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Makale / Article

Distribution of Selenoprotein W1 (Rs3786777) Genotypes in Turkish Preeclamptic Women

Türk Preemlampik Kadınlarında Selenoprotein W1 (Rs 3786777) Genotiplerinin Dağılımı

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Abstract

Objective: Preeclampsia is characterized by hypertension, proteinuria and edema during pregnancy, It causes. intrauterine growth retardation, premature birth, fetal and maternal mortality. The selenium takes place in the structure of selenoproteins which are mostly showing oxidoreductase activity in human. Some studies were reported that selenoproteins W (SelW) plays an important role as an antioxidant in the developing brain and embryo. SelW expression level in the fetal muscle and heart tissue depends on fetal selenium levels. SelW function is not completely elucidated yet. The purpose of this study was to determine whether common variation in selenoprotein W1 (SEPW1) alters the risk of preeclampsia (PE).

Materials and Methods: 82 pregnant women with PE and 85 healthy pregnant women from the same geographic region were included in the study. Allele-specific Polymerase Chain Reaction (ASPCR) analysis was used to identify polymorphism of the SEPW1 gene (rs3786777).

Results: Serum lipids, total protein and albumin levels were measured in all cases. We found that fetal weight, total protein and albumin levels significantly decreased in preeclamptic pregnancies compared to healthy pregnant ($p=0.001$, for each). Systolic and diastolic blood pressure, body mass index, total cholesterol and triglyceride levels were significantly increased in preeclamptic patients when compared to healthy control group ($p=0.001$, $p=0.001$, $p=0.001$, $p=0.05$, $p=0.01$, respectively). The frequencies of the CC, CA and AA genotypes were found as 23 %, 67 % and 10 % in pregnant women with PE and 27 %, 57 % and 16 % in healthy pregnant women, respectively. Our results indicated that the distribution of the SEPW1 genotypes and alleles did not differ significantly among subjects with or without PE ($p>0.05$).

Conclusions: In some study SelW is associated with fetal development, so we thought that its gene distribution may be involved in the occurrence of preeclampsia or its complication. SEPW1 polymorphism did not alter the risk of PE in our population. However, clarification by further studies in larger populations is needed. SEPW1 (rs3786777) polymorphism has no role in etiopathogenesis of preeclamptic Turkish women.

Keywords: Preeclampsia; Selenoprotein W1 gene; Polymorphism

Özet

Amaç: Preeklampsi, gebelik sırasında hipertansiyon, proteinüri ve ödem ile karakterizedir. İntrauterin büyüme geriliği, prematür doğum, fetal ve anne ölümlerine neden olur. Selenyum, insanda genellikle oksidoredüktaz aktivitesi gösteren selenoproteinlerin yapısında yer alır. Bazı çalışmalar selenoprotein W'nin (SelW) gelişen beyin ve embriyoda antioksidan olarak önemli bir rol oynadığını göstermektedir. Fetal kas ve kalp dokusunda SelW ekspresyon seviyesi, fetal selenyum seviyelerine bağlıdır. SelW işlevi henüz tam olarak aydınlatılamamıştır. Bu çalışmanın amacı, selenoprotein W1'in (SEPW1) yaygın varyasyonunun preeklampsi (PE) riskini değiştirip değiştirmediğini saptamaktır.

Materyal ve Metod: Çalışmaya aynı coğrafi bölgeden 82 preeklamptik ve 85 sağlıklı gebe alındı. SelW1 geninin polimorfizmini belirlemek için Allele Özgü Polimeraz Zincir Reaksiyonu (ASPCR) analizi kullanılmıştır (rs3786777).

Bulgular: Tüm olgularda serum lipidleri, total protein ve albumin düzeyleri ölçüldü. Preeklamptik gebeliklerde sağlıklı gebeye kıyasla fetal ağırlık, toplam protein ve albümin düzeyleri anlamlı olarak azaldığı bulundu ($p = 0.001$, her biri). Preeklamptik hastalarda sistolik ve diyastolik tansiyon, vücut kütle indeksi, total kolesterol ve trigliserid düzeyleri sağlıklı kontrol grubuna göre anlamlı olarak arttığı görüldü ($p = 0.001$, $p = 0.001$, $p = 0.001$, $p = 0.05$, $p = 0.01$) . CC, CA ve AA genotiplerinin sıklığı, preeklamptik gebelerde % 23, % 67 ve % 10, sağlıklı gebelerde % 27, % 57 ve % 16 olarak bulundu. Bulgularımız, SEPW1 genotiplerinin ve alellerinin dağılımının, preeklamptik olan veya olmayan gebeler arasında anlamlı farklılık göstermediğini ortaya koymuştur ($p> 0.05$).

