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Research paper

Association between chemerin rs17173608 and rs4721 gene polymorphisms and gestational diabetes mellitus in Iranian pregnant women

Zahra Hasanvand[a,1], Abdorrahim Sadeghi[a,b,1], Mohammad Reza Rezvanfar[c], Mohammad Taghi Goodarzi[d], Golzar Rahmannezhad[a], Farideh Jalali Mashayekhi[a,c,*]

[a] Department of Clinical Biochemistry and Genetics, Faculty of Medicine, Arak University of Medical Sciences, Arak, Iran
[b] Molecular and Medicine Research Center, Arak University of Medical Sciences, Arak, Iran
[c] Endocrinology and Metabolism Research Center, Arak University of Medical Sciences, Arak, Iran
[d] Research Center for Molecular Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

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ABSTRACT

Gestational diabetes mellitus (GDM) is defined as hyperglycemia detected during pregnancy and its risk is increased with obesity. Chemerin, an adipokine, has been proposed as potential mediators of insulin resistance in GDM. This case-control study was designed to assess the relation between chemerin SNPs rs4721 (or rs10278590) and rs17173608 and the development of GDM. One hundred thirty GDM pregnant women with GDM and 160 healthy pregnant women were enrolled in this study. The diagnosis of GDM was based on the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria. Chemerin rs4721 polymorphism gene was amplified through PCR, and SNP was detected using restriction enzyme *Alu*I. Genotyping for chemerin rs17173608 polymorphism was performed by using tetra-amplification refractory mutation system polymerase chain reaction (T-ARMS-PCR). Blood glucose level was measured by an enzymatic method. Our finding showed that the genotypes frequency of chemerin rs4721 polymorphism was significantly different between GDM and non-GDM groups ($\chi^2 = 7.44$, P = 0.02). The genotype of rs4721 was significantly associated with GDM in co-dominant and dominant genotypes (GG vs GT, OR = 2.3, 95%CI = 1.24–4.24, P = 0.008, and GG vs GT + TT, OR = 2.21, 95%CI = 1.23–3.99, P = 0.008, respectively). No significant difference was observed in allele frequency between case and control groups (P = 0.62). Moreover, the genotypes and allele frequencies of chemerin rs17173608 polymorphism did not show significant differences between GDM and non-GDM (P > 0.05). We concluded that the genotype of rs4721 was found to contribute significant risk to GDM while genotype of rs17173608 could not predict the risk of GDM.

1. Introduction

Gestational diabetes mellitus (GDM) is defined as a metabolic disorder of carbohydrate with onset or first recognition of pregnancy and occurs in 1–14% of pregnant women (Lowe et al., 2016; Siddiqui and George, 2017). Additionally, the prevalence of GDM is reported as ~5% of all pregnancies in Iran (Jafari-Shobeiri et al., 2015). Women with a history of GDM carry a high risk for the development Type 2 diabetes (T2DM) in the postpartum period (Lowe et al., 2016). GDM is also characterized by insulin resistance resulting in hyperglycemia leading to acute and chronic complications in both mother and newborn (Kim, 2010). Ample investigations in the other laboratories have reported maternal obesity, maternal age, dietary habit, genetic, ethnic origin, and family history of diabetes increase the risk of a GDM pregnancy (Strehlow and Mestman, 2005; Moosazadeh et al., 2017). Additionally, increase in the adipose deposits, obesity, could lead to the development of insulin resistance and as a predictor of diabetes (Pirjani et al., 2016). Adipokines secreted by adipose tissue have been proposed to be potential mediators of insulin resistance in GDM (Siddiqui and George, 2017). Chemerin is an adipokine suggested to play a role in the regulation of the glucose metabolism, adipogenesis and obesity, also in their metabolic complications such as diabetes and metabolic syndrome

Abbreviations: IADPSG, Association of Diabetes and Pregnancy Study Group; FBG, fasting blood glucose; 1hPPG, 1 hour Post Prandial Glucose; 2hPPG, 2 hours Post Prandial Glucose; GDM, gestational diabetes mellitus; MeS, metabolic syndrome; SNP, single nucleotide polymorphism; T-ARMS-PCR, tetra-amplification refractory mutation system polymerase chain reaction; T2D, Type 2 diabetes

* Corresponding author at: Department of Clinical Biochemistry and Genetics, Arak University of Medical Sciences, Iran.
E-mail address: mashayekhi@arakmu.ac.ir (F.J. Mashayekhi).

