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ORIGINAL ARTICLE

Association between the rs2241883 polymorphism of the fatty acid-binding protein-1 (FABP1) gene and obesity in a population of MASHAD study cohort

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Abstract

Background and Aims: The fatty acid-binding proteins (FABPs) gene polymorphisms are related to several metabolic properties. We investigated the association of SNPs rs2241883 of FABP 1 gene with obesity to evaluate the role of FABP1 gene in the pathogenesis of obesity in the population of MASHAD study cohort.

Methods: In this cross-sectional study, 2731 individuals (1883 Obese and 848 nonobese) aged 35 to 65 years old, were enrolled from the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) study cohort. DNA Quantitation was determined using the NanoDrop®-1000 instrument (NanoDrop-Technologies). The rs2241883 polymorphisms were genotyped by double ARMs PCR (double

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amplification refractory mutation system) reactions. Data analysis was carried out using SPSS 22 and a $p < 0.05$ was set for statistical significance.

Results: The results showed that after adjusting for confounding factors, subjects having the CC genotype for rs2241883 polymorphism were at a higher risk of BMI ≥ 30 mg/kg^2 with OR of 1.79 (CI = 1.05–3.07; $p = 0.03$) and 1.76 (CI = 1.04–2.99; $p = 0.04$) comparing with reference group using codominant and dominant models, respectively.

Conclusion: The results showed that CC genotype for rs2241883 polymorphism is related to an increased risk of the obesity in dominant and codominant models in a population of MASHAD study cohort.

KEYWORDS

atherosclerosis, ARMs PCR, FABPs, genotype, metabolic syndrome

1 | INTRODUCTION

Overweight and obesity are defined as abnormal or excessive body fat accumulation that presents a risk to health. A crude population measure of obesity is the body mass index (BMI), a person's weight (in kg) divided by the square of his or her height (in m). A person with a BMI of 30 kg/m^2 or more is generally considered obese. A person with a BMI equal to or more than 25 kg/m^2 is considered overweight (Sheng et al., 2006). Overweight and obesity are major risk factors for a number of chronic diseases, including diabetes mellitus, cardiovascular disease (CVD) and cancer (Aghasizadeh, Samadi, et al., 2021). Although it was once considered a problem only in high income countries, overweight and obesity are now dramatically on the rise in low- and middle-income countries, particularly in urban settings (Sheng et al., 2006).

The fatty acid-binding proteins (FABPs) family are intracellular lipid-binding proteins of low molecular weight, which are involved in the regulation of lipid metabolism, but also in inflammation (Shi et al., 2012). The solubility and intracellular trafficking of long-chain fatty acids involves cytosolic FABPs and other hydrophobic ligands (Parsamanesh et al., 2019; Shi et al., 2012). The FABPs family was discovered in 1972, and comprised at least nine members including liver (L-), heart (H-), adipocyte (A-), intestinal (I-), epidermal (E-), ileal (Il-), brain (B-), myelin (M-) and testis (T-) FABPs (Shi et al., 2012). Fatty acids are important substrates for the biosynthesis, breakdown and storage of lipid in hepatocytes, adipocytes and cardiac myocytes, and comprise up to 5% of all soluble cytosolic proteins (Shi et al., 2012). A-FABP have been reported to be associated with obesity and type 2 diabetes (Aghasizadeh, Zare-Feyzabadi, et al., 2021; Shi et al., 2012). The human FABP1 gene encodes FABP1 (Fatty Acid-Binding Protein 1). Liver-type fatty acid-binding protein (LFABP) is the other name of this protein. FABP1 is expressed in the liver where it accounts for 7%–11% of the total cytosolic protein, but is also expressed in the kidney, pancreas, stomach, intestine and lung (Smathers & Petersen, 2011; Vergani et al., 1990). In comparison with other members of the FABP family, FABP1 has a unique structure, which allows it to bind multiple ligands simultaneously (Wang et al., 2015). FABP1 participates in the metabolism, transport and binding of long-chain fatty acids (LCFAs), phytocannabinoids (and less so for synthetic cannabinoid receptor (CBR) agonists and antagonists), endocannabinoids, and some of the other hydrophobic molecules including bilirubin, monoglycerides, bile acids and fatty acyl CoA (Huang et al., 2016; Levi & Arias, 1969; Mishkin & Turcotte, 1974; Schroeder et al., 2016; Smathers & Petersen, 2011; Storch, 1993; Thumser & Wilton, 1996).

