The effect of overweight/obesity and FTO gene polymorphism on liver function-related parameters in Chinese adolescents

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ABSTRACT

Background. Overweight/obesity is an important risk factor for liver disease, affecting changes in liver function-related parameters. The fat mass and obesity associated (FTO) gene has been reported to have a link between overweight/obesity and liver fat metabolism. We studied the association of FTO rs9939609 variants with liver function-related parameters and overweight/obesity in Chinese adolescents aged 16 to 26 as freshmen.

Methods. We examined rs9939609 polymorphisms in 198 control and 173 overweight/obese people, and the genotypes of the samples were analyzed by Sanger sequencing. We investigated the effects of FTO gene polymorphism on overweight/obesity and liver function-related parameters.

Results. The values of aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) in overweight/obesity group were significantly higher than those in control group. The rs9939609 AA genotype increased the risk of overweight/obesity by 3.45 times independent of body mass index (BMI) compared with TT genotype, the rs9939609 (AA) genotype was significantly associated with AST and ALT.

Conclusion. FTO rs9939609 variants were associated with overweight/obesity and overweight/obesity has a significant influence on the increased liver function-related parameters. The rs9939609 (AA) positively correlated with AST and ALT levels. Overweight/obese patients should pay more attention to liver function-related parameters.

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INTRODUCTION

Overweight/obesity can increase the risk of metabolic diseases, especially hepatic steatosis and hepatic injury.[1,2] Liver is a vital metabolic organ, regulating protein and fat throughout the body.[3] However, excess fat in the liver often induces a variety of metabolic diseases such as non-alcoholic fatty liver disease (NAFLD), which is often associated with changes in liver function-related parameters.[4–6] Previously a link has been reported between obesity and elevated levels of liver enzymes and proteins in adolescents. Serum levels of aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) were raised in individuals with a high body mass index (BMI) and waist-to-hip ratio (WHR).[7,8] Albumin can be used to measure the nutritional status of humans.[9] Higher serum albumin levels have also been linked to abdominal obesity.[10]

The fat mass and obesity-associated (FTO) gene is the first candidate gene to be associated with an increased risk of obesity in humans.[11–13] FTO plays a role in regulating gene transcription through transformation of the methylation and demethylation state of nucleic acids,[14,15] which is highly expressed in the hypothalamus and liver tissue.[16,17] Experimental results have suggested that increased FTO expression leads to hepatic adipose deposition in a NAFLD model.[18–20] It was also observed that FTO gene transformed fat phenotype affects the course of NAFLD in humans.[21] These findings indicate that FTO may be involved in the regulation of gene expression in hepatic metabolic tissue.[22] Therefore, we explored the link between FTO and liver function-related parameters in the regulation of liver metabolism.

We verified the influence of overweight/obesity on liver function-related parameters and studied the correlation between of FTO rs9939609 polymorphism and overweight/obesity. We then explored the hypothesis that FTO may have a certain impact on liver function-related parameters. Finally, we assessed the interplay between FTO, overweight/obesity and liver function-related parameters in Chinese adolescents.

METHODS

Study population

We collected the physical examination data of freshmen in Huangjiahu hospital from 4 October 2020 to 2 November 2020. A total of 371 individuals (191 women and 180 men) were included. The inclusion criteria were (i) healthy adolescents aged between 16 and 26 years and (ii) subjects with no genetic relationship to each other. Those who were excluded included (i) alcohol abusers, (ii) carriers of hepatitis B or C, (iii) those with a history of drug-induced or autoimmune liver disease, (iv) those that took any medication that could affect liver function such as non-steroidal anti-inflammatory drugs, antibiotics, statins, antiepileptics and antituberculosis drug, herbal preparations, paracetamol overdose, and illicit drugs. Ethics committee approval and informed consent was obtained from all subjects before participation in the study.

Body mass index (BMI) calculation and grouping

BMI was obtained by dividing the weight in kilograms (kg) by the height in meters squared (m^2).[23] To obtain an accurate BMI value, the height and weight of participants were measured by specially trained professionals of the university hospital following standard procedures.[23] Weight and height were measured and recorded to the nearest 0.1 kg and 0.1 cm, respectively. The individuals were divided according to the international classification standards into the normal body weight group (BMI 18.5–23.9), and the overweight/obesity group (BMI $\geq$24).[24]

Measurement of liver function parameters

Blood samples were collected after fasting for 10 to 12 hours, and the levels of AST, ALT, GGT, ALP, total protein (TP), albumin (ALB) and globulin in serum were measured using an automatic analyzer (COBAS C501; Roche Diagnostics, United States). AST, ALT, GGT, and ALP were all measured by the rate method, TP was measured by the biuret method and ALB was measured by the bromocresol green method.