[1] Both authors contributed equally to this work.

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(Roman et al., 2012; Roh et al., 2007). Inconsistent findings have been reported about serum levels of chemerin in women with GDM (Yang et al., 2017; Pan and Ma, 2016; Fatima et al., 2017; Gorkem et al., 2016).The chemerin gene, also known as the retinoic acid receptor responder 2 (RARRES2), and tazarotene-induced gene 2 (TIG2) (Müssig et al., 2009; Goralski et al., 2007). Chemerin is located on chromosome 7q36.1 and is composed of 6 exons and 5 introns, which encodes a protein of 163 amino acids (Huang et al., 2016). rs17173608 (T > G) and rs10278590 (G > T) which has well known rs4721, are located in the intron 3 and 3′ UTR of chemerin, respectively and located within noncoding regions. It is suggested that these single-nucleotide polymorphisms (SNPs) probably affect only gene expression and not the function of the gene product (Müssig et al., 2009). In recent years, a number of polymorphisms in candidate genes such as adipokines that may influence susceptibility to GDM have been studied extensively (Zhang et al., 2013). In our previous study, we have also found an association between VDR gene polymorphisms and GDM in an Iranian pregnant women population (Rahmannezhad et al., 2016). Chemerin gene polymorphisms were studied in patients with metabolic syndrome (MeS) and diabetes (Huang et al., 2016; Hashemi et al., 2012; Mehanna et al., 2016). To our knowledge, no report has been published on chemerin gene polymorphism and risk for GDM. Because of the GDM and T2DM share a common genetic background, it is reasonable to evaluate the association between chemerin gene polymorphism and susceptibility to GDM. Therefore, the objective of this study was to find out the possible association between chemerin rs17173608 and rs4721 gene polymorphisms and GDM in an Iranian pregnant women population.

2. Study population and methods

2.1. Ethics statement and subjects

The study protocol was approved by the institutional ethics committee of Arak University of Medical Sciences (Arak, Iran), and written informed consent was obtained from all subjects. This case–control study was carried out on pregnant women in a teaching hospital in Arak University of Medical Sciences (Iran). GDM was defined based on International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria using 75 g Oral Glucose Tolerance Test at 24–28 weeks' gestation (OGTT) (0 min 5.1 mmol/l, 60 min 10.0 mmol/l, 120 min 8.5 mmol/l). GDM cases were detected when one or more of the plasma glucose levels exceeded the threshold value. Based on these criteria, 130 pregnant women with GDM and 160 with non-GDM were recruited to the study. Subjects with current or a previous history of pathological complications including diabetes, liver diseases, and pre-eclampsia were excluded from the study.

2.2. Genotype analysis

Genomic DNA was extracted from anticoagulated blood by using DNG plus Genomic Blood DNA Purification Kit (Sinaclon Co., Iran), in accordance with the manufacturer's instruction. Extracted DNA was stored at −20 °C until further use rs4721 chemerin gene polymorphism was screened using PCR-RFLP (restriction fragment length polymorphisms) method. The sequences of primers are presented in Table 1. PCR reactions were performed in a volume of 25 μl containing 12.5 μl of 2× PCR master mix (Sinaclon Co, Iran), 1 μl of each primer (10 pmol/μl), and 1 μl template DNA (~100 ng/μl). Amplification was carried out in a Peqlab thermal cycler for 30 cycles (45 s at 94 °C, 45 s at 60 °C, and 30 s at 72 °C), followed by a final extension of 10 min at 72 °C. Following PCR, aliquots (10 μl) of PCR product was digested with 0.5 U of the *Alu*I restriction enzyme (Fermentas, EU) at 37 °C for 3 h in 30 μl reaction volumes. Digested products were electrophoresed through 8% acrylamide gel, and visualized in the silver nitrate stained gel. The TT homozygous genotype was marked by a single 159 bp (undigested) fragment, GG homozygous genotype was digested into 2 bands of 98 bp and 61 bp and TG heterozygous genotype was digested into 3 fragments of 159, 98, and 61 bp.