When FABP1 can bind to heme, fatty acids and other molecules that are potentially toxic when unbound, it can play a significant role in preventing cytotoxicity (Wang et al., 2015). The location of FABP1 gene is on the short (p) arm of chromosome 2 from base pair 88,122,982 to base pair 88,128,131 (Dakour-Aridi et al., 2020). Metabolic conditions such as obesity may be associated with altered expression of this protein. According to studies among Chinese young adults, serum FABP1 levels have a strong relationship with lipid profile, body measurements and homeostatic parameters (Amiri-Dashatan et al., 2022; Shi et al., 2012). Individuals with higher serum FABP1 have increased BMI and insulin resistance. This increase in FABP1 acts as a compensatory upregulation of the protein in an attempt to cope with the metabolic stress related to obesity (Shi et al., 2012). The polymorphisms of FABP1 gene related to several metabolic conditions. Studies have shown that SNP rs2241883 at FABP1 is related to an increasing risk for developing nonalcohol fatty liver disease (NAFLD) (Javan et al., 2015; Khalesi et al., 2016; Najafi et al., 2015; Xue et al., 2016).

In order to define the role of FABP1 gene in the pathogenesis of obesity, we investigated the association of the SNPs rs2241883 of FABP 1 gene with obesity in the population of MASHAD study cohort (Valizadeh et al., 2021; Xue et al., 2016).

The minor allele frequency (MAF) of the rs2241883 variant (FABP-1), a missense single nucleotide polymorphism, is approximately 0.22. It has been reported to be associated with changes in the function of a fatty acid transporter protein and dyslipidemia (Fenger et al., 2015; Knüppel et al., 2013; Mansego et al., 2012; Wagh et al., 2012; Wang et al., 2018; Xue et al., 2016; Yamada et al., 2008).

To the best of our knowledge, no studies have been undertaken on the association between the rs2241883variant of the FABP-1 gene and susceptibility to dyslipidemia in an Iranian population. Therefore, the aim of this study was to assess the association between the FABP1 rs2241883 polymorphism and dyslipidemia in individuals taking part in the MASHAD cohort study, a prospective 10 years cohort study of a representative population from northeastern Iran.

2 | METHODS

2.1 | Study population

In this cross-sectional study, 2731 individuals (1883 obese and 848 nonobese) aged 35 to 65 years old, were recruited as part of the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) study cohort. Obesity was defined using the cutoff point value of BMI 30 kg/m^2. And BMI of <30 and $30 \geq kg/m^2$ were considered nonobese and obese subjects, respectively. Subjects with confirmed data regarding definite diagnosis of myocardial infarction (MI), stroke, diabetes mellitus, cancer, and taking some medication including hypertension (HTN) or lipid reducing drugs were excluded. All participants received informed consent and the project was approved by the Ethics Committee of the Mashhad University of Medical Sciences(IR.MUMS.medical.rec. 1386.250).

2.2 | Laboratory and anthropometric assessments

Anthropometric measurements, smoking status and other assessments have been described previously (Valizadeh et al., 2021). BMI as a measure of body fat based on body weight (kg) divided by squared height in meters (m^2). Biochemical parameters (fasting blood glucose (FBG), and blood pressure) and lipid profile were measured, and analyzed using a autoanalyzer BT3000 (Ghazizadeh et al., 2020).

