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Nrf2 rs6721961 and Oxidative Stress in Preeclampsia: Association with the Risk of Preeclampsia and Early-Onset Preeclampsia

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ABSTRACT

Preeclampsia as a multifactor hypertensive disorder of pregnancy is associated with enhanced placental oxidative stress. The Keap1-Nrf2 pathway protects cells against oxidative stress. We examined the possible association between the *Nrf2* variants in relation to oxidative stress parameters with the risk of preeclampsia. We studied 150 preeclampsia women and 150 women with a normal pregnancy to find the frequency of *Nrf2* rs6721961 genotypes using the PCR-RFLP method. Also, an association between the *Nrf2* genotypes with the levels of malondialdehyde (MDA) and total antioxidant capacity (TAC) was analyzed. Significantly lower TAC and higher MDA levels were found in preeclampsia patients compared to controls (P<0.0001). For the first time, we report an association between the *Nrf2* rs6721961 polymorphism and preeclampsia risk. The present study indicated that the GT genotype and the T allele of the *Nrf2* rs6721961 increased the risk of preeclampsia by 2.81 and 2.39 times, respectively. Also, the *Nrf2* TT genotype was associated with a 3.9-fold increased risk of early-onset preeclampsia. We detected a positive association between the levels of body mass index, MDA, and the *Nrf2* polymorphism with the risk of preeclampsia and a negative correlation between the level of TAC with the preeclampsia risk. Also, an association between the rs6721961 TT genotype with higher serum MDA levels was found. Our study suggests oxidative stress is involved in the pathogenesis of preeclampsia and the *Nrf2* rs6721961 polymorphism through alteration in the levels of oxidative stress parameters might increase the risk of preeclampsia and early-onset preeclampsia.

Keywords: Preeclampsia, oxidative stress, *Nrf2* variants, Malondialdehyde, total antioxidant capacity

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Introduction

Preeclampsia is a serious complication of pregnancy that occurs after 20 weeks of gestation (1) and increases maternal and fetal morbidity and prenatal mortality risk (2).

Abnormal placentation and impaired remodeling of the spiral uterine arteries with subsequent reduced placental perfusion are involved in the pathogenesis of preeclampsia. Reduced placental perfusion leads to hypoxia/ischemia of placenta and the release of cytotoxic factors into the maternal circulation (3). In preeclampsia, uteroplacental hypoxia/reoxygenation elevates free radical release and oxidative stress from the poorly perfused fetoplacental. These reactive oxygen species (ROS) pass through the ischemic placenta and propagate to different maternal tissues (4).

Oxidative stress is defined as an imbalance in the production of oxidants and the cellular antioxidant capacity, leading to disruption of redox signaling and oxidative damage to biomolecules such as lipids, proteins, and DNA (5). During normal cell metabolism through enzymatic and non-enzymatic reactions occur mainly in the mitochondria and also in the peroxisome, and the endoplasmic reticulum, the ROS such as free radicals, superoxide ($\cdot O_2^-$), hydroxyl radicals ($\cdot OH$), and non-radical molecules including hydrogen peroxide (H_2O_2) are produced (6). The excess amount of ROS can damage the cellular components and leads to cell death.

The nuclear factor erythroid 2-related factor 2 (Nrf2)-Kelch-like-ECH-associated protein1 (Keap1) pathway plays a key role in the protection of cells against oxidative stress through the induction of cytoprotective gene expression. The transcription factor of Nrf2 regulates the expression of genes encoding the antioxidant enzymes. Under physiological conditions, Nrf2 exists in the cell cytoplasm in a complex with Keap1, a negative regulator of Nrf2 (7). In oxidative stress conditions, Nrf2 is released from the Keap1-Nrf2 complex and translocated into the nucleus. In the nucleus, Nrf2 binds to the antioxidant response element (ARE) of the promoter of the target genes and enhances the expression of antioxidant genes (8). However, in redox balance, Keap1 moves to the nucleus and attaches to the Nrf2, and transports it to the cytoplasm for degradation in proteasomes (9).