Sonuç: Bazı çalışmalarda SelW1 fetal gelişim ile ilişkili olduğundan, gen dağılımının preeklampsi oluşumunda veya komplikasyonunda rol oynayabileceğini düşündük. SEPW1 polimorfizmi popülasyonumuzda PE riskini değiştirmedi görüldü. Bununla birlikte, daha büyük popülasyonlardaki daha ileri çalışmalarla aydınlatmaya ihtiyaç duyulmaktadır. SEPW1 (rs3786777) polimorfizminin preeklamptik Türk kadınlarının etyopatogenezinde herhangi bir rolünün olmadığı görüldü.

Anahtar Kelimeler: Preeklampsi; Selenoprotein W1 geni; Polimorfizm

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Introduction

Preeclampsia (PE), a unique hypertensive disorder of human pregnancy, is a major cause of maternal and perinatal mortality and morbidity. It affects approximately 5 % of pregnancies worldwide. Despite the extensive research, its etiology and pathogenesis still remain unexplained and it can not be treated effectively, yet[1]. Several genes were shown to be associated with PE disease occurrence, progression, and severity.

Selenium plays an essential role in the selenoprotein-induced defense system. Selenium blood levels have been widely utilized as a biomarker for oxidative stress-associated diseases. Various observational studies have reported that serum selenium levels were important for development of cardiovascular diseases[2]. Data on the role of selenium serum levels in cardiovascular disease remain inconclusive and in part contradictory. Apart from selenium blood levels, direct measurement of selenoproteins as biomarkers in cardiovascular disease has also been investigated[3]. Initial studies reported its role on atherosclerosis and coronary heart disease[4]. The selenium takes place in the structure of selenoproteins which are mostly showing oxidoreductase activity in human. Some studies were reported that selenoproteins W (SelW) was associated with fetal development. SelW expression level in the fetal muscle and heart tissue depends on fetal selenium levels. SelW function is not completely elucidated yet. The selenoproteins have been subdivided into three groups based upon the location of the selenocysteine[5]. The first group is the most abundant and includes proteins in which selenocysteine is located in the N-terminal portion of a relatively short functional domain such as SelW. The second group of eukaryotic selenoproteins is characterized by the presence of selenocysteine in C-terminal sequences. The remaining selenoproteins are placed in the third group[6]. SelW was detected in human tissues[7]. The changes of SelW expression levels in fetal tissues have been shown in some studies. It was reported that whole tissue selenium content of spontaneously aborted fetuses were closely correlated with selenium content of soil, especially in the muscle, brain and heart tissues. The fetal muscle and heart SelW content closely reflected the selenium status of the fetus[8].

The human SelW locus was shown to map to chromosome 19q13.3, spans approximately 6.3 kb and comprises six exons[9]. This locus has not yet been identified in any human syndromes or muscle disorders. However, it is specificly expressed in muscles during its proliferation suggesting its involvement in muscle development and related diseases. The gene lacks canonical TATA and CAAT boxes but has numerous Sp1 consensus binding sites upstream of multiple transcription start sites. SelW expression was found in all 22 human tissues assayed and showed highest expression in skeletal muscle and heart[7]. The exact function of SelW is not known but there are suggestions of several possibilities. As SelW is S-glutathionylated, it may have a redox function. The glial cells which have over expressed levels of SelW and its mRNA had greater survival rates compared to control cells or glial cells subjected to a radical generating compound[10]. It has been reported that SelW was related with an immediate response after exposure to hydrogen peroxide in proliferating myoblasts[11]. It is apparently important in the development of the fetus[12]. Selenoproteins with selenium are very important in response to oxidative stress, redox imbalance and regulation of various metabolic, and developmental processes. Increased circulating Se levels has been associated with 33% risk reduction of bladder cancer. On the other hand, there are little data on selenoprotein expression at the protein and genetic level from both human and animal studies[13]. Loflin et al suggested that SelW was involved in muscle growth and differentiation by protecting myoblasts from oxidative stress[11]. The importance of SelW gene variations and/or expression levels in various cancers has been investigated.[13,14] Currently, there are several studies in the literature showing the relationship between SEPW1 gene polymorphism and/or mRNA expression levels in colorectal and bladder cancers[13-15]. Although the pathophysiological mechanism of preeclampsia has not been clarified, it is considered to be linked to oksidative stress as a reason or result. It is suggested to contribute to greatly increased incidence of maternal and fetal complications in PE. Due to anti-oxidant roles of selenium and selenoproteins, their circulating levels and/or gene polymorphisms may have role in ethiopathogenesis of PE. In the present study, our aim was to investigate the possible risk of preeclampsia of the SEPW1 gene polymorphism for the first time.