2.3 | Genotyping

Blood was obtained from all participants using an anticoagulant tube comprising ethylene diamine tetra-acetic acid (EDTA). DNA samples were extracted by the salting out method (Mardan-Nik et al., 2019), and were stored at −20°C. Quantitation of DNA was determined using the NanoDrop®-1000 instrument (NanoDrop-Technologies). We selected the rs2241883 polymorphisms to explore the association, genotyped them by double ARMs PCR (double amplification refractory mutation system) reactions. The ARMS PCR reaction were performed in duplicate in a 13 µL final volume containing 2 µL of DNA samples, 6 µL of PCR Master Mix, 0.32 µL for forward and reverse outer primers and 0.52 for forward and reverse inner primers, respectively, for polymorphic region of rs2241883. PCR amplification was carried out by denaturation at 95°C for 5 min, followed by 31 cycles of 95°C for 1 min, 65°C for 1 min and 72°C for 1 min with a final extension at 72°C for 5 min. Three bands were identified: 208 bp for TT, 275 bp for CC and 539 bp. Genotyping reagents were purchased from Applied Biosystems (ABI-Veriti 96-well Thermal Cycler). Post PCR stage was undertaken using 2% agarose gel (Figure 1). Eventually, the FABP-1 genotypes were confirmed by Sanger sequencing (Figure 2). All sequenced sample were analyzed by Finch TV version 1.4.0.

2.4 | Statistical analysis

Data analysis was carried out using SPSS 22 (SPSS Inc.). Using Kolmogorov Smirnov tests, the normality of distribution of successive variables was evaluated. We defined descriptive analysis such as mean, frequency and standard deviation (SD) for all variables and represented them as mean ± SD for normally distributed variables or as median and IQR (interquartile range) for variables that are not normally distributed. We used the Student *t* test for variables that are usually distributed. A Mann–Whitney and Kruskal-Wallis tests were used for nonparametric results. After adjusting for sex, smoking, PAL. Multivariable Logistic regression analysis was used. Logistic regression modeling was used to test the relationship between genetic polymorphism and obesity. All analyses were two-sided, and a $p < 0.05$ was set for statistical significance.

3 | RESULTS

Demographic and baseline characteristics of the population between different groups are presented in Table 1. There was a significant difference in sex, age, smoking status, BMI, physical activity, total cholesterol (TC), FBG,

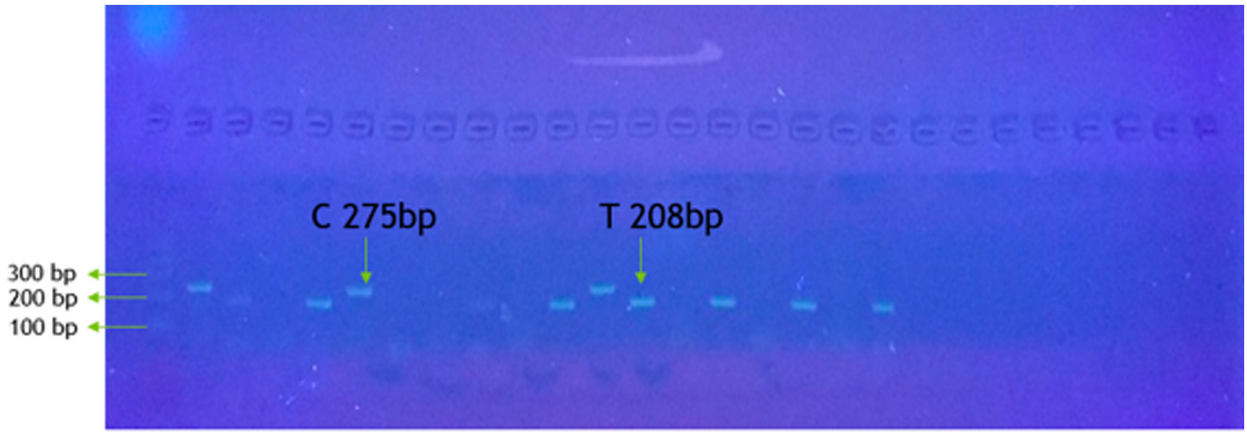

FIGURE 1 Agarose gel electrophoresis of samples genotyped using T-ARMS-PCR assay.

