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Podocalyxin levels in preeclampsia and relationship with severity of disease

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Abstract
Aim: In this study, we aimed to investigate the maternal serum levels of podocalyxin in patients with preeclampsia and its comparison with healthy pregnants.
Material and Methods: This is a cross-sectional observational study which included a total of 90 participants, of whom 60 patients had a diagnosis of pre-eclampsia and 30 women were normotensive throughout the pregnancy. We measured plasma levels of podocalyxinat presentation and compared the serum levels of pregnant women with normotensive patients.
Results: There was no significant difference in serum podocalyxin levelsin preeclampsia(PE) group compared with the control group (76 versus 66; p:0,551).When serum podocalyxin values of early-onset and late-onset preeclampsia groups were compared, there was no statistical difference (82.3±55.5 vs 71.3±36.9; p: 0.853). Podocalyxin was found to be lower in multiparous women than in nulliparous and the difference was statistically significant (65.8±21vs 94±63; p:0.001)
Discussion: Measurement of serum podocalyxin levels is not a useful biomarker in the diagnosis or follow up of preeclampsia.

Keywords
Preeclampsia; Podocalyxin; Serum level; Diagnosis

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Introduction

Preeclampsia (PE) is a medical condition that affects 5-10% of all pregnant women worldwide [1-4]. It occurs after the 20th week of pregnancy and is manifested by hypertension (> 140 / 90 mmHg) and proteinuria (>0.3gr in urine) [2]. PE is specific to pregnancy caused by poor placentation and resulting in multiorgan failure due to abnormal inflammatory response and vascular response [1]. Today, PE is defined as early-onset PE (EOPE) and late-onset PE (LOPE) onset with regard to the gestational week it developed and its progression. EOPE is defined as PE that occurs before the 34th week of pregnancy and constitutes 20% of all cases. LOPE develops after the 34th week of gestation and constitutes 80% of all cases [5-7]. Although less common, EOPE leads to a significantly higher risk factor for maternal death, perinatal death, preterm delivery, and low birth weight [8,9].

Despite meticulous research, the pathogenesis of preeclampsia has not been clearly established. Current hypotheses suggest that EOPE develops due to insufficient invasion of trophoblasts which in turn results in an impaired vascular control, while LOPE is thought to result from increased placental mass and surface triggering a devastating immune response [10-12].

Podocalyxin is one of the major podocyte-specific protein and is a member of the CD34 transmembrane sialomucin family. It originates from the apical membrane protein of glomerular podocytes in kidneys. Podocalyxin plays an important role in the development and functioning of kidneys, including glomerular filtration and urea formation [13,14]. Preeclamptic conditions result in the damage of podocytes and cause an increase in the urinary excretion of podocytes and podocalyxin. Increased excretion of urinary podocalyxin in PE has been determined in several studies that are positively associated with the severity of proteinuria accompanying preeclampsia [15-17].

While there are a lot of researches in the literature regarding the urinary excretion of podocalyxin in PE patients [18-21], maternal serum levels of podocalyxin have been investigated in remarkably fewer studies. Among these, two are remarkable, namely, the study conducted by Chen et al. evaluating the levels of maternal serum podocalyxin alone and another study conducted by Duckworth which included 47 different biomarkers including maternal serum level of podocalyxin as well [10,17].

There are studies reporting an increased urinary excretion of podocalyxin in kidney diseases, hypertensive diseases, and PE. But only one study evaluating maternal serum podocalyxin alone reported that the value of serum podocalyxin in PE patients had increased [10].

In our study, we aimed to determine the value of serum podocalyxin in PE patients and compare them with normotensive pregnant women.

Material and Methods

This cross-sectional study was conducted between September 2018 and December 2018 at Bursa Yüksek İhtisas Traininig and Research Hospital, Department of Gynegology and Obstetrics, Bursa, Turkey. Institutional Review Board approved the study protocol (IRB app no: 2011-KAEK-25 2018 / 05-18). Informed consent was obtained from all participants. A total of 90 pregnant women, 30 with normal pregnancy, 30 with EOPE, and 30 with LOPE were included in this study. The diagnosis of preeclampsia was established when the first detection of maternal hypertension occurred after 20th week and the simultaneous presence of one or more of the following situations: proteinuria (300 mg in a 24-h urine collection sample or 1 (+) protein by dipstick test on two random urine samples), maternal organ dysfunction such as renal failure, hepatic involvement, neurological involvement, HELLP syndrome and fetal growth retardation. Venous blood samples were obtained from maternal antebrachial veins at the time of delivery, centrifuged for 10 minutes at 4000 rpm (rotation per minute) and serum samples were preserved at – 80°C until biochemical assays were done. For normally distributed data, the unpaired t-test was used to compare numeric data, while the Pearson test was used for correlation test. For data with abnormal distribution, the Mann–Whitney test was used to compare numeric data, while the Spearman test was used for correlation test.

