Original Article

Comparison of CAT-21A/T Gene Polymorphism in Women with Preeclampsia and Control Group

Abstract

Background: Preeclampsia (PE) is one of the main causes of maternal and perinatal mortality and morbidity. Evidence shows that oxidative stress plays an important role in the pathophysiology of the PE. As catalase is a key enzyme in antioxidant enzymatic defense which protects cell from oxidative damage, in this study, we aimed to investigate the relationship between CAT-21A/T (rs7943316) polymorphism and PE susceptibility. **Materials and Methods:** This case–control study was conducted on 155 PE women and 159 normotensive pregnant women. Polymerase chain reaction-restriction fragment length polymorphism method was used for genotyping. **Results:** There was no association between CAT-21AT and TT genotypes and PE susceptibility. However, the CAT-21A/T polymorphism was associated with 1.6-fold higher risk of PE in dominant model (AA vs. AT + TT) (odds ratio [OR] 1.6 [95% confidence interval [CI]: 0.9–2.9]; $P = 0.04$). However, the CAT-21A/T polymorphism was not associated with PE in recessive model (TT vs. AA + AT) (OR 1.3 [95% CI: 0.8–2.1]; $P = 0.4$). **Conclusions:** The CAT-21A/T polymorphism could be a risk factor for PE susceptibility in dominant model.

Keywords: *CAT, polymorphism, preeclampsia*

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Introduction

About 10% of pregnant women suffer from hypertensive disorders of pregnancy. Among these disorders, preeclampsia (PE) is the most perilous since it is one of the main causes of maternal and perinatal mortality and morbidity.[1,2]

Despite many previous studies, the etiology of PE is still unknown. However, several factors involved in PE have been studied including abnormal trophoblastic invasion, immunological factors, endothelial cell activation, nutritional factors, genetic factors, and oxidative stress. Oxidative stress is caused by imbalance between reactive oxygen species (ROS) and the system's ability to omit active mediators or repair damage. As a result, lipids, proteins, carbohydrates, and nucleic acids are damaged, leading to cell death if the damage is extensive.[3] On the other hand, there is evidence that genetic and epigenetic factors also play a role in PE.[2]

Disorders in providing placental oxygen lead to ischemia and oxidative stress in the placenta and mother's blood. Under such conditions, a set of enzymatic and nonenzymatic antioxidants begin to control oxidative stress. Catalase, superoxide dismutase, and glutathione peroxidase are the most important antioxidant enzymes which play a key role in antioxidant defense system.[4] Catalase is an enzymatic antioxidant that exists in the peroxisome of nearly all aerobic cells. It facilitates the decomposition of H_2O_2 which is created as a result of chemical reaction to water and oxygen within cells. As a result, cells are protected against oxidative damage caused by ROS.[5,6]

The CAT gene on the short arm of chromosome 11 in position 13 encodes catalase production.[7] Three polymorphisms in the promoter region of the CAT have been identified: -21A/T (rs7943316), C-262T (rs1001179), and C-844T (rs769214). Moreover, -21A/T and C-262T polymorphisms are significantly associated with the activity of CAT promoter.[8] The relationship between polymorphisms and hypertension has been previously reported.[9-11]

Considering the relationship between oxidative stress and PE, we aimed to

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compare one of the polymorphisms of the CAT-21A/T gene in pregnant women with and without PE in order to gain new insight into the etiology of PE and identify high-risk individuals.

Materials and Methods

One hundred and fifty-five preeclamptic women and 159 normotensive pregnant women were selected from the ward of Obstetrics and Gynecology of Taleghani Educational Hospital of Shahid Beheshti University of Medical Sciences. Informed consent was obtained from all women, and the study protocol–in accordance with the Declaration of Helsinki–was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences.

PE was defined as the presence of increased blood pressure (≥140 mmHg systolic blood pressure [SBP] or ≥90 mmHg diastolic blood pressure [DBP] on two or more measurements at least 4 h apart) and proteinuria ≥0.3 g/24 h or protein: creatinine ratio greater or equal to 0.3 mg/dL, after 20 weeks of gestation. Women with chronic hypertension, underlying renal disease, and/or insulin-dependent diabetes, twins or multiple pregnancies, hydatidiform mole, hydrops fetalis, liver dysfunction, systemic lupus erythematosus, and all systemic diseases were excluded from the study.