Nrf2 regulates the expression of many antioxidant defense genes. These genes have vital roles in protection against hypertensive disorders of pregnancy such as gestational hypertension and preeclampsia (10,11). So, Nrf2 could play a role in the regulation of blood pressure. Also, Nrf2 regulates trophoblast function, migration, and invasion (12). The signaling pathway of Nrf2 in the placenta is disturbed in patients with preeclampsia and it might be involved in the pathogenesis of preeclampsia (13).

Nrf2 is encoded by the NFE2 like basic leucine zipper (bZIP) transcription factor 2 (*NFE2L2)* gene and consisted of 5 exons and 4 introns. The *NFE2L2* gene is located in the cytogenetic band 2q31.2 of chromosome 2 (gene ID: 4780), and its promoter region contains three functional polymorphisms of rs35652124, -214A>G; rs6706649, -212G>A; and rs6721961, -178A>C, all of which affect the expression of Nrf2 (14). Moreover, these polymorphisms have been associated with several oxidative stress-related diseases, such as acute lung injury (15), impaired forearm vasodilator response (16), and Parkinson's disease (17).

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The present study aimed to investigate the association of the *Nrf2* rs6721961 variants with oxidative stress, the serum levels of malondialdehyde (MDA), and total antioxidant capacity (TAC), and with the risk of preeclampsia.

Materials and Methods

We studied 150 women with preeclampsia including 95 mild- and 55-severe preeclampsia and 150 women with normal pregnancy. All women were referred to the obstetric clinics in Northern Iran, from September 2018 to October 2019.

The criteria for defining preeclampsia were systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, the excretion of more than 300 mg protein in 24 hours, a urine protein: creatinine ratio of more than 0.3 and equal or more than 30 mg/dl protein in a random urine sample (1+ reaction on a standard urine dipstick) (1). Severe preeclampsia was defined as blood pressure of more than 160/110 mmHg, proteinuria of more than 3+, headache, visual disturbances, upper abdominal pain, serum creatinine, and transaminase elevation, thrombocytopenia, and fetal growth restriction (18).

Women with multiple pregnancies or previous hypertension, diabetes mellitus, autoimmune diseases, and kidney, liver, and heart diseases were excluded from the study. Forty women had early-onset preeclampsia (preeclampsia before 34 weeks) (19) and 110 women had late-onset preeclampsia (preeclampsia after 34 weeks) (20). The study protocol was approved by the Ethics Committee of Kermanshah University of Medical Sciences (approval no: IR.KUMS.REC.1397.380) and performed according to the Helsinki Declaration.

Biochemical analysis

Total antioxidant capacity assay

Serum total antioxidant capacity was measured by a commercially available kit (Kiazist, Hamedan, Iran). The basis of the measurement was the reduction of Cu^{+2} by serum antioxidants to Cu^{+1} in the presence of a chromogen reagent to produce a colored complex measured at 450 nm.

Malondialdehyde assay

Serum MDA was measured to evaluate the lipid peroxidation level in the samples. Among the various markers of oxidative stress, MDA, an end-product of lipid peroxidation, is frequently measured as a marker of oxidative stress and lipid peroxidation. Serum MDA level was measured by a commercially available kit (Teb Pazhouhan Razi, Tehran, Iran). The assay was based on a reaction between MDA and thiobarbituric acid (TBA) under high temperature and acidic conditions to form an MDA-TBA complex, which can be quantified by colorimetric analysis. A microplate reader (ELx808, BioTek, Winooski, VT, United States) was used to measure the absorbance at 540 nm.

Genotyping

EDTA-treated whole blood was used for the extraction of DNA by the phenol-chloroform protocol (21). The purity and the quantity of extracted DNA were measured by the NanoDrop 2000 spectrophotometer (Thermo Scientific, USA).

