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Association between chemerin rs17173608 polymorphism and obesity in Iranian women

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Abstract

Chemerin is a novel adipokine that regulates adipogenesis and adipocyte metabolism. Circulating levels of chemerin significantly correlated with body mass index (BMI) and obesity. In this study, we investigate the association of *chemerin* rs17173608 polymorphism and obesity risk. A total of 300 Iranian women was subjected to genotyping. Genotype determination was performed by tetra-amplification refractory mutation system-PCR (T-ARMS PCR) method. Our finding showed a significant association between GT (OR:2.8, 95% CI: 1.6-4.9, P<0.001) and GG (OR: 8.4, 95% CI: 2.1-33.8, P: 0.003) genotypes with overweight and obesity respectively. In the dominant genetic model (comparison of GT+GG vs. TT), GT+GG genotypes showed increased risk of overweight and obesity. Here we suggest that, for the first time, *chemerin* rs17173608 polymorphism is significantly associated with overweight and obesity in Iranian women.

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Introduction

Obesity is a complex, multifaceted disease resulting from a combination of genetic background, environmental, and lifestyle factors, and are intrinsically associated with increased risk of associated disease, such as hypertension, dyslipidemia, and type 2 diabetes (Mokdad *et al.*, 2003). According to recent reports, about 1.5 billion people are overweight and a third of them obese (Bozaoglu *et al.*, 2010). Although the prevalence of obesity has reached 50% in developed countries, many developing countries face this health problem, especially among women (Low *et al.*, 2009). The prevalence of obesity among Iranian women has increased dramatically to 20.8% from 16.5% over 3 years (1998 to 2001) according to a national study(Azizi *et al.*, 2005).

Adipose tissue is now known as the biggest endocrine organ of the human body. This tissue secretes a number of adipocytokines with multiple functions in metabolic profile and immunological process (Shin *et al.*, 2012). Chemerin is a newly discovered adipocytokine that regulates adipocyte development and metabolic function as well as immune function (Bozaoglu *et al.*, 2007; Goralseki *et al.*, 2007). Chemerin, also known as retinoic acid receptor responder protein 2 (RARRES2), tazarotene-induced gene 2 protein (TIG2), or RAR-responsive protein TIG2, is a protein that is encoded by the *RARRES2* gene in humans (Duvic *et al.*, 1997; Roh *et al.*, 2007). *Chemerin* gene expression was significantly elevated in the adipose depots of the obese compared with lean animals and was predominantly expressed by adipocytes rather than stromal and vascular cells in adipose tissue (Shin *et al.*, 2012). In human, the expression of *chemerin* is increased in obese individuals and circulating chemerin levels have been shown to correlate with body mass index (BMI), waist-to-hip ratio and adipocyte volume (Bozaoglu *et al.*, 2007; Goralseki *et al.*, 2007; Stell *et al.*, 2009). However, to date, there is no clinical study regarding the relationship between *chemerin* gene polymorphisms and obesity risk. Therefore, we investigated the association of rs17173608 *chemerin* gene polymorphism and obesity risk in Iranian women.

Material and methods

subjects

The present case-control study was performed on 300 unrelated Iranian women with an age range 16-46 years. BMI was calculated as weight in kg divided by (height)^2 in m^2. The BMI classification was as follows: normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese (≥30 kg/m^2). Therefore, 141 normal, 99 overweight and 60 obese women participated in this study. Ethical approvals for recruitment were obtained from the local Ethics Committee of Shiraz university of medical sciences and informed consent were obtained from all individuals. Blood samples were collected in EDTA-containing tubes.

Genotyping

Genomic DNA was isolated from peripheral blood leukocyte using standard methods. Genotyping of *chemerin* rs17173608 was carried out using Tetra amplification refractory mutation system polymerase chain reaction (T-ARMS-PCR) as described previously by Hashemi *et al.*, 2012. The sequence of the primers is shown in Table 1. PCR amplification was carried out in 25 µl reaction mixture by using 100-200ng DNA, 0.5µl dNTP 10mM, 0.75 µl MgCl2 50 mM, 10 pm/µl of each primers, 0.3 U Taq DNA polymerase 5 U/µl (Cinnagen, Iran). The PCR consisted of an initial denaturation for 5 min at 95 °C, followed by 30 cycles of denaturation at 95 °C for 30 s, annealing at 65 °C for 30 s, and extension at 72 °C at 30 s, with a final extension at 72 °C for 5 min. PCR products were detected on 2% agarose gel containing ethidium bromide.

Statistical analysis

All the calculation and statistical analyses were performed by the Statistical Package for Social Sciences (SPSS) software version 18. The Anthropometric characteristics were presented as mean ± SD (standard deviation). One-way analysis of ANOVA was used to compare Anthropometric

characteristics based on the obese and control groups. Genotype and allelic frequencies were compared between the groups by chi-squared test. Multivariate logistic regression was performed to evaluate the association of *chemerin* rs17173608 genotypes and obesity risk. Differences were considered significant when $p< 0.05$.

Results

Figure 1. shows the electrophoresis pattern of T-ARMS-PCR for detection of *chemerin* rs17173608 polymorphism. Anthropometric characteristics of the study population are shown in Table 2. There were significant differences in weight and BMI between the three groups.

Table 1. The primer sequences for detection of *chemerin rs17173608* polymorphism.

polymorphism	Primers	Sequence (5' to 3')
Chemerin rs17173608	F1 (G allele):	ATTGCTATAGTCCAGTGCCCTTCG
	R1 (T allele):	CCAGTTCCCTCTGTCGGCTTAA
	Fo	GTCAGACCCATGCAGTTTTCAAAC
	Ro	GAGTTCCTCTCTCAAGCATCAGGG

Table 2. Anthropometric characteristics in subjects.