Genomic DNA extraction and genotyping

Genomic DNA was extracted from 200 μl ethylenediaminetetraacetic acid-treated whole blood using salting out method and frozen at − 20°C until analysis. The analysis of CAT-21A/T rs7943316 polymorphism was performed by polymerase chain reaction (PCR)-restriction fragment length polymorphism method. The fragment containing the CAT-21A/T polymorphism was amplified using the forward: 5-AATCAGAAGGCAGTCCTCCC-3′ and reverse: 5′-TCGGGGAGCACAGAGTGTAC-3′ primers. The total volume of the PCR mixture was 25 μl containing 150 ng genomic DNA, 20 pM of each primer, 0.1 mM dNTP, 1.5 mM $MgCl_2$, 2.5 μl PCR buffer ×10, and 1 U of Taq polymerase (Fermentas, Lithuania). The PCR conditions were as follows: 5 min at 94°C followed by 30 cycles of denaturation at 94°C for 30 s, annealing at 62°C for 30 s, extension at 72°C for 30 s, and a final extension at 72°C for 5 min. The 250-bp PCR product was digested by HInfI restriction enzyme (Fermentas, Lithuania) and incubated at 37°C overnight. The digested products were separated by electrophoresis on 2.5% agarose gel. The CAT-21T allele had no HInfI cleavage site and only produced a 250-bp fragment. However, the CAT-21C allele had one HInfI cleavage site and was digested to 177 and 73 bp fragments.

Statistical analysis

Statistical analyses were performed using SPSS software (version 23; SPSS Inc., Chicago, IL, USA). The clinical and demographic characteristics of the both groups were compared via independent Student's *t*-test or Fisher's exact test. The independent effect of each polymorphism and haplotype on PE risk was assessed via logistic regression analysis. Values of $P < 0.05$ were considered statistically significant.

Results

The demographic and clinical data of 155 PE pregnant women and 159 normotensive pregnant women are presented in Table 1. The maternal age of women did not differ between the two groups. The birth weight and gestational age of neonates were significantly lower in PE group. The SBP and DBP were higher in this group. The frequency of prim parity was significantly different between PE women and normotensive women (49 vs. 31, $P = 0.04$).

Table 2 depicts the allelic and genotypic frequencies of CAT-21A/T (rs7943316) polymorphism in the PE women and controls. The CAT-21A/T (rs7943316) polymorphism

Table 1: Demographic characteristics of PE women and controls

Variable	Controls (*n*=159)	PE (*n*=155)	*P*	OR (95% CI)
Maternal age (mean±SD, years)	28.2±6.1	29.6±7.5	NS	
Gestation age (mean±SD, days)	269±17	259±26	<0.001	
Birth weight (mean±SD, g)	3200±450	2810±470	<0.01	
SBP (mean±SD, mmHg)	117±9.2	150±21.8	<0.0001	
DBP (mean±SD, mmHg)	72.2±11.4	90.9±13.5	<0.0001	
Prim parity, *n* (%)	50 (31)	76 (49)	0.04	2 (1.3-3.1)

NS: Not significant, SD: Standard deviation, OR: Odds ratio, CI: Confidence interval, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PE: Preeclampsia

Table 2: Allelic and genotypic frequency of CAT-21A/T rs7943316 polymorphism in PE women and control group

CAT-21A/T rs7943316	PE (*n*=155)	Control (*n*=159)	*P*	OR (95% CI)
AA, *n* (%)	44 (28.4)	60 (37.7)		1
AT, *n* (%)	70 (45.2)	64 (40.3)	0.13	1.5 (0.9-2.5)
TT, *n* (%)	41 (26.5)	35 (22)	0.12	1.6 (0.9-2.9)
Dominant (AT + TT vs. AA)			0.04	1.6 (1-2.6)
Recessive (TT vs. AA + AT)			0.4	1.3 (0.8-2.1)
Allele				
A, *n* (%)	158 (51)	184 (58)		1
T, *n* (%)	152 (49)	134 (42)	0.09	1.3 (1-1.8)

