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ORIGINAL ARTICLE

Maternal serum endothelial cell-specific molecule-1 level and its correlation with severity of early-onset preeclampsia

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ABSTRACT

Preeclampsia (PE), the primary pathology of which is endothelial cell (EC) dysfunction, has long-lasting effects such as cardiovascular disease. Therefore, it was decided to investigate the maternal serum concentrations of EC-specific molecule-1 in patients with early-onset preeclampsia (E-PE). This study was conducted on 33 pregnant women with E-PE and 35 healthy pregnant women matched for gestational age. EC-specific molecule-1 level was measured using a commercially available enzyme-linked immunosorbent assay kit. The mean EC-specific molecule-1 concentrations were not significantly different between the groups (651.7 ± 632.2 pg/mL vs. 425.9 ± 263.0 pg/mL, p=.056). Among women with E-PE, the median EC-specific molecule-1 concentration did not differ significantly by disease severity (p=.115). EC-specific molecule-1 is not involved in the pathogenesis of E-PE. However, some studies in the literature report that EC-specific molecule-1 concentrations increased during the diagnosis of PE. Therefore, well-designed studies with a large sample are needed in cases of E-PE.

IMPACT STATEMENT

- **What is already known on this subject?** There is an increased risk of cardiovascular disease (CVD) in early-onset preeclampsia (E-PE) which is linked with endothelial dysfunction. Endothelial cell (EC)-specific molecule-1 stands out as an important marker in EC dysfunction related conditions such as preeclampsia.
- **What the results of this study add?** This study showed that EC-specific molecule-1 is not associated with the CVDs risk linked with endothelial dysfunction in E-PE. Additionally, there was also no significant relationship was detected between the severity of E-PE and EC-specific molecule-1 concentrations.
- **What the implications are of these findings for clinical practice and/or further research?** Endothelial cell-specific molecule-1 is not involved in the pathogenesis of E-PE. Moreover, advantageous and easy-to-measure markers are needed in larger sample studies to better understand the aetiology of E-PE.

KEYWORDS

Biomarker; cardiovascular diseases; endocan; endothelial cell activation; endothelial dysfunction; predict

Introduction

Hypertensive disorders during pregnancy such as preeclampsia (PE) and eclampsia are serious conditions with significant maternal and/or foetal morbidity and/or mortality. The prevalence of PE is between 2% and 8%. Proteinuria onset after 20 weeks and high blood pressure characterised by endothelial cell (EC) dysfunction are its main characteristics (Purde et al. 2015; Köninger et al. 2018). Some risk factors are held responsible for this; obesity, maternal age of ≥35 years and nulliparity (Brosens et al. 2019). The aim of the studies conducted using biophysical markers (e.g. maternal body mass index (BMI) and mean arterial pressure), placental, inflammatory, endothelial and metabolic biomarkers or a combination thereof, is to indicate an abnormal response to placentation and predict PE. However, a test/method that predicts PE or confirms its diagnosis before its clinical occurrence has not yet been found. Dividing PE into two types by determining the cut-off period as 34 weeks is a widely accepted approach (early/placental and late onset/maternal). Furthermore, it can also be classified as vascular remodelling/placental invasion or inflammation/metabolic depending on its underlying pathophysiology (Eastabrook et al. 2018). Oxidative stress occurs due to the effect of placental hypoperfusion/hypoxia/ischemia, which is followed by cellular apoptosis, inflammation and the delivery of antiangiogenic factors to the maternal circulation. Eventually, numerous factors such as soluble fms-like tyrosine kinase-1 and placental growth factor released by the placenta contribute to EC damage and the development of PE (Herraiz et al. 2018).

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On the other hand, when the placenta was examined in early-onset preeclampsia (E-PE), it has been observed that the vessels tend to develop acute atherosis. In brief, the events that occur during the formation of atherosis are intravascular inflammation, macrophage infiltration, EC dysfunction and changes in lipid metabolism. Atherosclerosis may spread to the whole body. It is possible that a lower level of hypertension in the placental bed may also occur in other organs (Brosens et al. 2019). In elderly people, the primary pathology of atherosclerosis is also EC dysfunction (Gimbrone and García-Cardeña 2016). In addition, higher concentrations of serum EC-specific molecule-1 were demonstrated in conditions characterised by the vascular involvement of atherosclerosis (Roudnicky et al. 2013).