Genotyping

Genomic DNA was extracted from blood using the blood DNA extraction kit (Tiangen Biochemical Technology Co. Ltd., Beijing), and FTO gene was classified by Sanger sequencing. Detection of rs9939609 was done using a previously published set of primers,[25] it was synthesized by Wuhan Shenggong Bioengineering Company. Forward primer: 5-TCC CAC TCC ATT TCT GAC TGT TAC-3 and Reverse primer: 5-AAT TCA AAA CTG GCT CTT GAA TGA-3 . Reactions were performed in 20 µL volumes, containing 14.3 µl of ddH_2O, 2 µl of Buffer, 0.8 µl of $MgCl_2$, 0.4 µl of dNTP, 0.4 µl of each primer, 0.1 µl of Taq DNA polymerase, and 1.6 µl of DNA template (All reagents were from Beijing Tiangen Biotech Co., Ltd).

The cycling conditions for rs9939609 were 94 °C for 3 minutes, followed by 30 cycles of 94 °C for 30 seconds, 55 °C for 30 seconds, 72 °C for 30 seconds, and a final extension of 72 °C for 10 minutes.

Statistical analysis

SPSS 23.0 was used for statistical analysis. Non-parametric Mann–Whitney U-tests and Kruskal–Wallis were used to compare two or three groups. Measurement data were expressed as median (P25, P75). Genotype and allele frequencies in obesity and controls of FTO rs9939609 concerning BMI status were assessed for an association by Pearson Chi-square test. Risk assessment was done using single-factor logistic regression analysis. Multivariate linear regression was used to analyze the effects of FTO gene polymorphism on liver enzymes. $p<0.05$ was considered statistically significant. Bonferroni correction was used for different polymorphic analyses with a p value of 0.025 as a significant truncation value.

RESULTS

Population characteristics

Three hundred and seventy-one subjects were divided into case and control groups according to BMI status. BMI, AST, ALT, AST/ALT, GGT, and ALP were significantly increased in individuals with overweight/obesity when compared to the control group (Table I).

FTO polymorphism and the risk of overweight/obesity

The genotypes and allele frequency of rs9939609 are shown in Table II. Genotypes were in with Hardy–Weinberg equilibrium ($p > 0.05$) for both cases and controls.

The results showed that there were significant differences in genotype and allele frequency between the groups. And the genotype frequency of rs9939609 (AA) in the overweight/

TABLE I. Liver function-related parameters and grouping

Characteristic	Control group	Overweight/Obesity group	p value
Age (year)	23 (20.75–24)	23 (21–24)	0.218
Gender (female/male)	119/79	85/88	0.034
Height (m)	1.6 (1.57–1.66)	1.67 (1.58–1.73)	<0.001
Weight (kg)	50 (45.93–54)	67.5 (60–75)	<0.001
Body mass index (kg/m²)	20.60 (19.61–22.24)	27.12 (25.43–29.00)	<0.001
AST (U/L)	18 (16–21)	19 (17–23.5)	0.044
ALT (U/L)	13 (11–16)	17 (13–25.5)	<0.001
AST/ALT	1.4 (1.2–1.62)	1.14 (0.835–1.36)	<0.001
GGT (U/L)	17 (13–22)	24 (17–35)	<0.001
ALP (U/L)	57.5 (46–68)	63 (53–77)	0.001
Total proteins (g/L)	68.75 (66.08–70.93)	68.4 (65.80–70.85)	0.338
Albumin (g/L)	42.9 (41.98–44.5)	43.1 (41.6–44.85)	0.718
Globulin (g/L)	25.6 (23.7–27.33)	25 (23.15–27)	0.101
Albumin/globulin ratio	1.69 (1.57–1.82)	1.73 (1.6–1.875)	0.294

AST aspartate transaminase ALT alanine transaminase GGT gamma-glutamyl transferase
ALP alkaline phosphatase

obesity group was significantly higher than that in the control group (p=0.02). The AA genotype remained associated with overweight/obesity risk after adjustment for variables.