Exclusion criteria were multiple pregnancies, pregnancies with fetal anomalies, pregnants with chronic disease, pregnants with PE history or HT disease, chorioamnionitis, diabetes mellitus, gestational diabetes, premature rupture of membranes.

Venous blood samples were taken and doppler parameters of the umbilical artery were measured in hospital admissions before delivery. Doppler ultrasonography measurements were measured by an experienced obstetrician using GE P6 ultrasonography device (GE, HEALTH CARE, UK).

Collected blood was taken with EDTA and centrifuged at 1000 rpm. All collected samples were stored within 30 minutes sampling and stored at -80o C for future analysis. The measurement of podocalyxin (Human Podxl/Podocalyxin ELISA kit Sino Geno Clon, Catalog no: SG-10475, Hangzhou, China) was performed according to the instructions included in the kits with the enzyme-linked immunosorbent assay (ELISA) method by Biochemistry Department of Bursa Yüksek İhtisas Training and Research Hospital. Serum podocalyxin levels were determined as picogram/milliliter (pg/ml) according to absorption degree in the kits (detection range: 26 pg/ml-1500 pg/ml; sensitivity: 6 pg/ml; detection wave length: 450 nm).

SPSS 20 (Chicago, IL, USA) program was used in all statistical analysis calculations. The Kolmogorov-Smirnov test was used in the comparison of the groups and the data are shown as mean ± standard deviation. ANOVA test was used in comparison of EOP, LOP, and control groups. The Pearson correlation analysis was applied to determine the correlation between parameters. Values with $p<0.05$ were considered statistically significant.

Results

In our study, the medical records of 90 patients were analyzed. Sixty patients had been diagnosed with PE and 30 patients constituted the control group. PE group was further subdivided into LOPE and EOPE groups both of which included 30 participants each.

Demographic data of the patients are given in Table 1.There was no statistical difference between groups in terms of gravidity, parity, and miscarriage rates. There was a statistically significant difference between the birth weight (EOPE vs LOPE:1750±747vs 2844±693; p:0:001) parameters. As a result

Table 1. Demographic data of the patients

	Group 1 (EOPE) n=30	Group 2 (LOPE) n=30	P- value Group 1 & 2	Group 3 (Healthy Controls) n=30	P- value Group 1& 3	P-value Group 2 & 3
Age (years,mean)	30,6 ± 6,1	28,8 ± 7,8	0.551	25,4 ± 5	0,007	0,98
Gravidity (median)	2	2	0,84	2	0,915	0,600
Parity (median)	1	1	0,999	1	0,609	0,609
Abortion (median)	0	0	0,347	0	0,443	0,028
Gestational week of diagnosis (mean)	32,2 ± 2,4	37 ± 1,5	0,001	38 ± 1,1	0,001	0,704
Birthweight (gram, mean)	1750 ± 747	2844 ± 693	0,001	3229 ± 434	0,001	0,057
Umbilical artery Pulsatility Index	0,96 ± 0,45	0,78 ± 0,31	0,090	0,75 ± 0,13	0,041	0,938
Blood urea nitrogen(mg/dL)	22,5 ± 4,2	10,9 ±9	0,929	8 ±2,9	0,070	0,159
Blood creatinine level (mg/dL)	0,69 ± 0,12	0,65 ± 0,13	0,473	0,67 ± 0,13	0,812	0,844
BMI(mean)	33 ± 4,2	34 ±4,8	0,595	27 ±5,5	0,001	0,001
Podocalyxin (pg/ml)	82,3 ± 55,5	71,3 ± 36,9	0,853	66,3 ± 15,6	0,362	1,0