Endothelial cell-specific molecule-1, which has recently been named endocan (ESM-1), is a soluble dermatan sulphate proteoglycan. It is considered a biomarker for EC activation/dysfunction. It has been shown to be released in cases of cell adhesion, tumour and inflammation in the human body. In normal or pathologic processes, inflammatory mediators and angiogenic growth factors may affect EC-specific molecule-1, with which they are in a close relationship (Sarrazin et al. 2006; Aparci et al. 2015). Many studies have also demonstrated the influence of the vascular endothelial growth factor (VEGF) family, whose relationship with PE has been shown, with EC-specific molecule-1 (Chang et al. 2015). Schuitemaker et al. demonstrated through plasma EC-specific molecule-1 measurements that healthy pregnant women exhibited a decrease compared with healthy non-pregnant women, and detected that EC-specific molecule-1 decreased in healthy pregnant women from the first trimester until the end of pregnancy (Schuitemaker et al. 2018).

In a study comparing healthy pregnant women and patients with PE, it was detected that serum EC-specific molecule-1 level was higher in preeclamptic pregnant women, although there was no correlation with its severity (Adekola et al. 2015). There are studies that demonstrate that EC-specific molecule-1 concentrations are also in high in late-onset preeclampsia (L-PE). In addition, preeclamptic women have an increased risk of cardiovascular diseases (CVDs) and metabolic disorders in ensuing years (Powe et al. 2011; Gooding and Johnson 2016). EC-specific molecule-1, which was demonstrated to be high in CVDs, was also found to be high in the placenta in PE (Chang et al. 2015). It may be beneficial to study EC-specific molecule-1 concentrations both in acute phases of E-PE and with respect to the long-term effects of PE.

The aim of this study was to evaluate EC-specific molecule-1 concentrations in E-PE and address its relationship with its severity.

Methods

This observational case-control study was designed at Cengiz Gokcek Women's and Children's Hospital, Gaziantep, Turkey, in the Department of Obstetrics and Gynecology between December 2017 and September 2018. The study protocol was approved by the Ethics Committee for Clinical Research of the Gaziantep University (reference number: 362, date 06 November 2017). The study was conducted according to the principles of the Declaration of Helsinki. All subjects included in the study gave oral and written informed consent. The study population consisted of 33 women with a singleton pregnancy who were diagnosed as having E-PE between 26 + 0 and 33 + 6 weeks of gestation. Thirty-five gestational age-matched healthy pregnant women who delivered at term were included in the study as the control group. The gestational age was determined by calculating the days from the last menstrual period and was supported by ultrasonographic measurements at the first trimester of gestation.

E-PE was defined as new-onset of hypertension (on two occasions at least 4 h apart, diastolic and/or systolic blood pressure of 90 and/or 140 mm Hg) between the 20th and 34th week of pregnancy with a concomitant proteinuria (300 mg in a 24-h urine or 1 (+) protein by dipstick test on two random urine samples). Diastolic and/or systolic blood pressure up to 110/160 mm Hg was considered mild, and higher values were considered to be severe (ACOG 2019). In the E-PE group, neonates assessed as small for gestational age (SGA) were defined as birth weight <10th percentile for gestational age with Turkey's national nomogram as the reference for foetal growth (Topçu et al. 2014). Maternal BMI (kg/m^2) was measured as the ratio of the weight (kg) to the square of the height (m).

The exclusion criteria were as follows: (1) pregnant women with any systemic condition (such as chronic hypertension, diabetes mellitus, thyroid diseases, liver and kidney diseases), (2) women with a history of drug use throughout pregnancy, (3) pregnant women who had fever at the time of first admission, (4) history of medication for PE treatment at the time of first admission, (4) pregnancies complicated with premature membrane rupture or chorioamnionitis, (5) patients who had foetal congenital abnormalities or genetic syndromes, (6) smoking, (7) multiple gestation and (8) active labour. Healthy subjects who had a normal pregnancy and outcomes without any foetal-neonatal complications were accepted into the control group. Four patients in the control group and two patients in E-PE group were excluded from study because they declined to participate. Incomplete feto-maternal data were seen in one patient in the control group and one patient in the E-PE group. Two patients in the control group had low birth weight and SGA at birth. These patients were also excluded from the study. The remaining 33 pregnant women with E-PE and 35 healthy subjects were eligible for inclusion in the study (Figure 1).