Materials And Methods

Study subjects

Women were examined between July 2014 and April 2016, and comprised 167 primiparous singleton pregnancies. Gestational age was established on the basis of menstrual dates and confirmed by first trimester ultrasonography. Differential diagnosis of PE was made according to the current American College of Obstet-

ricians and Gynecologists (ACOG) guidelines[16]. These guidelines define PE as sustained pregnancy-induced hypertension with proteinuria. Protocol of screening and diagnosis of PE were adapted from the guidelines and protocols from Department of Obstetrics and Gynecology, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey. Hypertension was defined as sustained blood pressure readings of ≥ 140/90 mmHg (with reading taking place > 6 h apart). ACOG defines proteinuria as urine protein concentrations of ≥ 300 mg/day (or 1+ on a urine dipstick) on two or more random specimens collected > 4 h apart. All of the subjects were submitted to uterine artery Doppler and maternal echocardiography at 24 weeks gestation. All participants, patients and healthy controls were of Turkish origin, from Istanbul. Exclusion criteria for all subjects were tobacco use, twin pregnancies, preexisting maternal chronic medical problems, chromosomal or suspected ultrasound fetal abnormalities, maternal heart disease, and use of antihypertensive medication, diabetes mellitus and renal disease at the 1-year follow-up visit. Patients were followed until term to verify the fetoneonatal and maternal outcomes. The evolution of gestation was followed until term by an investigator, blinded to the results of maternal echocardiography. All participants were informed about the survey and freely signed and dated the consent form. The protocol was approved by the Ethics Committee of Medical Faculty in Sakarya University and was conducted in accordance with the Declaration of Helsinki.

Blood collection

Medications were ceased at least 24 hours before the blood collection. Blood samples were collected in EDTA-containing tubes and plain biochemistry tubes after an overnight fasting. After immediate centrifugation (3.000xg) for 10 min at 4°C, plasma samples were separated in Eppendorf tubes and frozen immediately at -80 oC until analysis. Routine biochemical parameters were measured by enzymatic colorimetric methods with commercially available kits (Cobas 8000, Roche Diagnostics GmbH, Mannheim, Germany).

Genotyping

Blood for DNA isolation was collected into EDTA-containing tubes and DNA was extracted from peripheral blood leukocytes using a commercial kit (Invitrogen Life Technologies Corporation, Carlsbad, CA, USA). Isolated DNA samples were stored frozen at -80°C.

