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Association between miRNA-152 polymorphism and risk of preeclampsia susceptibility

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Abstract

Background Preeclampsia (PE) is one of the main causes of death among the pregnant women as well as newborns. Although the etiological cause of preeclampsia is not yet clear, a range of risk factors has been suggested. MicroRNAs (like miRNA-152) are small non-coding molecules that play a role in a wide spectrum of biological processes, such as cell proliferation and angiogenesis. This study aimed to investigate the possible relationship of miRNA-152 rs12940701 polymorphism and the risk of preeclampsia among the pregnant women as compared with the control group.

Methods Genotyping of miRNA-152 rs12940701 polymorphism was performed using blood and placenta samples of 223 preeclampsia women and 229 normotensive pregnant women by a polymerase chain reaction-restriction fragment length polymorphism method.

Results The results obtained from maternal blood showed an increase in T alleles for PE women, that there was no significant difference between the PE and control group (OR = 1.7, $P = 0.19$). In addition, no significant difference was found in the TT genotype between the two groups (11.6% vs. 7%, OR = 1.4, $P = 0.3$). Similarly, the results obtained from placental samples were identical.

Conclusions A lack of relationship between the polymorphism of miRNA-152 rs12940701 gene and preeclampsia development has been shown.

Keywords Preeclampsia · miRNA-152 · Polymorphism · Gene

Introduction

Preeclampsia (PE) is a disorder which occurs during the pregnancy, and is known to have a multifactorial etiology. The prevalence of PE is estimated to be 2–5% and 10% in developed and developing countries, respectively. In Iran, the prevalence of PE was reported to be 1–8%. PE is known as one of the main causes of mortality among the mothers as well as newborns [1, 2]. This disorder initially involves the placenta; it starts with cytotrophoblast invasion and ends with failure in the function of endothelial cells [2, 3]. It has been suggested that chronic renal failure, mothers aged <19 and over 40, infections, arthrosclerosis, placental barrier damage followed by the presence of trophoblasts in the mother's blood circulation, and chronic hypertension are the risk factors for PE [4–6]. This disorder can also cause fetal problems, including intrauterine growth restriction, stillbirth and abnormal heart beats, low Apgar score, and need for intensive care unit [7, 8]. Etiological factors for PE have not yet been fully identified, inasmuch as it is referred to as "the disease of theories". The possible theories include the inflammatory immune responses, angiogenesis factors, genetic background and changed function of prostaglandins, endothelial cell damage, and abnormal placental invasion [3, 4].

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MicroRNAs (miRNA) are small non-coding RNA molecules containing 19–25 nucleotides of single-strand RNA and are capable of playing a role in a wide spectrum of biological processes. miRNAs bind to the 3′-UTR region of target gene to regulate the expression of mRNA [9, 10]. Single-nucleotide polymorphism (SNP) may change the properties of miRNAs, thereby either affecting their maturation or changing their ability to bind to target mRNA [11].

Current understanding of the details on genetic program required for the pattern of growing vessels in placenta is not fully developed. A range of factors such as vascular endothelial growth factor (VEGF), angiopoietin, placental growth factor (PGF), and fibroblast growth factor (FGF) are suggested as the possible factors; among which the VEGF has been thoroughly studied and approved as an important physiological and pathological factor in placental angiogenesis [2, 12]. On the other hand, miRNA-152 plays a role in cell proliferation, colony formation, and angiogenesis. The miRNA has an impact on the angiogenesis and response to hypoxia by targeting hypoxia-inducible factor 1α (HIF-1α) and VEGF [12, 13]. HIF-1α as a miRNA-152 target gene is known to regulate cellular adaptation which its expression is increased in the placenta in response to hypoxia and binds to the hypoxia-response elements of several target genes (such as VEGF), that are involved in the modulation of angiogenesis [2, 14].

One of the causes of dysregulation of miRNA expression are variations or single-nucleotide polymorphisms in their genes [15]. With this in mind, we aimed to investigate the relationship between the miRNA-152 (rs12940701) polymorphism and the risk of PE in pregnant women. This polymorphism is associated with C to T change at the 3′-UTR region of this miRNA, affecting the methylation of gene. The effects of miRNAs on the risk for various cancers like breast cancer and papillary thyroid have been investigated in a number of studies. The results showed that the mutation in miRNA-152 increases the risk of these types of tumors [16]. To the best of our knowledge, there are no published data on the possible relationship between miRNA-152 polymorphisms and PE.