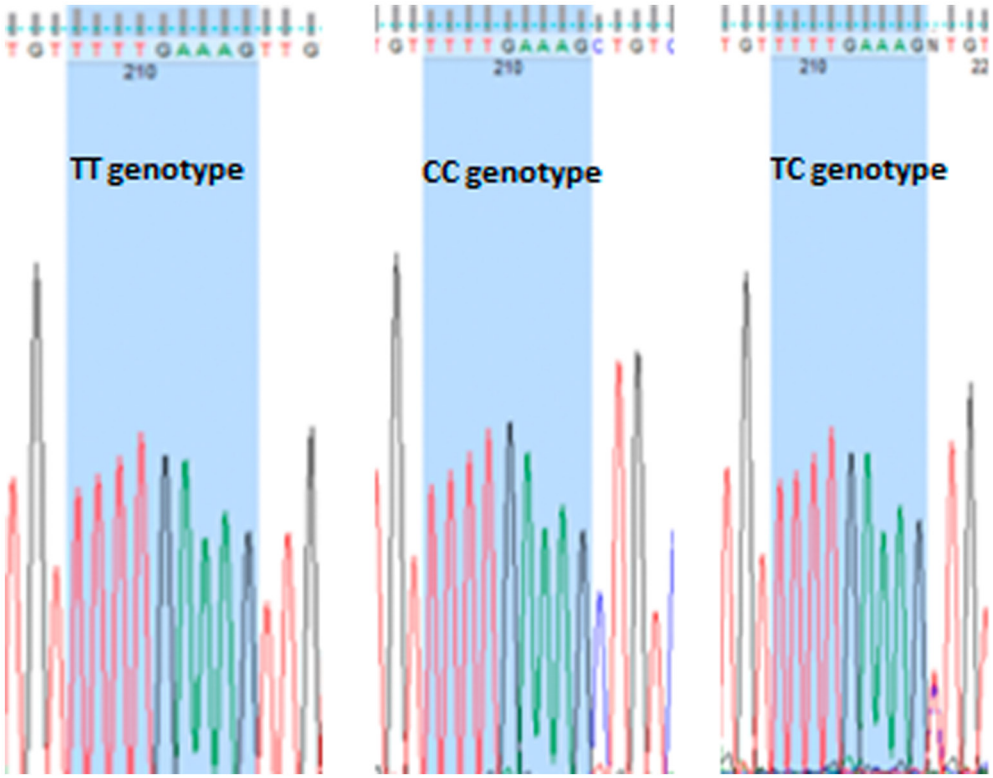

FIGURE 2 Representative chromatograms of sequenced samples showing three genotypes

hs-CRP, TG and frequency of genotype between the obese and nonobese groups ($p < 0.001$ for all variables).

According to the association between obesity and the genetic polymorphism in Table 2 individuals with CC genotype were at a higher risk of high level of BMI. Furthermore, as shown in Table 3, after adjusting for confounding factors, subjects who carried the CC genotype for rs2241883 polymorphism were at a higher risk of BMI ≥ 30 mg/kg^2 with OR of 1.79 (CI = 1.05–3.07; $p = 0.03$) and 1.76 (CI = 1.04–2.99; $p = 0.04$) compared to reference group using codominant and dominant models, respectively.

4 | DISCUSSION

The results showed that subjects with the CC genotype for rs2241883 polymorphism were at a higher risk of BMI ≥ 30 mg/kg^2 compared to reference group using codominant and dominant models, respectively, in a population of MASHAD study cohort.

In a similar study to ours, Shi et al. (2012) reported an association between liver fatty acid-binding protein (FABP1) with obesity and insulin resistance in Chinese young people under 30 years old. They suggested that (FABP1) plays a significant role in adiposity. They were

TABLE 1 Baseline characteristics of the study population.