EOPE: early onset preeclampsia LOPE: late onset preeclampsia

Table 2. Comparison of podocalyxin values in patients via smoking, proteinuria, BMI, umbilical artery pulsatility index, preterm delivery, parity, and blood pressure parameters

	Number of patients	Podocalyxin (pg/ml)	P- value
Systolic arterial blood pressure • > 160mmHg • < 160mm/Hg	 44 46	 73,4 ± 46,5 73,2 ±31,1	0,521
Diastolicarterial blood pressure • > 110 mm/Hg • < 110 mm/Hg	 18 72	 77,8 ± 68,0 72,2 ± 28,4	0,333
Parity • Nulliparous • Multiparous	 24 66	 94 ± 63,2 65,8 ± 21,7	0,001
Proteinuria • Positive • Negative	 52 38	 76,6 ± 48,6 68,8 ± 19,8	0,873
BMI* • > 30 kg/m² • <30 kg/m²	 56 34	 76,4 ± 47,3 68,3 ± 19,0	0,963
Time of delivery • Preterm • Term	 39 51	 80,8 ± 51,2 67,5 ± 25,8	0,191
Umbilical Artery Doppler Ultrasound • PI > 1 • PI < 1	 28 62	 71,8 ± 55,6 74± 29,4	0,080
Smoking Cigarette Status • Yes • No	 5 85	 67,1 ± 15,5 73,7 ± 40,1	0,579

*BMI: Body Mass Index

Table 3. Comparisons between combined preeclampsia group and the control group

	Preeclampsia n=60	Group 3 (Healthy Controls) n=30	P- value
Podocalyxin Mean (pg/ml)	76	66,3	0,551
BMI*(mean)	33,6	27,6	0,001
PNR** (mean)	32	21	0,001
NLR*** (mean)	5	8	0,001
PLR**** (mean)	160	138	0,587
Birth weight	2297	3229	0,001
Smoking cigarette • Yes	2(3,3%)	3(10%)	0,196
Age	29,7	25,4	0,005
Delivery type • cesarean	55(91,6%)	14(46,6%)	0,001
Umblical Artery > 1 Number of patients	35(58,3%)	3(10%)	0,002

*BMI: Body Mass Index **PLR: Platelet-to- Lymphocyte Ratio
***PNR: Platelet-to-Neutrophil Ratio ****NLR: Neutrophil-to-Lymphocyte Ratio

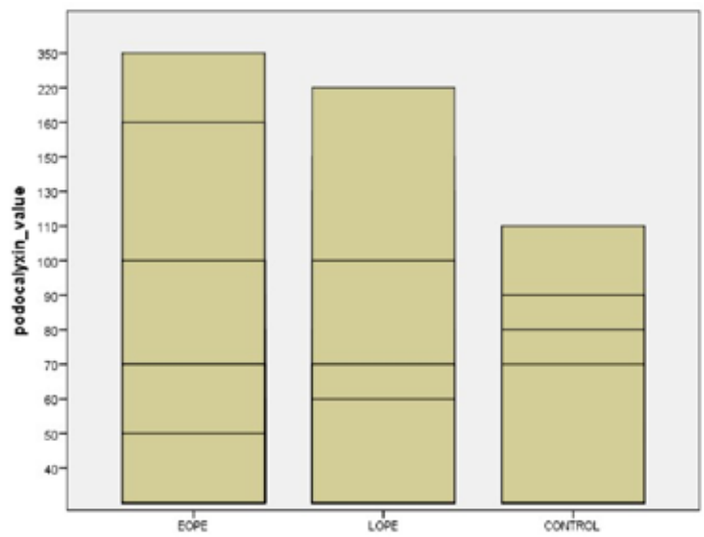

Figure 1. Levels of Serum podocalyxin in EOPE, LOPE, and control groups.

of comparison of all groups with respect to serum podocalyxin values, no significant difference was found between the groups. Regarding serum podocalyxin values in EOPE and control group, there was no significant difference (EOPEvs control: 82.3±55.5 vs 66.3±15.6; p:0.362). There was no significant difference between LOPE and control group (71.3± 36.9 vs 66.3±15.6; p:1.0), either.

The values of podocalyxin were compared via different characteristics such as smoking, proteinuria, BMI, umbilical artery pulsatility index, preterm delivery, parity and blood pressure parameters within all patients and results are given in Table 2. When the parities were analyzed, we determined that the podocalyxin values of the multiparas were lower than the nulliparous women and the difference between them was statistically significant (65.8±21 versus 94±63; p:0.001).