Every woman in the study population underwent an obstetric ultrasound examination and a foetal–maternal assessment was conducted by one of the authors. Obstetric anamneses were obtained from all subjects. The demographic data for gestational age, gravidity, parity, maternal age and BMI were recorded. Maternal venous blood samples were taken for measurement of EC-specific molecule-1 level after the diagnosis of E-PE in the outpatient clinic. These samples were quickly centrifuged at 1500×*g* for 10 min, plasma and serum samples were separated, and serum samples were stored at −80 °C until the day of analysis. All patients with E-PE were hospitalised. A

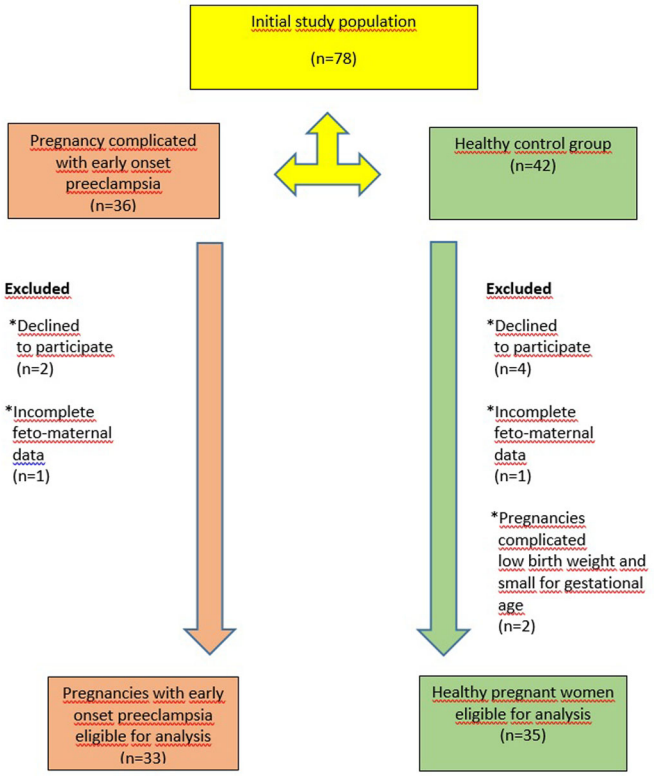

Figure 1. Flowchart of the pregnant women recruited in the study.

betamethasone injection was administered immediately after hospitalisation. The pregnancy was immediately terminated in emergencies arising from maternal or foetal causes. Otherwise, blood pressure was measured every four hours during periods of rest. Hypertension can be confirmed within a shorter interval in patients with blood pressure ≥110 mm Hg diastolic and ≥160 mm Hg systolic in order to give timely antihypertensive treatment. Delivery should be postponed for at least 24–48 hours if maternal/foetal status permit. A betamethasone injection for lung maturation (two dosages of 12 mg at 24-h intervals) was given within the said period. The control group's samples were obtained during routine obstetric care examinations in the third trimester of pregnancy. These pregnant women were then followed up until delivery.

Serum EC-specific molecule-1 concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit specifically produced to detect human EC-specific molecule-1 with a high sensitivity and specificity (Elabscience Biotechnology Inc, Houston, TX). The measurements were undertaken in accordance with the company's protocols. The kit uses the sandwich-ELISA principle. A biotinylated detection antibody specific for human EC-specific molecule-1 and avidin-horseradish peroxidase conjugate was used in the measurements. Spectrophotometry at a wavelength of 450 nm ± 2 nm was used for the detection of optical density, which is proportional to the concentration of human EC-specific molecule-1. The intra-assay and inter-assay variation coefficients were 6.36% and 6.09%, respectively.