Variables	BMI < 24.99 mg/kg^2	BMI 24.99–29.99 mg/kg^2	BMI ≥ 30 mg/kg^2	*p*-value
Gender, male	486 (65.1%)	576 (50.7%)	250 (29.4%)	**<0.001**
Age range (years)	49.0 (14.0)	49.0 (12.0)	50.0 (11.0)	0.063
Smoking status				
Nonsmoker	472 (63.3%)	789 (69.6%)	617 (72.6%)	**<0.001**
Ex-smoker	81 (10.9%)	133 (11.7%)	85 (10.0%)	
Current smoker	193 (25.9%)	212 (18.7%)	148 (17.4%)	
Physical activity level	1.65 (0.4)	1.58 (0.4)	1.51 (0.3)	**<0.001**
Fasting blood glucose (mg/dL)	80.0 (16.0)	84.0 (19.0)	86.0 (24.0)	**<0.001**
Serum cholesterol (mg/dL)	181.0 (50.0)	191.0 (53.0)	194.0 (51.0)	**<0.001**
Serum low density lipoprotein cholesterol (mg/dL)	110.9 (45.4)	113.6 (49.7)	116.6 (45.1)	0.086
Serum high density lipoprotein cholesterol (mg/dL)	43.3 (15.4)	41.0 (16.4)	41.0 (15.7)	**<0.001**
Serum triglyceride (mg/dL)	93.0 (62.0)	127.0 (95.0)	141.0 (97.0)	**<0.001**
hs-CRP (g/dL)	1.3 (1.5)	1.68 (2.4)	2.69 (4.5)	**<0.001**
Codominant				
TT	449 (27.1%)	701 (42.4%)	505 (30.5%)	0.126
CC	27 (21.3%)	48 (37.8%)	52 (40.9%)	
CT	270 (28.5%)	386 (40.7%)	293 (30.9%)	
Dominant				
TT/CT	719 (27.6%)	1087 (41.7%)	798 (30.6%)	**0.04**
CC	27 (21.3%)	48 (37.8%)	52 (40.9%)	
Recessive				
TT	449 (27.1%)	701 (42.4%)	505 (30.5%)	0.55
CT/CC	297 (27.6%)	434 (40.3%)	345 (32.1%)	
Allele				
T	1168 (27.4%)	1788 (42.0%)	1303 (30.6%)	0.27
C	324 (26.9%)	482 (40.1%)	397 (33.0%)	

Note: Student t and Mann–Whitney tests were used. Significantly association was shown as bold values.

Abbreviation: hs-CRP, high sensitivity C-reactive protein.

measured anthropometric measurements, serum FABP1 and biochemical characteristics in 372 people including 200 obese and 172 normal-weights. FABP1 levels were significantly higher in obese subjects than the other subjects. In young Chinese adults serum FABP1 levels correlated to anthropomorphic measurements, lipid profile and glucose homeostatic parameters (Shi et al., 2012).

The data from another study among Spanish population were revealed the influence of common variant of LFABP gene on the risk of type 2 diabetes and insulin resistance. They observed two groups of people. At the first time 1502 subjects without any serious disease and with high genotyping call rate and for repetition 805 subjects were observed. The results showed that rs2197076 SNPs of FABP-1 gene and one haplotype of it were associated with an elevated risk of type 2 diabetes (Mansego et al., 2012).

Peng and his coworkers wanted to investigate the association between FABP1 Gene Promoter Region Polymorphism with altered serum triglyceride levels. In this study they selected 1182 subjects (male/female: 817/365, aged 18–72 years) from the people who visiting the hospital for medical check-ups in China, but they had no acute disease like CVD, Type 1 diabetes or pregnancy and also not receiving any drugs related to lipid measures. High levels of FABP1 increase the risk of CVD and metabolic disorders. They indicated that subjects with the rs2919872 G>A variant have associated with serum TG concentration (Peng et al., 2015).

Association of single-nucleotide polymorphisms rs2197076 and rs2241883 ofFABP1gene with polycystic ovary syndrome (PCOS) was investigated by Xue et al. (2016). This study was done on 221 PCOS cases (mean age 29.32 years) and 198 controls (mean age 31.43 years) from Shandong. The allele frequency analysis indicated a significant relation of SNPs rs2197076 and rs2241883 of FABP1 gene with PCOS.

TABLE 2 Association between the Genetic variant and obesity before adjusting for confounding factors.