	Control	Overweight	obese	P
Age (year)	29.1±5.3	29.7±4.9	29.5±6.5	0.67
Height (cm)	161.8±6.3	161.5±6.5	161.4±7.1	0.43
Weight (kg)	58.6±7.2	7.5±7.2	82±15	<0.001
BMI (kg/m²)	22.2±1.9	26.9±1.3	33.7±3.5	<0.001

The genotype and allele frequencies of the *chemerin* rs17173608 in control, overweight and obese subjects were shown in Table 3. As shown in the table, the TT genotype frequency is 67.4%, 41.4% and 50% in the control, overweight and obese groups, respectively; while the frequency of GG genotype is 2.1%, 5.1% and 13.3% respectively in the above mentioned groups. Also, the G allele frequency in the control group was 17%, while in overweight and obese groups were 32%. Multivariate logistic regression showed that women with TG and GG genotypes, as compared to TT genotype, had a higher risk for overweight and obesity (Table 4). In the dominant effect of the A allele (comparison between GT+GG vs. TT) GT+TT genotypes were associated with overweight and obesity risk. *Chemerin* rs17173806 polymorphism showed a significant association with overweight and obesity.

Discussion

In this study, we present novel findings of an association between *chemerin* rs17173608 gene polymorphism and risk of obesity in women. The *chemerin* rs17173608 polymorphism increased the risk of overweight and obesity in our population. The results show that rs17173608 *chemerin* genetic polymorphisms may specifically contribute to the development of adiposity.

Table 3. Genotype and allele frequencies of the *chemerin* rs17173608 in the subjects.

		Chemerin genotypes		Allele	Allele
BMI	TT(%)	GT(%)	GG(%)	T(%)	A(%)
BMI<25	95 (67.4)	43(30.5)	3 (2.1)	233 (83)	49 (17)
30>BMI≥25	41 (41.4)	53 (53.5)	5 (5.1)	135 (68)	63 (32)
BMI≥30	30 (50)	22 (36.7)	8 (13.3)	88 (68)	38 (32)

Obesity and overweight represent major health burdens worldwide. Obesity plays a central role in the pathogenesis of several conditions, including insulin resistance, type 2 diabetes mellitus (T2DM), hypertension, atherosclerosis and coronary artery disease (Hamdy *et al.*, 2006). Recent evidence

demonstrates the role of chemerin in the development of obesity-related insulin resistance and inflammation (Fülöp *et al.*, 2014; Sell *et al.*, 2009). Furthermore, the expression of chemerin is increased in obese individuals (Bozaoglu *et al.,* 2007; Goralski *et al.*, 2007), and circulating chemerin levels have been shown to correlate with BMI and adipocyte volume (Bozaoglu *et al.,* 2009; Sell *et al.*, 2009). Several studies have shown that circulating chemerin levels are elevated in both obese humans and obese/diabetic experimental animals (Bozaoglu *et al.*, 2007; Ernst *et al.*, 2010; Sell *et al.*, 2010). Bozaoglu *et al.*, (2009) reported that chemerin levels was associated positively with BMI and the markers of inflammation and metabolic syndrome in human. Alfadda *et al.*, (2012) have found a positive, statistically significant correlation between circulating chemerin and BMI. They detected a gender-related difference in chemerin mRNA expression and reported that women express more chemerin mRNA than men in both subcutaneous and visceral tissues. These finding suggest that chemerin may play a role in the pathophisiology of obesity, especially in women. Thus, we investigated the relationship between *chemerin* rs17173608 polymorphism and obesity. To date, there is no clinical study regarding the impact of *chemerin* polymorphism on obesity in women. Mussing *et al.*, (2009) reported that *chemerin* rs17173608 and rs10278590 polymorphisms were associated with increased visceral fat mass in non-obese subjects, although these polymorphisms were not associated with total adiposity. In the present study, we found that chemerin rs17173608 polymorphism is associated with overweight and obesity in women. This polymorphism is located in intron 2 of the *chemerin* gene and appears to show potential clinical significance.

Table 4. The association between BMI and chemerin rs17173608 genotypes

Condition	Genotype	OR(95%CI)	P
	TT	0.34(0.2-0.6)	<0.001
30>BMI≥25	GT	2.8(1.6-4.9)	<0.001
	GG	3.8(0.9-16.9)	0.07
	TG+GG	2.9(1.7-4.9)	<0.001
	TT	0.48(0.3-0.9)	0.02
BMI≥30	GT	1.6(0.8-3.1)	0.15
	GG	8.4(2.1-33)	0.003
	GT+GG	2.1(1.1-3.8)	0.02

Reference group: BMI<25.

In conclusion, our finding showed that *chemerin* rs17173608 gene polymorphism may contribute to susceptibility to overweight and obesity in Iranian women. Larger studies with different ethnicities are required to validate our findings.

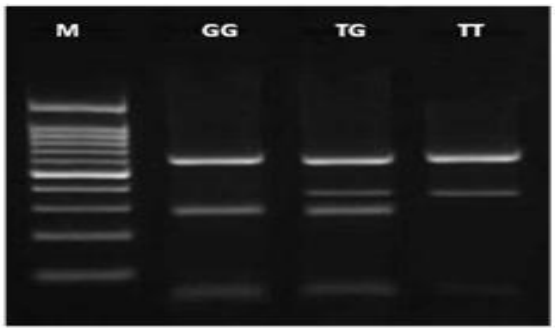

Fig. 1. Electrophoresis pattern of T-ARMS PCR for the detection of SNP in *chemerin* rs17173608. M; DNA marker. Product sizes were 262 bp for G allele, 332 bp for T allele, and 549 bp for two outer primers (control band).

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