Statistical analysis

Frequency and percentage analyses were used for some variables during data analysis. In addition, an independent samples *t*-test (Student's *t*-test) was used for the comparison of the EC-specific molecule-1 concentrations by the variable groups formed. The SPSS (IBM SPSS Statistics for Windows, Version 22.0, IBM Corp., Armonk, NY) statistical program was used for all statistical calculations.

Results

A week after admission, only one of the patients in the E-PE group gave birth. The pregnancy of the other patients had to be terminated either immediately or as soon as the administration of betamethasone was completed. The demographic data and biochemical parameters of the E-PE group were compared with those of the control group (Table 1). No teenage pregnancies were found in the E-PE group when the maternal ages were examined. There were seven pregnant women aged ≥35 years in the advanced maternal age (AMA) group in the E-PE group, the average EC-specific molecule-1 concentrations of whom were not statistically different from those who were aged <35 years ($p = .801$). The EC-specific molecule-1 concentrations of the eight AMA pregnancies in the control group did not differ from those of women aged <35 years in control group ($p = .226$). The EC-specific molecule-1 concentrations of all AMA pregnancies in both groups did not differ from those of the women aged <35 years ($p = .507$). In the E-PE group, the EC-specific molecule-1 concentrations of the women whose gestational age was <32 weeks did not differ from those whose gestational age was ≥32 weeks ($p = .250$).

No difference was detected between EC-specific molecule-1 concentrations in the severe ($n = 24$) band mild E-PE ($n = 9$) groups ($p = .115$). When Pearson's correlation was applied between the severity of proteinuria measured with a dipstick and EC-specific molecule-1 concentrations in the E-PE group, a statistically insignificantly negative relationship was detected ($r = -0.115$, $p = .523$).

No difference was found when the EC-specific molecule-1 concentrations of the women having their first pregnancy (68 women in both groups) and those having their ≥2nd pregnancies were compared ($p = .635$).

As there were few SGA infants in the E-PE group (four infants), their EC-specific molecule-1 concentrations could not be compared.

When the EC-specific molecule-1 concentrations of those with a BMI <30 kg/m^2 and ≥30 kg/m^2 were compared, no difference was observed in all pregnant women ($p = .084$). When the EC-specific molecule-1 concentrations of those with a BMI <30 kg/m^2 and ≥30 kg/m^2 were compared, no difference was observed in the E-PE group ($p = .148$). When the EC-specific molecule-1 concentrations of those with a BMI <30 kg/m^2 and ≥30 kg/m^2 were compared, no difference was observed in the control group either ($p = .223$). When the EC-specific molecule-1 concentrations of those in the E-PE group with high and low uric acid concentrations were analysed, no difference was detected ($p = .398$).

Table 1. The demographic data and biochemical parameters of the groups.

Variables	E-PE ($n = 33$)	Control ($n = 35$)	t	p Value
Age (years)	29.1 ± 6.4	29.2 ± 6.9	−0.030	.976
Body mass index (kg/m^2)	31.2 ± 4.9	31.0 ± 7.8	0.111	.912
Gestational age at blood sampling (weeks)	31.1 ± 2.2	30.5 ± 2.0	1.278	.206
Gravidity	2.9 ± 1.7	3.4 ± 2.1	−1.025	.309
Parity	1.4 ± 1.4	1.8 ± 1.6	−0.990	.326
Systolic blood pressure (mm Hg)	172 ± 17	102 ± 10	20.244	<.001*
Diastolic blood pressure (mm Hg)	110 ± 11	65 ± 7	18.972	<.001*
Spot urine proteinuria by dipstick test	3.1 ± 1.2	0.2 ± 0.4	13.468	<.001*
Haemoglobin (g/dL)	12 ± 1.4	11.6 ± 1.1	1.174	.245
Haematocrit (%)	35.9 ± 3.9	34.2 ± 2.5	2.065	.043*
Platelets ($\times 10^3/\mu L$)	201 ± 82	243 ± 58	−2.462	.016*
White blood cells (μL/mL)	10.6 ± 2.8	10.0 ± 2.6	0.873	.386
Uric acid (mg/dL)	5.7 ± 1.3	3.8 ± 0.7	7.047	<.001*
Albumin (g/dL)	2.9 ± 0.8	3.5 ± 0.3	−3.605	.001*
Blood urea nitrogen (mg/dL)	10.4 ± 3.8	7.1 ± 2.0	4.477	<.001*
Creatinine (mg/dL)	0.67 ± 0.15	0.49 ± 0.11	5.558	<.001*
Alanine aminotransferase (IU/L)	24.6 ± 31.3	12.5 ± 9.3	2.197	.032*
Aspartate aminotransferase (U/L)	33.5 ± 36.4	16.2 ± 6.9	2.757	.008*
Lactic acid dehydrogenase (units/L)	352.6 ± 188.1	205.6 ± 60.0	4.393	<.001*
Birth weight (g)	1611 ± 444	3234 ± 342	−16.923	<.001*
Endocan level (pg/mL)	651.7 ± 632.2	425.9 ± 263.0	1.942	.056