The genotypes of the *Nrf2* rs6721961 were identified by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The PCR primers were designed using the Allele ID

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7.0 (Primer BioSoft, USA) and the Gene Runner software (version 3.02, Hastings Software Inc.) (Table 1). To detect the genotypes, 10 µL of the PCR products of the *Nrf2* gene were digested with NgoMIV (New England Biolabs, R0564S) restriction enzyme according to the manufacturer's instructions, and the digested products were separated on a 3% agarose gel (Table 1).

Table 1. Amplification and digestion of the Nrf2 rs6721961 G>T

Polymorphism	Primer sequence (5′ → 3′)	Allele	Region	Annealing temperature (°C)	Amplicon size (bp)	Enzyme	Product sizes (bp)
rs6721961	F: GAAAGGCGTT GGTGTAGGAG R: GAATGGAGAC ACGTGGGAGT	G /T	Promoter	62	278	NgoMIV	GG (215, 63) GT (278, 215 , 63) TT (278)

* F: Forward; R: Reverse

Statistical analysis

The clinical and biochemical characteristics of the studied groups were compared by Student's unpaired *t*-test, and Mann-Whitney *U* test, as appropriate. The Kolmogorov-Smirnov test was used to detect the normality of the data. Allele and genotype frequencies of the *Nrf2* in patients and controls were compared by the χ^2 test. The odds ratios (ORs) were calculated by the regression analyses to examine the potential association between the *Nrf2* genotypes with the risk of preeclampsia by ORs with 95% confidence intervals (CIs). The clinical and biochemical parameters were compared between the *Nrf2* genotypes by the analysis of variance (ANOVA). The SPSS statistical software package version 16.0 was used for statistical analysis. The P-value < 0.05 was considered at a statistically significant level.

Results

Clinical characteristics of studied subjects

Table 2. Clinical, demographic, and biochemical characteristics of study subjects.

	All preeclamptic Patients n=150 Mean ± SD	P value	Severe Preeclampsia n=55 Mean ± SD	P value	Mild Preeclampsia n=95 Mean ± SD	P value	Controls n=150 Mean ± SD
Maternal age (Years)	31.31 ± 6.16	<0.001	32.40±5.96	<0.001	30.62±6.23	<0.001	27.19±5.99
Gestational age (Weeks)	35.12 ± 3.77	<0.001	34.09±3.82	<0.001	35.75±3.64	<0.001	38.97±1.14
Body mass index (Kg/m^2)	34.43 ± 5.85	<0.001	33.17± 5.68	<0.001	35.07 ± 5.90	<0.001	29.93 ± 5.16
Systolic blood pressure(mm Hg)	148.64± 13.25	<0.001	157.52± 15.93	<0.001	143.24 ± 7.37	<0.001	108.93±13.33
Diastolic blood pressure (mm Hg)	93.56 ± 8.55	<0.001	98.20 ± 10.51	<0.001	90.84 ± 5.86	0.006	75.74 ± 5.76
Serum TAC (mM)	3.48 ± 1.16	<0.001	3.33 ± 0.85	<0.001	3.57 ± 1.31	<0.001	4.28 ± 1.02
Serum MDA (µM)	4.38 ± 0.72	<0.001	5.04 ± 0.45	<0.001	3.99 ± 0.56	<0.001	3.50 ± 0.48

TAC: Total antioxidant capacity; MDA: Malondialdehyde

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Demographic and clinical characteristics of patients and controls are demonstrated in Table 2. The levels of body mass index (BMI), systolic, and diastolic blood pressure in patients were significantly higher than those in controls. Gestational age was significantly lower in severe- and mild- preeclampsia women compared to controls (Table 2).

Significantly lower TAC and higher MDA levels were found in all preeclamptic patients, and in patients with severe- and mild- preeclampsia compared to controls (P<0.001). The TAC level in severe preeclamptic patients was not significantly different from patients with mild preeclampsia (P=0.18). However, severe preeclamptic patients had significantly higher MDA level compared to patients with mild preeclampsia (P<0.001) (Table 2).

Systolic blood pressure was significantly higher in patients with early-onset preeclampsia (153.7±16.1 mm Hg, P=0.012) compared to late-onset preeclampsia (146.8±11.6 mm Hg).

