with female subjects, who accounted for 57.5% of the whole population, male subjects had significantly higher mean WC, DBP, Hcy [(19.4±15.7) vs. (12.5±7.0) μmol/L, $P<0.001$), aspartate transaminase (AST), and ALT [(28.8±14.9) vs. (23.3±12.9) IU/L, $P<0.001$] levels, but lower TC, HDL-C, and folate [(12.7±5.9) vs. (14.8±6.3) nmol/L, $P=0.001$] levels (Table 1).

In this population, 49 (13.6%) of the total subjects, including 26 (17.0%) males and 23 (11.1%) females, had an elevated ALT concentration (>40 IU/L). In univariate analysis, BMI ($r=0.187$, $P<0.001$), WC ($r=0.265$, $P<0.001$), TG ($r=0.176$, $P<0.001$) and folate concentrations ($r=-0.107$, $P=0.04$) were significantly associated with ALT concentration. Consistently, a lower prevalence rate of elevated ALT was observed in subjects with higher folate concentrations (≥12 vs. <12 nmol/L, 9.9% vs. 17.8%, odds ratio (OR)=0.51; 95% confidence interval (CI): 0.27–0.94, $P=0.03$), and higher prevalence rates of elevated ALT were observed in subjects with higher BMI (≥28 vs. <28 kg/m^2, 21.5% vs. 11.4%, OR=2.1; 95% CI: 1.1–4.1, $P=0.02$) or higher WC (≥90 vs. <90 cm, 18.5% vs. 10.0%, OR=2.0; 95% CI: 1.1–3.8, $P=0.02$).

Table 1 Characteristics of the study population

Characteristic	Male (n=153)	Female (n=207)	P
Age (year)	58.6±9.8	57.5±9.2	0.263
BMI (kg/m^2)	25.5±3.0	25.8±3.5	0.403
WC (cm)	90.2±9.8	85.8±8.3	0.000
SBP (mmHg)	152.5±11.0	152.8±11.1	0.844
DBP (mmHg)	93.6±7.5	91.8±8.3	0.029
TC (mmol/L)	4.8±1.3	5.0±1.0	0.029
TG (mmol/L)	1.6±1.0	1.7±0.9	0.439
HDL-C (mmol/L)	1.2±0.3	1.3±0.3	0.000
FPG (mmol/L)	5.5±1.2	5.5±1.1	0.921
Folate (nmol/L)	12.7±5.9 (11.4)	14.8±6.3 (13.7)	0.001
Hcy (μmol/L)	19.4±15.7 (14.9)	12.5±7.0 (10.8)	<0.001
ALT (IU/L)	28.8±14.9 (26.0)	23.3±12.9 (20.0)	<0.001
AST (IU/L)	27.3±10.9 (25.4)	24.8±8.3 (24.0)	0.022

BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; FPG: fasting plasma glucose; Hcy: homocysteine; ALT: alanine aminotransferase; AST: aspartate transaminase. Data are presented as mean±standard deviation (SD), some with median in parenthesis

With adjustment for age and study centers, BMI, WC, TG, and the ln(folate) (Table 2; each $P<0.01$, except BMI, $P=0.011$) in males and BMI, WC, fasting plasma glucose (FPG), and the ln(folate) (Table 2; each $P<0.01$, except BMI, $P=0.018$ and ln(folate), $P=0.030$) in females were significantly associated with the ln(ALT).

In the multivariate analysis (Table 3), the association between BMI and ALT concentration was eliminated, but ln(folate) was still negatively associated with ALT concentration regardless of gender (males, $P=0.036$; females, $P=0.044$). WC significantly predicted ALT concentration only in females ($P=0.002$). In addition, TG significantly predicted ALT concentration only in males ($P=0.031$), and FPG was positively related to ALT concentration only in females ($P=0.008$).

Table 2 Partial R-square (P-R) for major explanatory factors of ALT concentration*

Characteristic	Male				Female			
	β	SE	P	P-R	β	SE	P	P-R
BMI	0.035	0.014	0.011	0.043	0.024	0.010	0.018	0.028
WC	0.014	0.004	0.002	0.063	0.015	0.004	<0.001	0.065
SBP	0.002	0.004	0.695	0.001	0.003	0.003	0.359	0.004
DBP	−0.001	0.006	0.915	<0.001	0.007	0.005	0.141	0.011
TC	0.011	0.033	0.740	<0.001	0.057	0.041	0.166	0.010
TG	0.146	0.043	<0.001	0.074	0.066	0.038	0.086	0.015
HDL	−0.124	0.148	0.404	0.005	−0.140	0.117	0.231	0.007
FPG	0.020	0.041	0.623	0.002	0.098	0.036	0.007	0.036
ln(Hcy)	−0.092	0.081	0.259	0.009	−0.159	0.090	0.078	0.015
ln(folate)	−0.280	0.103	0.007	0.048	−0.211	0.096	0.030	0.017

* The model is ln(ALT)=age+study center+single factor. BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; FPG: fasting plasma glucose; Hcy: homocysteine