Genotyping for the SEPW1 (rs3786777) gene polymorphism was performed by Allele-specific PCR (ASPCR) method. This method is a unique method used to detect single nucleotide changes in DNA. It provides a faster and more specific description than other similar methods. The method is based on binding specific primers to the region where the mutation is based. The presence of a match between the primer and the DNA template in the PCR mixture indicates whether there is a mutation. If the examined sample has mutation, amplification is positive for the mutation-specific region; if there is no mutation, the band is not visible. The Primer pairs; Common primer; 5' – TCTGGACCATACTGGCTTAC – 3' Primer C (normal allele binding primer); 5' – ATGAACCTCAGGAACAGC – 3' Primer A (mutant allele-binding primer); 5' – ATGAACCTCAGGAACAGA – 3' were used. These primers result in a PCR product of 79 bp. PCR mixture for SEPW1 gene is given on Table 1. Two PCR tubes were prepared for each sample. The common primer was pipetted into both tubes, primer C only into the first tube, primer A only into the second tube. The amplification product in normal homozygous individuals (CC genotype) is amplified only in the first tube (in the C tube), in the mutant homozygous individuals (AA genotype), in the amplification product only in the second tube (in the A tube), in the heterozygous individuals (the CA genotype) (Both in C and in A tube) (Table 2). Amplification temperatures for the selenoprotein W1 gene; PCR conditions were as follows: initial denaturation at 95 oC for 5 min, followed by 35 cycles of denaturation at 94 oC for 30 s, annealing at 55 oC for 30 s, and elongation at 72 oC for 30 s. The final amplicon extension has been performed at 72 oC for 5 min. The amplified PCR products were separated on 3 % agarose gel in 1x Tris borate EDTA buffer followed by staining with ethidium bromide solution. The rs3786777 genotypes were identified by visualization under ultraviolet light.

Statistical analysis

SPSS Statistic 17.0 program were used for the analyses of the patients and control values. Hardy–Weinberg equilibrium was tested by Chi-square analysis. Genotype and allele frequencies were compared between cases and controls by Chi-square analysis. Odds ratio (OR) and respective 95 % confidence intervals (CIs) were reported to evaluate the effects of any difference between allelic and genotype distribution. Mann–Whitney U test and t-test were performed for the analysis of clinical characteristics and biochemical parameters. A two-sided p value ≤ 0.05 was considered

statistically significant.

Table 1: The SEPW1(rs3786777) genetic PCR mixture (final volume 25 µl)

	Stock solution of molarity	Working solution of molarity	Final molarity
PCR Buffer	10X	____	1X
Primers C, A, Common	100 µM	10 µM	0.4 µM
dNTPs	100 mM	2 mM	0.2 mM
Taq Polymerase	5U/µM	____	1 U
DNA	____	____	~50ng

Table 2. Bands formed after electrophoresis of the SEPW1 gene

Amplification PCR Product	Normal homozygous (AA)		Heterozygous (AG)		Mutant homozygous (GG)	
	A tube	G tube	A tube	G tube	A tube	G tube
Selenoprotein P1 (79 bç)	▬		▬	▬		▬

Table 3. Clinical characteristics and biochemical parameter values of preeclamptic and healthy pregnant groups (M±SD).

	Healthy pregnant controls	PE patients	p
Age (years)	35.87 ± 5.79	36.19 ± 6.10	0.726
Systolic Blood Pressure (mm Hg)	107.73±16.48	155.49±13.82	0.001
Diastolic Blood Pressure (mm Hg)	68.56±11.73	101.41±11.35	0.001
Body Mass Index (kg/m2)	27.93±4.01	31.42±4.22	0.001
Fetal weight (g)	3144.86±547.03	1883.08±1023.94	0.001
Total Protein (g/dl)	6.78±0.45	6.16±0.69	0.001
Albumin (g/dl)	3.74±0.27	3.33±0.51	0.001
HDL-Cholesterol (mg/dl)	64.00±14.52	67.04±17.66	0.210
LDL-Cholesterol (mg/dl)	141.90±28.88	147.73±50.16	0.327
Total Cholesterol (mg/dl)	230.54±41.95	245.12±64.19	0.05
Triglyceride (mg/dl)	196.82±74.82	231.69±108.82	0.01

Results

The clinical characteristics of subjects included in the present study are summarized in Table 3. The patient (36.19 ± 6.10) and control (35.87 ± 5.79) groups were similar in age (M±SD). We found that fetal weight, total protein and albumin levels significantly decreased in preeclamptic pregnancies compared to healthy pregnant group (p=0.001, for each). The patient group had higher systolic and diastolic blood pressure, body mass index, total cholesterol and triglyceride levels than the control group (p=0.001, p=0.001, p=0.001, p=0.05, p=0.01, respectively). The SEPW1 (rs3786777) gene polymorphism was successfully genotyped in 82 women with PE and 85 control subjects. Frequencies of SEPW1 genotypes and alleles observed in patients with PE and pregnant healthy women are shown in Table 4. The frequencies of the CC, CA and AA genotypes were found as 23 %, 67 % and 10 % in pregnant women with PE and 27 %, 57 % and 16 % in healthy pregnant women, respectively. Our results indicated that the distribution of the SEPW1 genotypes and alleles did not differ significantly among subjects with or without PE (p>0.05).