Genotyping

Table 3 depicts the frequencies of *Nrf2* rs6721961 genotypes and alleles in preeclamptic patients and controls. The frequencies of *Nrf2* rs6721961 (G>T) genotypes and alleles were significantly different comparing all preeclampsia patients, severe- and mild- preeclampsia with controls. The frequency of the *Nrf2* GT genotype in all patients with preeclampsia (41.3%) was significantly higher than that in controls (20.7%; P<0.001) and was associated with 2.81-fold increased risk of preeclampsia (95% CI, 1.68-4.71; P<0.001). Further, a significantly higher frequency of the T allele (24%) in patients compared to controls (11.7%, P<0.001) was associated with 2.39-fold increased risk of preeclampsia. Significantly, higher frequencies of GT and TT genotypes were detected in patients with severe preeclampsia (43.6 and 5.5%, respectively) compared to controls (20.7 and 1.3%, P<0.001, and P=0.027, respectively) that increased the risk of severe preeclampsia by 3.35 (P<0.001) and 6.28 (P=0.027) times, respectively. Also, in severe preeclampsia, a significant increase in the frequency of the T allele (27.3%) was associated with 2.83-fold enhanced the risk of severe preeclampsia (P<0.001). As indicated in Table 3, the presence of GT compared to the GG genotype increased the risk of mild preeclampsia by 2.6 times (P=0.001). Also, in the presence of the T allele, the risk of mild preeclampsia was enhanced by 2.14-fold (P=0.002). There were significant differences in the genotypes frequency of the *Nrf2* rs6721961 between patients with early-onset compared to late-onset preeclampsia (χ^2=9.1, P=0.014). The frequency of TT genotype was significantly higher among patients with early-onset preeclampsia (19%, P=0.002) compared to late-onset preeclampsia (1.5%) which was associated with 3.9-fold increased the risk of early-onset preeclampsia (95% CI, 1.27-12.17; P = 0.017). Further, the frequency of the T allele was significantly higher in early-onset preeclampsia (32.5%; P=0.038) compared to late-onset preeclampsia (20.9%) which was associated with 1.82-fold enhanced the risk of early-onset preeclampsia (95% CI, 1.03-3.21; P=0.039). The mean level of MDA was significantly higher comparing early-onset (4.6± 0.8 µM) with late-onset preeclampsia (3.85± 0.7 µM, P<0.001). Also, significantly lower mean level of TAC was detected comparing early-onset with late-onset preeclampsia (3.45±1.1 versus 3.95±1.2 mmol/l, P=0.011)

Table 4 shows the association of *Nrf2* genotypes with TAC and MDA values in all participants. As shown in Table 4, carriers of the *Nrf2* GT genotype compared to individuals carrying the GG genotype had a significantly higher level of serum MDA (4.13 ± 0.71 versus 3.84 ± 0.76 µM, P= 0.005). The serum TAC

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level was higher in carriers of the GG genotype (3.95 ± 1.13 mmol/L) than those carrying the GT and TT genotypes (3.76 ± 1.21 and 3.41 ± 1.14 mmol/L), but the differences did not reach the statistically significant level (P=0.24) (Table 4).

Table 3. Genotype and allele frequencies of Nrf2rs6721961 in studied groups.

Parameter	Geno type	All PE patients (%)	P, OR (95%CI)	Severe PE	P, OR (95%CI)	Mild PE	P, OR (95%CI)	Controls (%)
Nrf2 G>T	GG	83 (55.3)		28(50.9)		55 (57.9)		117 (78)
	GT	62 (41.3)	<0.001,2.81[a] (1.68-4.71)	24(43.6)	<0.001,3.35[a] (1.70-6.60)	38 (40)	0.001,2.60[a] (1.47-4.62)	31 (20.7)
	TT	5 (3.3)	0.115,3.52[b] (0.66-18.60)	3(5.5)	0.027,6.28[b] (0.99-39.31)	2 (2.1)	0.44,2.12[b] (0.29-15.50)	2 (1.3)
	G	228 (76)		80(72.7)		148 (77.9)		265 (88.3)
	T	72 (24)	<0.001,2.39 (1.53-3.71)	30(27.3)	P<0.001, 2.83 (1.64-4.91)	42 (22.1)	0.002,2.14 (1.31-3.51)	35 (11.7)

*PE: Preeclampsia. Comparisons were made with controls. [a]Comparing GT with GG genotype. [b]Comparing TT with GG genotype

Table 4. Association between Nrf2 rs6721961genotypes and MDA and TAC levels in all studied subjects.