E-PE: early-onset preeclampsia group; control: control group.
Values are given as mean ± SD.
*$p < .05$ indicates statistical significance.

Discussion

Our hypothesis in this current study was that EC-specific molecule-1, as an EC dysfunction marker, would be increased in women with E-PE. In contrast to our hypothesis, we found no significant difference in maternal EC-specific molecule-1 concentrations between the E-PE and healthy pregnancies. There was also no significant relationship was detected between the severity of E-PE and EC-specific molecule-1 concentrations.

The placenta is the interface between the mother and the foetus. The development of the placental villi should be completed for placental circulation. The course of development should involve vasculogenesis, angiogenesis, enlargement of the placental vascular tree, and placental growth, respectively. Initially, the vessels grow from 18 to 20 days post-conception from the ECs. Angiogenesis and placentation continue to develop, and the constituted vascular casts from pregnancies complicated by E-PE have demonstrated important differences in the placental vessels compared with healthy pregnancies. In addition, in a study where placental ECs were isolated from term placentae, the ECs obtained from PE pregnant women were found to be less viable than those obtained from the control group. ECs have a reduced proliferation rate and are more susceptible to apoptosis; these phases precede the patients' diagnosis. In addition, the angiogenic imbalance has been shown to drive the progression of PE. The diagnosis is made based on the clinical symptoms when the patient is admitted (Charolidi et al. 2019). The PE findings obtained when placentas were examined were ischaemic lesions, shallow placental implantation, decidual arteriopathy and uteroplacental malperfusion. These findings can be observed in E-PE and L-PE. However, more findings were observed in E-PE. In light of clinical examinations, there is a possibility of severe PE occurrence in E-PE compared to L-PE (Stanek 2019). Although the onset of the event dates back to earlier periods, its outcome affects the future quality of life and wellbeing of the woman and the infant. Physicians mostly focus on the time when the patient clinically presented with hypertension. The development of chronic progression following acute events is not fully understood. CVD risk was detected to be 2–7 times as high, especially in E-PE except for short-term implications (Hooijschuur et al. 2019). Tests to be used for detecting and predicting these progressions are needed. Studies are needed on how to follow-up patients for the risk of CVD development, the measures to be taken, and the treatment to be administered (Stanek 2019). Moreover, the cost of the events both for the mother and the baby is of concern. The financial burden of PE may increase to high levels due to its long-lasting effects (Eddy et al. 2018).

There are many studies in the literature that demonstrate that EC-specific molecule-1 concentrations increase in cases of hypertension. Furthermore, patients with hypertension treated with valsartan and amlodipine were detected to have significantly lowered EC-specific molecule-1 concentrations. EC-specific molecule-1 stands out as a new marker in EC dysfunction-related conditions (Balta et al. 2014; Aparci et al. 2015). Patients with PE had a higher VEGF family. Meanwhile, the VEGF family was shown to increase EC-specific molecule-1 concentrations. Spreza-Gozdziewicz et al. observed that there was no difference between E-PE and L-PE in terms of maternal serum EC-specific molecule-1 concentrations in healthy pregnant women. In addition, they detected in their analyses that PE severity and EC-specific molecule-1 concentrations were not correlated (Szpera-Goździewicz et al. 2020). Adekola et al. showed higher serum EC-specific molecule-1 concentrations in patients with PE than in the control group, but subgroup analysis revealed no differences in the severity of the condition (mild/severe PE) or the gestational age at diagnosis (E-PE/L-PE) (Adekola et al. 2015). Further, in a study conducted with only E-PE patients, a comparison with a control group revealed no difference between maternal serum EC-specific molecule-1 concentrations (Yuksel et al. 2015).