Table 3 Multivariable regression models of the association of ALT concentrations with major explanatory factors*

Characteristic	Male			Female		
	β	SE	*P*	*β*	SE	*P*
Age	−0.005	0.005	0.229	−0.003	0.004	0.468
BMI	−0.006	0.022	0.802	−0.012	0.014	0.369
WC	0.009	0.007	0.199	0.017	0.006	0.002
TG	0.099	0.046	0.031			
FPG				0.091	0.034	0.008
ln(folate)	−0.209	0.100	0.036	−0.180	0.089	0.044

* The model is ln(ALT)=age+study center+all the significant factors in Table 2. BMI: body mass index; WC: waist circumference; TG: triglycerides; FPG: fasting plasma glucose

4 Discussion

The characteristics of relatively high ALT concentrations (Shen *et al.*, 2003) and low folate concentrations (Forman *et al.*, 2005) in hypertensive populations make them particularly suitable for evaluating the possible association between folate and ALT concentrations in patients with hypertension. This is the first study to report on the role of traditional risk factors and folate status in the elevation of ALT concentration in Chinese hypertensive adults without known hepatic diseases. In agreement with previous studies (Salvaggio *et al.*, 1991; Sull *et al.*, 2009; Kim and Jo, 2010), there was a positive linear association between BMI and ALT concentration. However, following multivariate regression analysis, this association disappeared ($P>0.05$), while WC and folate concentration remained as significant predictors for ALT concentration.

Previous studies reported that the ALT concentration was highly associated with the metabolic syndrome (Park *et al.*, 2005; Oh *et al.*, 2006). Abdominal obesity has been proposed to play an important role in the mechanism of metabolic syndrome. WC has proven to be a better surrogate for abdominal obesity than BMI or waist-to-hip ratio in Chinese populations (Feng *et al.*, 2006). Abdominal obesity leads to high levels of free fatty acids and cytokines, which may lead to fat accumulation and infiltration and decreased hepatocyte integrity (Kern *et al.*, 2001; Tamura and Shimomura, 2005). Consistent with our results, truncal obesity was reported (Angulo, 2002) to be an important risk factor for nonalcoholic fatty liver diseases, even in patients with a normal BMI. Accordingly, ALT concentration was also significantly correlated with other components of the metabolic syndrome (TG or FPG) in our study. The possible gender difference should be further evaluated in future studies.

While folate deficiency is recognized as being causally related to cardiovascular diseases (Wald *et al.*, 2002), its role in hepatic injury is uncertain. Increasing evidence suggests that changes in methionine/folate metabolism may contribute to the development of hepatic injury (Qin *et al.*, 2012a). Welzel *et al.* (2007) observed that low folate concentration was significantly associated with higher ALT concentration in hepatitis B surface antigen-positive patients. Our results further proved that low folate levels, which are independent of traditional risk factors, may predict a higher ALT concentration in hypertensive Chinese adults without known hepatic diseases. We did not find a significant association between the plasma Hcy level and ALT concentration. We speculate that the hepatic Hcy level (Antoniades *et al.*, 2009) or the folate concentration itself (Verhaar *et al.*, 2002), but not plasma Hcy level, was more closely related to the change in ALT concentration.

Kim *et al.* (2005) reported that ALT concentration was independently associated with the incidence of stroke. A population increase in serum folate concentration after folic acid fortification produced a significant decrease in stroke mortality (Yang *et al.*, 2006). These results showed that low folate concentration may be one of the explanations for increased ALT concentration and for the increased risk of cardiovascular diseases, especially stroke. Most importantly, our previous study showed that a daily dose of 0.8-mg folic acid treatment may be beneficial in lowering serum ALT concentration, particularly in men and/or in subjects with ALT concentrations of >40 IU/L (Qin *et al.*, 2012a).

Our study had the following strengths. This was a multicenter survey in China and all of the centers achieved similar results, which suggests that our findings may be applicable to populations in different regions of China. However, caution is needed in generalizing our findings from this hypertensive Chinese population to other populations. Furthermore, we did not collect detailed information on alcohol consumption in this study. However, an association between alcohol consumption and ALT concentration was eliminated after adjustment for BMI or WC (Lee *et al.*, 2001), suggesting that this information may not have affected our results. We also did not have detailed information regarding other important variables, such as alkaline phosphatase and bilirubin levels.

In summary, this multicenter study demonstrated that high WC and low folate concentration were important factors underlying the association between BMI and ALT concentration in Chinese hypertensive adults. Our data lend further support to the suggestion that folic acid supplementation in this population may be beneficial to liver health.

Compliance with ethics guidelines

Yan ZHANG, Xian-hui QIN, Jian-ping LI, Yi-min CUI, Ze-yuan LIU, Zhi-gang ZHAO, Jun-bo GE, De-ming GUAN, Jian HU, Yan-ni WANG, Fu-min ZHANG, Xin XU, Xi-ping XU, and Yong HUO declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000(5). Informed consent was obtained from all patients for being included in the study.

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