Parameters	Nrf2 rs6721961			
	GG n=200	GT n=93	TT n=7	P
TAC (mmol/L)	3.95 ± 1.13	3.76 ± 1.21	3.41 ± 1.14	0.24
MDA (µM)	3.84 ± 0.76	4.13 ± 0.71	4.23 ± 0.81	0.005

TAC: Total antioxidant capacity; MDA: Malondialdehyde

Based on the logistic regression analysis, the levels of BMI (OR: 1.164, 95% CI=1.108–1.222), and MDA (OR: 9.528, 95% CI=5.611–16.178), and the frequency of GT genotype (OR: 2.81, 95% CI=1.68–4.71), dominant and codominant genetic models of the *Nrf2* rs6721961 (OR: 2.86, 95% CI=1.731–4.732; OR: 0.569, 95% CI= 0.324–1.00, respectively) were associated with the preeclampsia risk. However, the TAC level was inversely related to the risk of preeclampsia (OR: 0.519, 95% CI=0.413–0.654) (Table 5).

Table 5. Association between different parameters with the risk of preeclampsia.

Variable	P	OR	95% CI
BMI (Kg/m^2)	<0.001	1.164	1.108-1.222
TAC (mmol/L)	<0.001	0.519	0.413-0.654
MDA (µM)	<0.001	9.528	5.611-16.178
Nrf2 rs6721961 G>T	<0.001	2.81	1.68-4.71
GT vs. GG	<0.001	2.862	1.731-4.732
TT + GT vs. GG	0.048	0.569	0.324-1.00
GT vs. GG + TT			

BMI: Body mass index; TAC: Total antioxidant capacity; MDA: Malondialdehyde

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Discussion

Persistent oxidative stress plays a key role in the pathogenesis of preeclampsia. In this field, the involvement of the *Nrf2* polymorphism, as the master regulator molecule of the oxidant- antioxidant system, and its association with oxidative stress parameters in preeclamptic patients could be suggested. There is increased oxidative stress and ROS formation during pregnancy through enhanced activity of placental mitochondria (22). In normal pregnancy, increased ROS production is coupled with concomitant elevation of antioxidant capacity to prevent oxidative damage (23). However, in preeclampsia, the excessive production of ROS is higher than the antioxidant capacity, resulting in oxidative stress with the consequence of endothelial dysfunction and cellular damage (4,24).

Increased serum level of MDA levels in patients with preeclampsia have been shown in previous studies (25). Our findings indicated that the MDA level increased in preeclamptic women compared with healthy pregnant women and there was an association between the MDA level and the risk of preeclampsia. Also, in early-onset compared with late-onset preeclampsia, a significantly higher level of MDA was detected. Significantly, elevated serum MDA level has been demonstrated in severe preeclampsia compared to mild preeclampsia which could be associated with the severity of the disease. A significant positive correlation between MDA level and blood pressure was reported in pregnant women (26). Increased MDA level, a lipid peroxidation product, might play a key role in the pathology of preeclampsia by inducing endothelial dysfunction (3,27).

In the present study, the TAC level was significantly lower in all preeclamptic patients compared to controls and the level of TAC was negatively correlated with the risk of preeclampsia. Also, we observed a significantly lower TAC level in early-onset than late-onset preeclampsia. There are inconsistent reports related to the TAC level in patients with preeclampsia; both increased and decreased TAC levels have been reported (28,29). Taken together, our findings suggest that higher levels of MDA and lower levels of TAC were significantly associated with an increased risk of preeclampsia and early-onset preeclampsia.