Liver function-related parameters and FTO rs9939609 polymorphism

The comparison of liver enzyme and protein parameters in FTO

TABLE II. Risk analysis of FTO rs9939609 polymorphism in overweight/obesity adjusted for age and gender

Item	Control (*n*=198) (%)	Overweight/obesity (*n*=173) (%)	OR (95% CI)	p value	Adjusted OR (95% CI)	p value
T T	139 (70.2)	109 (63)	Ref		Ref	
T A	55 (27.8)	52 (30.1)	1.2 (0.765–1.899)	0.42	1.083 (0.668–1.755	0.75
A A	4 (2)	12 (6.9)	3.826 (1.2–12.19)	0.02	3.445 (1.032–11.50)	0.04
Dominant model						
T T	139 (70.2)	109 (63)	Ref		Ref	
T A+A A	59 (29.8)	64 (37)	1.383 (0.897–2.134)	0.14	1.238 (0.780–1.966)	0.36
Recessive model						
T T+T A	194 (97.9)	161 (93.1)	Ref		Ref	
A A	4 (2.1)	12 (6.9)	3.615 (1.144–11.425)	0.03	3.356 (1.016-11.089)	0.05
Allele						
T	333 (84.1)	270 (78)	Ref		Ref	
A	63 (15.9)	76 (22)	1.488 (1.027–2.155)	0.04	1.393 (0.945–2.054)	0.09

TABLE III. Liver function-related parameters and FTO rs9939609 polymorphism

Item	T T	T A	A A	p value
Weight (kg)	55 (49.125–62.85)	57 (50–70)	73 (59.4–87.45)	<0.001
Body mass index (kg/m^2)	22.97 (20.31–25.76)	23.91 (20.83–28.06)	29.03 (24.20–32.69)	<0.001
AST (U/L)	19 (16–21)	19 (17–22)	26.50 (21–36)	<0.001
ALT (U/L)	14 (11–18)	15 (11–22)	41.50 (16.75–63.75)	<0.001
AST/ALT	1.33 (1.12–1.54)	1.25 (0.91–1.5)	0.68 (0.53–1.28)	<0.001
GGT (U/L)	18 (14–28.75)	20 (15–29)	26 (18.25–36.75)	0.09
ALP (U/L)	59 (48–71.75)	62 (51–73)	71 (52.5–81.75)	0.17
Total proteins (g/L)	68.5 (65.9–70.5)	68.70 (65.9–71.6)	68.85 (66.1–70.78)	0.55
Albumin (g/L)	42.85 (41.83–44.5)	43.30 (41.9–44.9)	43.45 (41.63–44.93)	0.56
Globulin (g/L)	25.40 (23.33–27)	25.50 (23.4–27.5)	25.80 (24.1–27.48)	0.66
Albumin/globulin	1.72 (1.58–1.83)	1.68 (1.59–1.85)	1.65 (1.58–1.84)	0.82

AST aspartate transaminase ALT alanine transaminase GGT gamma-glutamyl transferase ALP alkaline phosphatase

TABLE IV. Models of multiple regression analysis in FTO variants and liver enzyme parameters

Dependent variable	Independent variable	B (SD)	p value
Aspartate transaminase (AST, U/L)	Genotype		
	Additive model		
	T A	1.521 (0.669)	0.02
	A A	9.321 (1.542)	<0.001
	Dominant model	8.701 (1.526)	<0.001
	Recessive model	2.359 (0.669)	<0.001
	Sex	0.964 (0.596)	0.11
	Age	–0.328 (0.107)	0.005
	BMI	0.129 (0.091)	0.16
Alanine transaminase (ALT, U/L)	T A	2.996 (1.213)	0.014
	A A	21.723 (2.795)	<0.001
	Dominant model	20.491 (2.769)	<0.001
	Recessive model	5.007 (1.241)	<0.001
	Sex	4.068 (1.080)	<0.001
	Age	–0.325 (0.194)	0.094
	BMI	0.948 (0.165)	<0.001
AST/ALT ratio	T A	–0.023 (0.037)	0.53
	A A	–0.148 (0.086)	0.09
	Dominant model	–0.139 (0.085)	0.10
	Recessive model	–0.037 (0.036)	0.31
	Sex	–0.205 (0.033)	<0.001
	Age	–0.003 (0.006)	0.58
	BMI	–0.044 (0.005)	<0.001

Dominant indicates TT and TA vs AA for rs9939609. Recessive indicates TT vs TA and AA for rs9939609

gene polymorphism showed the AST, ALT and AST/ALT were significantly different (Table III).