Materials and methods

In total, 233 women with PE (86 placental samples and 147 maternal blood samples) and 229 normotensive pregnant women (87 placental samples and 142 maternal blood samples) were identified and their samples were genotyped in the Department of Obstetrics and Gynecology of Ali-ibn-Abi Taleb Educational Hospital (Zahedan, Iran). Of the 233 PE patients, 101 cases (43.3%) had early onset and 132 (56.7%) had late onset PE. Written informed consents were signed and approved by all women who participated in this study. Women in the control group had no history of PE in their family. PE occurs after 20 weeks of pregnancy. The clinical symptoms included a systolic and diastolic blood pressure (SBP, DBP) of ≥ 140 and ≥ 90 mmHg, respectively, which was measured at two separate times. Also, protein concentration in PE was estimated to be ≥ 300 mg in 24-h urine, in the urine dipstick test was reported as 2+. The difference between PE and pregnancy-mediated hypertension is the presence of proteinuria in the case of PE [17].

According to the gestational age at which clinical signs of the disease occurred, PE can be divided into early onset PE (EOPE) (diagnostic criteria development before 34 weeks of gestation) and late onset PE (LOPE) (diagnostic criteria development after 34 weeks of gestation) [18]. The study exclusion criteria were as follows: hydatidiform mole, liver dysfunction, chronic hypertension, underlying renal disease, multiple pregnancies, hydrops fetalis, diabetes, systemic lupus erythematosus, and all systemic diseases. Venous blood samples were collected in EDTA-containing tubes and placental samples were collected in tubes. In addition, the maternal blood and placental samples were collected in terms of gestational age at delivery and kept at -80ºC until DNA extraction. Genomic DNA was extracted using the salting-out method. Using restriction fragment length polymorphism (PCR–RFLP), genotypes of miRNA-152 SNP rs12940701 were identified. The forward and reverse primers and the amplicon characteristics are shown in Table 1. The PCR–RFLP Master Mix was prepared as follows: a final volume 15 µL, 0.8 µL of 10 µM forward and reverse primer solutions, 1.5 µL buffer (10X), 0.5 µL of dNTPs 10 µM, 1 µL of Taq DNA polymerase, 1 µL of DNA (100 ng/µL), and 0.75 µL of 50 mM $MgCl_2$. The PCR reaction program was set as follows: denaturation at 95 °C for 5 min followed by 30 cycles at 95 °C for 25 s, annealing at 61 °C for 20 s to

Table 1 Primers and PCR product of miRNA152

SNP	Primer 5′→3′	Product size (bp)	Restriction enzyme	Digest products (bp)
rs12940701	F: TCTGTCATGCACTGACTGCTC R: GGGCATGCTTCTGGAGTCTA	170	DdeI	C:170 T:100 and 70

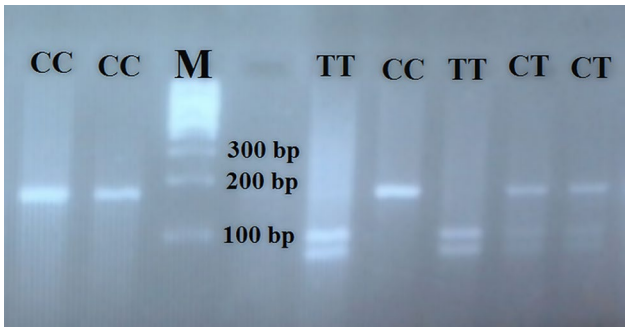

Fig. 1 The PCR–RFLP results of the miRNA-152 rs12940701 polymorphism; M, 100bp DNA marker. PCR product has 170 bp size, which is undigested in CC homozygous individuals (see in figure). Heterozygous samples show three bands at 170 bp, 100 bp, and 70 bp. Samples with only 100 bp and 70 bp bands were homozygous TT

72 °C for 25 s, and a final extension at 72 °C for 5 min. PCR products (8.9 µL) were digested by adding 1 µL of buffer, 0.3 µL of DdeI (Thermo, USA) followed by incubating at 37 °C for 16 h and storage at – 20 °C. The digested products were then obtained by gel electrophoresis at 80 V for 60 min with a 4% agarose gel (Fig. 1).