As oxidative stress increases, several biochemical pathways are activated to enhance cellular defense against oxidative stress. The Keap1-Nrf2/ARE signaling pathway is the main cellular defense mechanism against oxidative or electrophilic stress. In the presence of ROS, Nrf2 is activated by disassociation from its repressor protein in the cytoplasm, Keap1, and translocated to the nucleus to regulate the transcription of genes encoding antioxidant enzymes (8).

The *Nrf2* gene variants can affect the expression and the activity of Nrf2 protein, susceptibility to several diseases, and the survival of patients (30). Marzec et al. showed that two functional polymorphisms of the *Nrf2* promoter region (rs6721961 and rs6706649) inhibit promoter activity by>50% (15). Another study reported that the T allele of the rs6721961 polymorphism was associated with low expression of Nrf2 (31). The T allele of the *Nrf2* rs6721961 was significantly associated with increased risk of breast cancer (31), adenocarcinoma (32), thromboembolism in women (33), impaired vasodilator responses (16), and hypertension (34).

It has been demonstrated that the *Nrf2* gene polymorphisms, rs35652124 (-653A/G) and rs6721961 (-617C/A), were associated with blood pressure in Japanese hemodialysis patients. Also, subjects carrying the AA genotype of the *Nrf2* rs35652124 and rs6721961 exhibited significantly higher systolic and

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diastolic blood pressure (34). Furthermore, another study showed that the rare TT genotype of the *Nrf2* rs6721961 was associated with an increased risk of cerebrovascular disease, and pregnant women carrying the GT genotype had higher blood pressure compared to the carriers of the GG genotype (35).

Our findings for the first time revealed that the *Nrf2* rs6721961 polymorphism was significantly associated with an increased risk of preeclampsia. Our data demonstrated that the GT genotype and the T allele of the *Nrf2* rs6721961 increased the risk of preeclampsia by 2.81 and 2.39 times, respectively. Also, the GT genotype and the T allele of the rs6721961 were associated with 3.35- and 2.83-fold enhanced the risk of severe preeclampsia, respectively, and 2.6- and 2.14-fold increased the risk of mild preeclampsia, respectively. In addition, our results showed a significant association between early-onset preeclampsia and the *Nrf2* rs6721961 polymorphism. In early-onset preeclampsia, the T allele frequency was significantly higher compared to late-onset preeclampsia. It seems that genetic predisposition is involved in the pathogenesis of preeclampsia, especially early-onset preeclampsia.

The T allele of the *Nrf2* rs6721961 reduces the Nrf2 expression (31). Decreased Nrf2 level could be involved in the downregulation of antioxidant gene expression, resulting in increased production of the ROS. Interestingly, this functional data support our finding that the pregnant women carrying the *Nrf2* TT genotype had higher MDA levels. Accordingly, the T allele of the *Nrf2* rs6721961 could be related to increased oxidative stress and the risk of preeclampsia in pregnant women.

Conclusion

In summary, our study suggests that higher levels of MDA and lower levels of TAC were significantly associated with an increased risk of preeclampsia. For the first time, our study indicated that the *Nrf2* rs6721961 polymorphism is associated with the risk of preeclampsia and early-onset preeclampsia. In addition, an association between the *Nrf2* rs6721961 TT genotype with higher serum MDA levels in pregnant women was found. Our findings indicate the role of oxidative stress in the pathogenesis of preeclampsia and the early-onset preeclampsia suggests the *Nrf2* rs6721961 polymorphism through alteration in the oxidative stress parameter level is involved in the susceptibility to preeclampsia and early-onset preeclampsia.

One of the limitations of our study was the absence of information related to the environmental factors such as diet and the physical activity of studied women that might effect on oxidative stress parameters.

A similar study with larger sample size in different ethnicities is suggested. Also, epigenetic studies could help to detect the interaction of the *NFE2L2* gene with environmental factors.

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