Association of FTO variants with liver function-related parameters

FTO rs9939609 was strongly associated with AST and ALT in the additive, dominant, and recessive models. ALT had the highest correlation coefficient. Moreover, it was not associated with AST/ALT after adjustment (Table IV).

DISCUSSION

We evaluated the role of the FTO gene in overweight/obesity and liver function-related parameters in Chinese adolescents. We found that FTO rs9939609 polymorphism is closely related to overweight/obesity, and overweight/obesity has a significant effect on the elevation of liver function-related parameters. The newly discovered FTO rs9939609 polymorphism is an important risk factor in the elevation of AST and ALT levels. To our knowledge, this is the first study to evaluate the role of FTO rs9939609 polymorphism on liver function-related parameters in Chinese adolescents.

A strong relationship between FTO rs9939609 polymorphism and BMI has been reported previously.[26–28] Our study showed that the body weight and BMI of rs9939609 AA genotype individuals were significantly higher than other genotypes, the risk of obesity of rs9939609 AA genotype individuals was 3.826 times higher than TT genotype individuals, and the risk of obesity of A allele was 1.488 times higher than T allele. In a recent genome-wide association study (GWAS) study, 6 single nucleotide polymorphisms (SNP) from the FTO gene, including rs9939609, were identified to be associated with obesity in 1110 obese patients and 10 852 Han Chinese controls.[29] Although rs9939609 is the most common SNP in the Chinese population, it has a higher risk allele frequency (41%) in the European population.[30] In our results, the frequency of the A allele in the control group was only 15.9%, which was similar to 13.2% in the Chinese Han population reported previously,[29] indicating racial and geographic differences in the frequency of this locus of FTO.

Our results showed a significant difference in AST, ALT, AST/ALT, GGT, and ALP levels between the overweight/obesity group when compared to the control group, indicating the role of overweight/obesity on various liver enzyme parameters. Some studies have shown that variation in serum liver enzymes in the adolescent population is associated with BMI. A study of 934 adolescents and adults found that AST, ALT and GGT had a significant positive correlation with BMI.[31] Stranges *et al.* evaluated the relationship between body fat and liver enzymes and suggested that central adiposity can predict increased ALT and GGT.[32] Several reports suggest that ALP is expressed by pre-adipocyte cells and is key to the transformation of pre-adipocytes into adipocytes.[33,34] Studies of ALP levels in normal people found that ALP in obese is higher than in lean people.[35,36] It was therefore proposed that ALP may have a role in the regulation of intracellular fat deposition.[37,38] In addition, there was evidence that albumin is widely expressed in adipose tissue of extremely obese patients,[39] and some studies have reported that elevated albumin is associated with abdominal obesity.[10] However, other studies have not observed differences in albumin levels between obese and non-obese normal individuals.[35] We did not find serum albumin to be associated with obesity. Differences in study populations and sample sizes may account for the different results.

We found FTO to be positively correlated with AST and ALT levels in additive, dominant and recessive models, independent of BMI. Few studies have explored the link between FTO and liver function-related parameters. In a rat model of NAFLD induced by a high-fat diet, the increased expression level of FTO was associated with hepatic adipose deposition.[20] Lipopolysaccharide (LPS)-induced FTO expression may contribute to the alteration of mRNA m6A modification in chicken liver.[18] Additionally, FTO rs9939609 variation increases the risk of hepatic steatosis as proposed by several studies in European HIV/Hepatitis C virus co-infected patients[40] and in Chinese patients with non-alcoholic steatohepatitis.[41] FTO likely serves as a component of metabolic hormone signal transduction in liver adipogenesis.[42] Although these trial designs were different from ours, these studies supported our finding that the FTO gene may lead to changes in the AST and ALT. Besides, the FTO gene can alter food intake and plasma metabolism of hormones,[43] and the excess energy can lead to accumulation of fat. However, the signaling pathway of FTO in liver adipogenesis is unclear. Further functional investigations are needed to elucidate its molecular mechanisms.

Our study has a small sample size and our preliminary data needs confirmation in larger independent cohorts.

Conclusion

Our findings suggest that FTO rs9939609 polymorphism was closely correlated with overweight/obesity and liver enzyme parameters. Overweight/obesity was associated with elevated biochemical markers of liver damage, which reflects the adverse effect of overweight/obesity on the liver. On the other hand, the rs9939609 AA genotype is positively correlated with AST and ALT levels, independent of BMI. It supports the hypothesis that the role of the FTO gene in liver metabolism is independent of overweight/obesity.

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Conflicts of interest. None declared

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