Hentschke et al. found in their study that EC-specific molecule-1 concentrations were high in the E-PE group; however, this study was conducted on maternal plasma (Hentschke et al. 2018). Chang et al. examined the placentae of patients with L-PE and detected that the expression of EC-specific molecule-1 mRNA and protein concentrations had increased in those patients (Chang et al. 2015). The study by Chew et al. included both E-PE and L-PE patients and high concentrations of EC-specific molecule-1 were also detected in the placenta. Chew et al. detected that the EC-specific molecule-1 concentrations were also high in foetal ECs, decidual cells and maternal ECs in the placenta of pregnant women with PE (Chew et al. 2019). When Schuitemaker et al. compared EC-specific molecule-1 in healthy pregnant women in their study, they found a remarkable increase in EC-specific molecule-1 concentrations at the time of diagnosis of E-PE and L-PE. They reported an increase in the EC-specific molecule-1 concentrations at $\geq$32 weeks in E-PE. They also reported no increase in the EC-specific molecule-1 concentrations in the placenta but observed an increase in maternal ECs (Schuitemaker et al. 2018). In the present study, although a mild increase in EC-specific molecule-1 concentrations was observed in E-PE, it was not statistically significant. In this study, no correlation was detected in the severe E-PE group. Also in this study, no increase was detected at $\geq$32 weeks in the severe E-PE group. The results of the studies in the literature were inconclusive. The differences in the results of the studies may be due to the fact that they were performed without separating the E-PE/L-PE groups or mild/severe groups. It may also be based on the fact that different inclusion criteria were used in E-PE or different samples (plasma, serum or placenta) were studied, and that the number of pregnant women in the studies differed and were insufficient.

There are publications showing an increased risk of CVDs with increased BMI, as well as numerous publications reporting an increased risk of PE with increased BMI (Kachur et al. 2017). In the present study, patients with obesity were evenly distributed across the groups. Our results show that EC-specific molecule-1 is not affected by obesity. In addition, adolescent women who had PE in their first pregnancy were detected to be at risk for chronic hypertension in subsequent pregnancies and the later stages of their lives (Sibai et al. 1986; Brosens et al. 2019). In this current study, which did not include any adolescent pregnancies, and no difference was found in EC-specific molecule-1 concentrations between women having their first pregnancy and those having their $\geq$2nd pregnancies. The fact that there were no adolescent pregnancies may have affected this result. PE development is considered to be a risk factor for metabolic syndrome and CVDs in AMA pregnancies, particularly with the coexistence of SGA (Hooijschuur et al. 2019). In this study, EC-specific molecule-1 concentrations in AMA pregnancies did not differ. Higher uric acid concentrations have also been suggested as a predictor of PE, as well as CVDs, cerebrovascular diseases and unhealthy obesity (Eastabrook et al. 2018). In the present study, it was observed that there was no difference in EC-specific molecule-1 concentrations in the patients with normal and high uric acid concentrations in the E-PE group.

The fact that smoking, which is among the factors that might affect ECs, was excluded from evaluation is considered a strength in this study. The major limitation of our study is that the number of patients with E-PE was quite low. A causal relationship has not been established between EC-specific molecule-1 and PE because of the cross-sectional design. We did not measure angiogenic growth factors (such as VEGFs and placental growth factor) and antiangiogenic biomarkers (such as soluble fms-like tyrosine kinase-1). The fact that it was not possible to measure EC-specific molecule-1 concentrations in the placentae of the patients is another limitation.

PE is known to develop as a result of endothelial dysfunction and several molecules/markers have been studied to elucidate the exact pathogenesis of the disease. However, to date, there have been studies concerning this issue and the findings were inconclusive. Hence, further investigations with larger sample sizes are needed in order to elucidate the role of EC-specific molecule-1 and other endothelial markers in the etiopathogenesis of PE.

Disclosure statement

The authors declare that they have no conflicts of interest.

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