Statistical analysis

The test results were entered in the database included in the SPSS software (version 23; USA). The clinical and demographic characteristics of both groups were compared using independent Student's *t* test. Additionally, the independent effect of each polymorphism on PE risk was assessed by logistic regression analysis. The odd ratios with 95% confidence intervals were used to determine the association between the polymorphisms and PE. A *P* value of ≤ 0.05 was considered statistically significant.

Results

Table 2 presents the clinical and demographic characteristics of the PE and control groups. There was not an age difference between the PE and control groups. Nevertheless, a significant difference was found between the PE and control groups in terms of the gestational age at delivery, the newborn's birth weight. Of the 233 PE patients, 101 case (43.3%) had early onset and 132 (56.7%) had late onset PE. The analysis of both maternal blood and placenta samples showed no significant difference between late-onset PE and early-onset PE groups with respect to miRNA-152 polymorphism.

miRNA152 rs12940701 polymorphism and PE

The frequency of genotypes and miRNA-152 rs12940701 polymorphism alleles for PE and control groups (placenta and maternal blood) are given in Tables 3 and 4. CT, CC genotypes frequency in blood sample of mothers was not different from that of TT genotype (OR = 1.7, *P* = 0.19). Additionally, no significant increase in the frequency of TT genotype was found between the PE and control groups (11.6% vs. 7%, OR = 1.4, *P* = 0.3). In spite of increased T alleles for PE women, the evaluation of frequency showed that there was not a significant difference between the case and control groups (genotype *P* = 0.3). As with polymorphism

Table 2 Demographic characteristics of PE women and controls

Variable	Controls (*N* = 229)	PE (*N* = 233)	*P* value
Maternal age (mean ± SD, years)	28.2 ± 6.3	27.4 ± 6.6	0.2
Gestation age (mean ± SD, days)	269 ± 14	251 ± 22	< 0.0001
Birth weight (mean ± SD, kg)	3.06 ± 0.41	2.87 ± 0.49	< 0.001
SBP (mean ± SD, mmHg)	115 ± 9.3	144 ± 22.2	< 0.0001
DBP (mean ± SD, mmHg)	71.6 ± 11.6	90.7 ± 13.8	< 0.0001

Table 3 genotypic frequencies of maternal miRNA-152 rs12940701 polymorphism in the control and PE groups

miRNA-152 rs12940701	PE (*N* = 142)	Controls (*N* = 147)	*P*-value	OR (95% CI)
CC, *n* (%)	79 (53.7)	69 (48.6)		1
CT, *n* (%)	51 (34.7)	63 (44.4)	0.1	0.7 (0.4–1.1)
TT, *n* (%)	17 (11.6)	10 (7.0)	0.3	1.4 (0.6–3.5)
Recessive (TT vs. CT+ CC)	(17 vs 130)	(10 vs 132)	0.19	1.7 (0.8–1.9)
Dominant (CT + TT vs. CC)	(68 vs 79)	(73 vs 69)	0.38	0.8 (0.5–1.3)
Allele				
C, *n* (%)	209 (71.1)	201 (70.1)		1
T, *n* (%)	85 (28.9)	83 (29.9)	0.9	1.01 (0.7–1.4)

Table 4 Allelic and genotypic frequencies of the placental miRNA-152 rs12940701 polymorphism in the control and PE groups

miRNA-152 rs12940701	PE ($N=86$)	Control ($N=87$)	*P*-value	OR (95% CI)
CC, *n* (%)	47 (54.7)	45 (51.7)		1
CT, *n* (%)	30 (34.9)	37 (42.5)	0.1	0.8 (0.4–1.5)
TT, *n* (%)	9 (10.5)	5 (5.7)	0.3	1.7 (0.5–5.5)
Recessive (TT vs. CT+ CC)	(9 vs. 77)	(5 vs 82)	0.26	1.9 (0.6–6)
Dominant (CT + TT vs. CC)	(39 vs. 47)	(42 vs 45)	0.70	0.9 (0.5–1.6)
Allele				
C, *n* (%)	124 (72.1)	127 (73)		1
T, *n* (%)	48 (27.9)	47 (27)	0.1	1.5 (0.9–2.4)

in maternal, the results obtained from placental samples were identical. Hence, this polymorphism did not show any association with the PE. There was no significant difference between late-onset PE and early-onset PE groups with respect to miRNA-152 polymorphism (data not shown).