Table 4. Distribution of genotypes and allele frequencies of SEPW1(rs3786777) polymorphism in patient with PE and control groups.

Gene	PE patients n (%)	Healthy pregnant controls n (%)	p	OR (CI 95%)
SEPW1 polymorhism	82	85		
Genotypes				
CC	19 (23)	23(27)		1
CA	55 (67)	48 (57)	0.479	0.721 (0.351-1.482)
AA	8 (10)	14 (16)	0.677	1.446 (0.501-4.173)
Alleles				
C	93 (57)	94 (55)		1
A	71 (43)	76 (45)	0.795	1.059 (0.687-1.632)

Discussion

In the present study, fetal weight, total protein and albumin levels of preeclamptic pregnancies were found to be lower than those of healthy pregnancies. We investigated the relationship of SEPW1 gene polymorphisms with the risk of preeclampsia. We found that SEPW1 polymorphism did not alter the risk of PE in our population.

It has been shown that the single nucleotide polymorphism (SNP) had effect on interaction between selenium and SelW expression levels, in vivo. Selenoprotein synthesis is highly dependent on dietary Se intake and so it is to be expected that the influence

of the SNPs described here could be modified by Se intake. For that reason, it will be vital in future work to combine genotyping for selenoprotein SNPs with measures of Se status. The effects of such gene-diet interactions might be underlying mechanism for selenoproteins as a risk factor of some diseases such as cardiovascular diseases, preeclampsia.

Selenoprotein deficiency led to oxidant hyperproduction of T cells and thereby suppressed T cell proliferation in response to T cell receptor stimulation. The highest concentrations of SelW were found in the heart and muscle tissues which are the tissues affected in selenium deficiency disorders.[17,18,19] These findings supports that the selenoprotein, SelW, performs an important role in these tissues but the significance of its role has not been discovered yet.[6] The data are convincing that SelW has an antioxidant or redox function, the question remains whether this is a primary function and not a secondary one. There is some information suggesting that selenoproteins mediate T cell immunity through antioxidant mechanisms.20 SEPW1 polymorphisms have been studied in colorectal and bladder cancer patients.[13,14] The mechanism of anticarcinogenic activity of selenoproteins may be related to prevention of oxidative damage and maintenance of redox state. Tumor suppressor protein p53 is a redox-dependent transcription factor controlling the cell cycle and DNA repair. In vitro SEPW1, may influence cancer cell growth via p53 alternations.[13] Over-expression of SEPW1 promotes cell cycle progression associated with p53 ubiquitination and degradation.[13,21] Hawkes et al. reported that SEPW1 depletion induced a delay in cell progresion in breast cancer and prostate epithelial cells at the G1/S transition.[13,22,23] The delayed cell cycle progression by SEPW1 depletion was not associated with the loss of antioxidant protection. Glutathione peroxidase-1 (GPX1) silencing did not affect the cell cycle. This observation may show that the antioxidantive role of SEPW1 reported by Jeong et al is not the main function of this selenoprotein.[24] Pellatt et al. analyzed selenoprotein genes regulating oxidative stress and/or carcinogenesis in breast cancer.[25] However, in this study, there was no relationship between SEPW1 polymorphism and breast cancer risk. The same polymorphism was not related with risk of PE in our study.

In present study, there were several limitations. Firstly, it was not designed to investigate the association between SEPW1 gene polymorphism and plasma/serum SelW and selenium levels in the mothers and their infants. Secondly, the number of individuals in the patient and control groups are limited and selected from the same center.

In some study, SelW is associated with fetal development, so we thought that its gene distribution may be involved in the occurrence of preeclampsia or its complications. SEPW1(rs3786777) polymorphism did not alter the risk of PE in our population. However, clarification by further studies in larger populations is needed.

Conflict of interest The authors declare that they have no conflicts of interest related to the publication of this manuscript.

Kaynaklar

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