		BMI < 24.99	BMI 24.99–29.99		BMI≥30	
Variables	**SNP *n* (%)**	**OR (CI 95%)**	**OR (CI 95%)**	***p*-value**	**OR (CI 95%)**	***p*-value**
Codominant	TT	Ref.	Ref.	Ref.	Ref	Ref
	CT	Ref.	0.92 (0.75–1.11)	0.38	0.97 (0.78–1.19)	0.74
	CC	Ref.	1.14 (0.70–1.85)	0.6	1.71 (1.06–2.77)	**0.03**
Dominant	TT/CT	Ref.	Ref.	Ref.	Ref	Ref
	CC	Ref.	1.18 (0.73–1.90)	0.51	1.74 (1.08–2.79)	**0.02**
Recessive	TT	Ref.	Ref.	Ref.	Ref	Ref
	CT/CC	Ref.	0.94 (0.78–1.13)	0.49	1.03 (0.85–1.26)	0.75
Allele	T	Ref.	Ref.	Ref.	Ref	Ref
	C	Ref.	0.97 (0.83–1.14)	0.72	1.09 (0.93–1.30)	0.27

Note: Model 1. Before adjusting for confounding factors. Logistic regression analysis was used. Significantly association was shown as bold values.

TABLE 3 Association between the Genetic variant and obesity after adjusting for confounding factors.

		BMI < 24.99	BMI 24.99–29.99		BMI ≥30	
Variables	**SNP *n* (%)**	**OR (CI 95%)**	**OR (CI 95%)**	***p*-value**	**OR (CI 95%)**	***p*-value**
Codominant	TT	Ref.	Ref.	Ref.	Ref	Ref
	CT	Ref.	0.98 (0.79–1.19)	0.81	1.05 (0.83–1.34)	0.69
	CC	Ref.	1.11 (0.67–1.83)	0.68	1.79 (1.05–3.07)	**0.03**
Dominant	TT/CT	Ref.	Ref.	Ref.	Ref	Ref
	CC	Ref.	1.12 (0.68–1.84)	0.65	1.76 (1.04–2.99)	**0.04**
Recessive	TT	Ref.	Ref.	Ref.	Ref	Ref
	CT/CC	Ref.	0.99 (0.81–1.21)	0.92	1.12 (0.89–1.41)	0.32
	C	Ref.				

Note: After adjusting for sex, smoking, PAL. Multivariable Logistic regression analysis was used. Significantly association was shown as bold values.

SNPs of LFABP gene effect on metabolism of lipids and cellular signaling pathways (Saberi-Karimian et al., 2021). The association of FABP1 polymorphisms with liver diseases as steatotic hepatocellular carcinoma was well known (Bahrami et al., 2016). Wang et al. (2018) wanted to realize the association between two SNPs of FABP1 rs1545224 and rs2241883 and hepatitis B virus-related liver cirrhosis (LC) and hepatocellular carcinoma (HCC). The study was performed on 1000 individuals including 250 healthy people, 250 CHB patients, 250 LC patients and 250 HCC patients in China. Results showed the influence of FABP1 rs1545224 and rs2241883 on the aptitude of LC and HCC in healthy individuals or CHB carriers. FABP1 rs1545224 polymorphism increases the HCC risk in LC patients in China.

In another study by Bu et al. (2011), association of single nucleotide polymorphisms (SNPs) in FABP1-5 with type 2 diabetes mellitus (T2DM) was investigated. Analysis were done on 650 DNA samples (control and T2DM from) in America. The results showed the distinct role of DNA polymorphisms in the FABP5 gene in outbreak and developing of T2DM. The rs454550 SNP of FABP5 have an acute association with T2DM but the other SNPs are not so.

5 | CONCLUSIONS

The CC genotype for rs2241883 polymorphism appears to be related to an increased risk of the obesity in dominant and codominant models in a population of MASHAD study cohort.

AUTHOR CONTRIBUTIONS

We declare that we contributed significantly towards the research study; MGH, ARP, and MV designed the experiments. MA, MV, AM, RZF, HSTA, and FSH performed the experiments. MA, MH, FNSD, and MSK wrote the manuscript. EAB, SHAB, HE, HGH, and NSH carried out the data analysis. MA, MV, and GAF revised the manuscript. All authors reviewed, considered, and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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