Table 1
Primer sequences for the detection of chemerin gene polymorphisms.

Gene	Primer	Sequence (5′ to 3′)
rs4721 G > T	Forward	CGCTTTATTATCATGGCTGGGG
	Reverse	AGGTCAGAAGCCTGGGAGGAAA
rs17173608 T > G	FI (G allele)	ATTGCTATAGTCCAGTGCCCTTCG
	RI (T allele)	CCAGTTCCCTCTGTCGGCTTAA
	FO	GTCAGACCCATGCAGTTTTCAAAC
	RO	GAGTTCCTCTCTCAAGCATCAGGG

Chemerin rs17173608 gene polymorphism was assessed using Tetra amplification refractory mutation system polymerase chain reaction (T-ARMS-PCR) method as described previously with some modifications (Hashemi et al., 2012). Briefly, PCR condition were performed in a volume of 25 μl containing 12.5 μl of 2× PCR master mix (Sinaclon Co, Iran), 0.7 μl of each FI, and RI primers (10 pmol/μl), and 1 μl template DNA (~100 ng/μl). The sequences of the primers designed are shown in Table 1 (Hashemi et al., 2012). Amplification was done with an initial denaturation step at 95 °C for 5 min, followed by 35 cycles of 45 s at 95 °C, 45 s at 64 °C, and 45 s at 72 °C with a final step at 72 °C for 5 min (Peqlab, Germany). PCR products were electrophoresed through 8% acrylamide gel, and visualized in the silver nitrate stained gels. The genotypes were defined as GG (262 bp), TT (332), GT (262 and 332 bp) and 549 bp for two outer primers (control band).

2.3. Biochemical parameters assay

Serum glucose levels were measured based on glucose oxidase method using a commercially available kit (Pars Azmon, Iran). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

2.4. Data analysis

The Hardy–Weinberg (HW) distribution of the genotypes in the GDM and control groups was assessed. All data were analyzed using SPSS 16.0 software. The biochemical data were compared between the studied groups using the *t*-test. Comparisons in frequency of the chemerin genotypes and allotypes were performed using the chi-square test. The odds ratios (ORs) and 95% confidence intervals (CIs) for the VDR genotype were calculated using logistic regression analysis after adjustment for age. The associations between genotypes and anthropometric and biochemical characteristics was performed using one-way ANOVA with Tukey's post-hoc test. A P value < 0.05 was considered statistically significant.

3. Results

In this study, the population included 130 pregnant women with GDM (age 28.8 ± 3.5 years) and 160 normal pregnant women as the control group (age 28.1 ± 3.8 years). There was no significant difference between the groups regarding age (P = 0.117). The baseline demographic and serum biochemical measurements of the GDM and control groups are presented in Table 2. A significant difference was observed between BMI of the GDM and non-GDM pregnant women (P = 0.0001). The fasting blood glucose (FBG), 1 h- and 2 h-postprandial blood glucose (1hPPG and 2hPPG, respectively) levels were all significantly higher in GDM group compared to control group (all P < 0.001). Noticeably it was found, was the finding that women with a family history of T2DM were at increased risk for developing of GDM (χ^2 = 22.88, OR: 4.18, 95%CI: 2.27–7.71, P = 0.0001).

The genotype/allele frequencies of the rs4721 chemerin gene

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