Discussion

In the present study, the relationship between the rs12940701 polymorphism of the miRNA-152 gene and the PE was investigated for the first time. The aim of this study was to compare the frequency of the polymorphism in maternal blood and placenta samples of patients with PE and the control group. Our results indicated that there was no significant difference in the genotypes between the two groups, thereby lacking the relationship between the rs12940701 polymorphism of the miRNA-152 gene and the risk of PE. Development of the new biomarkers can be employed as a useful strategy for earlier diagnosis and more efficient management of the common pregnancy disorders, such as PE, gestational diabetes, and recurrent pregnancy loss. Nowadays, miRNAs have been introduced as new biomarkers for pregnancy disorders [19]. Studies have suggested the relationship between the insufficient expressions of miRNAs and gestational disorders. For example, reports have shown that a reduction in miRNA-126 expression is associated with increased expression of miRNA-15b in PE patients. MiRNA-126 and miRNA-15b have pro-angiogenic and angiostatic roles, respectively [20, 21]. MiRNA-152 is a member of the miRNA-148/152 family whose gene is located on chromosome 17q21.32 [22]. MiRNA-152 plays a role in various cellular processes, such as proliferation, invasion, and angiogenesis. It has been suggested that miRNA-152 suppresses the tumor growth in patients with cancer [23]. Polymorphisms can affect the expression, maturation, and function of miRNAs [24].

Numerous studies have examined the role of miRNAs in the pathogenesis of PE [25]. The first report on the expression of miRNAs in PE patients was presented by Pineles et al. [26]. It has been suggested that the expression of HLA-G is controlled by miRNA-152 which target the 3'-UTR of HLA-G mRNA, thereby down-regulating its expression. It may be considered as a novel potential biomarker and therapeutic target for PE [27]. Li et al. suggested that the examination of the serum levels of miRNAs in PE patients could be used as diagnostic biomarkers. Their results showed an increase in the expression of miRNA-152, miRNA-183, and miRNA-210 in the serum of PE patients at 20 weeks of gestation, while the expression of above-mentioned miRNAs continued until the third trimester of pregnancy in the control group. Consequently, they suggested the possible role of these miRNAs for the prediction of PE [28]. However, Gunel et al. reported a reduction in the expression of miRNA-152 in the serum of PE patients [29].

One of the hallmarks of PE is hypoxia, which leads to placental insufficiency [30]. HIF-1α is a transcription factor whose expression in the placenta is increased in response to hypoxia [14]. No study so far has investigated the relationship between expression of HIF-1α and miRNA-152 in PE patients. Xue-lei Tang et al. demonstrated the induction of the miRNA-152 expression in response to hypoxia under the HIF-1α regulation in cervical cancer cells, which has an inhibitory effect on the growth of cancer cells [31]. Since the relationship between miRNA-152 and HIF-1α expressions and the hypoxia in PE has not been studied, further studies are recommended to explore the relationship. However, some studies have investigated the relation between this polymorphism and several disorders, such as cancer and asthma. Motovalibashi et al. reported the relationship between the polymorphism of miRNA-152 gene and the reduction of the age of breast cancer risk [32]. Zhou et al. revealed the genotype CT and the allele C of polymorphism rs1707 in the miRNA-152 gene are associated with increased risk of asthma [33]. Furthermore, comparison of the frequencies of genotype for this SNP in the control group with that in the European population (HapMap and 1000 genome project) demonstrated that these populations were either largely similar to each other or slightly different. This may indicate the accuracy of genotyping for this SNP [15].

In conclusion, the results from this study showed a lack of relationship between the polymorphism of miRNA-152 gene and preeclampsia development.

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consents were obtained from the study participants. Also, the study protocol was approved by the ethics committee of ZAUMS.

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