OR: Odds ratio, CI: Confidence interval, PE: Preeclampsia

was not in Hardy–Weinberg equilibrium in the studied population. The frequency of CAT-21AT and TT genotypes was higher in PE women (45.2 and 26.5%, respectively) compared to control group (40.3 and 20.5%, respectively); however, the differences were not statistically significant. Although there was no association between CAT-21A/T polymorphism and PE in recessive model, the CAT-21A/T polymorphism was associated with PE susceptibility in dominant model (AA vs. AT + TT) (odds ratio [OR] 1.6 [95% confidence interval (CI): 1–2.6]; $P = 0.04$).

Discussion

The results of the current study showed that the -21A/T (rs7943316) polymorphism of the catalase gene is associated with 1.6-fold higher risk of PE in the dominant model. However, the -21A/T polymorphism was not related to PE in the recessive model.

Glutathione levels is needed for maintaining homeostasis, increasing lipid peroxide, and modifying protein. Under oxidative stress, glutathione levels decrease, causing vascular and tissue damage.

Since catalase is an anti-oxidative enzyme, some studies have assessed the relationship between the activity of this enzyme and its polymorphisms and hypertension, diabetes, and other diseases.[12]

In some cases, single-nucleotide polymorphisms (SNPs) of antioxidative enzymes make an alteration in the enzyme's catalytic activity because of modifications they make in the protein structure, peptide signal sequence, RNA primary transcript, and alterations in promoter and regulatory gene elements.[13] Therefore, the idea that polymorphisms could also change enzyme activity and make them more susceptible to diseases related to oxidative stress (such as hypertension, cerebrovascular accident, and PE) is not farfetched.

Previous studies corroborated the relationship between CAT polymorphism and hypertension. In one study on the relationship between CAT polymorphism and the risk of cerebral stroke in patients with hypertension, 667 patients with untreated hypertension (306 with cerebrovascular accident and 361 without cerebrovascular problem) were included. The results showed that the -21 AA CAT genotype is accompanied with an increased risk of cerebrovascular accident in men with hypertension (OR = 1.77; 95% CI: 1.01–3.07). The results were also in line with ours, as they highlight the importance of dominant model. Moreover, this genotype increased the risk of cerebrovascular accident in male smokers and alcohol consumers, which may indicate the interaction between genetic and environmental factors. On the other hand, the -21 AT and -21 TT genotypes had a protective effect against cerebrovascular accidents in men with hypertension and moderate physical activity (OR = 0.3) and men without stress (OR = 0.01).[14]

The importance of other polymorphisms was found in another study, in which 1474 participants (273 men and 286 women) with hypertensive family members had hypertension, the researchers found that the combination of two SNPs (CAT-262 CT or TT and CAT-844 AA) in the catalase gene promoter region was significantly associated with hypertension.[15]

Few studies have been done on the relationship between catalase activity and its gene polymorphism and PE. One study showed that the serum activity of catalase in erythrocytes was lower in 47 women with PE (2.11 ± 1.34 U/g hemoglobin), compared with 48 healthy pregnant women (3.99 ± 3.15 U/g hemoglobin) and 50 healthy nonpregnant women (11.86 ± 7.56 U/g hemoglobin) ($P < 0.05$).[16]

Other researches had assessed catalase activity in gestational week 15 in women who were later afflicted by PE compared with pregnant women without PE. However, no significant difference was found between the two studied groups. The researchers concluded that if enzyme activity is different in those with PE, it is due to the oxidative stress accompanied with PE and not its cause.[17] However, further research in terms of other polymorphisms and other populations is necessary to investigate this issue.

Conclusion

In the present study, there was a significant relationship between CAT-21 A/T polymorphism and PE in the dominant model. However, further studies especially on the other polymorphisms are required to better understand the relationship between catalase polymorphism and PE.

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Conflicts of interest

There are no conflicts of interest.

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