In Table 3, the combined preeclampsia groups were compared with the control group and a statistically significant difference was found between them with regard to the parameters of BMI (33.6 vs 27.6; p:0.001), platelet-to-neutrophil ratio (PNR) (32 vs 21; p:0.001), platelet-to-lymphocyte ratio (PLR) (160 vs 138; p:0.001), neutrophil- to-lymphocyte ratio (NLR) (5 vs 8; p:0.001) and modes of delivery (cesarean section 55 vs 14; p:0.001). Additionally, preeclampsia groups (both EOPE and LOPE) podocalyxin value were compared to control group'sand there was no statistically significant difference between them (p:0,551) (Table 3).

In Figure 1, a histogram comparison of serum levels of podocalyxin in EOPE, LOPE, and control groups were given. Although EOPE group has the highest mean value, the differences between the groups did not reach statistical significance.

Discussion

This study was one of the first in the literature to evaluate maternal serum levels of podocalyxine in PE patients. As a result, we could not determine a statistically significant difference between the groups when compared with each other with regard to the serum podocalyxin values of the PE patients and the control group. Additionally, in our study, there was no significant difference in maternal serum levels of podocalyxin between subgroups EOPE and LOPE.

The podocytes, which are glomerular epithelial cells, are stationed on the outer surface of the glomerular basement membrane. The podocytes and their foot processes control the filtration of capillary plasma proteins from the capillary lumen to the Bowman's cavity. The glomerular basement membrane together with podocytes determines the permselectivities (selective permeability) of plasma proteins. In addition, negatively charged glycoproteins such as podocalyxin on the cell surface protect podocytes and limit the passage of negatively charged molecules that cross the glomerular filtration barrier. Spillage in podocyte glycoproteins damages the glomerular filtration barrier and causes the appearance of plasma proteins in the urine. Due to the development of PE, impairment in the renal barrier causes podocyte damage and thus leads to increased levels of podocalyxin in the urine. In the literature, various studies have shown that urinary podocalyxin values increase in PE patients compared to normotensive patients. In our study, we predicted that the level of podocalyxin in maternal serum would not change.In the literature stated that podocytes are located on the outer surface[16]. In case of severe damage, podocalyxin levels are expected to be increased in the urine considering that protein leaks into the lumen but maternal serum levels did not increase. In our study, we determined similar levels of maternal serum podocalyxin in EOPE/LOPE and normotensive patient groups (Figure 1).

In a study by Palacios de Franco et al., they measured the urinary podocalyxin values of normotensive and PE patients during the postpartum period and 3 years after birth and stated that the values of urinary podocalyxin did not differ between normotensive and PE patients after 3 years. They also showed that the postpartum urinary podocalyxin decreased before proteinuria in PE patients. They determined that after 3 years, serum creatinine, urinary podocalyxin and proteinuria all normalized, although a small number of patients still suffered proteinuria [21].

In postpartum period, podocyte damage improves after birth, and probably, for this reason, urinary excretion of podocalyxin also decreases back to normal values. The podocyte damage caused by PE is temporary and the urinary excretion of podocalyxin returns to normal after PE resolves completely after delivery. The damage in the podocytes which are on the outer surface of the glomerular basement membrane can lead to increased excretion of podocalyxin in the urine while maternal serum levelsof podocalyxin may not be/or slightly affected in PE [22].

Our hypothesis supports that there is no statically differenc ebetween the values of PE and control group maternal serum podocalyxin obtained in our study, that is why maternal serum levels may not change in podocyte damage.

In another study in the literature, they examined the urinary excretion of podocalyxin in patients who have complicated membranous nephropathy (MN). In the study, the authors determined that podocalyxin was poured into the urine from damaged podocytes in diabetic nephropathy and determined that increased urine levels of podocalyxin in active glomerulonephritis and diabetic nephropathies. They also reported that urinary podocalyxin was a useful biomarker in the diagnosis of MN. In this study, it was reported that urinary excretion of podocalyxin increased and the urinary increase occurred due to pouring of podocalyxin from the surface of podocytes [23]. The conclusion of this study supports our hypothesis that preeclampsia also induces a hyperpermeable state in glomerular cells resulting in excessive excretion of protein waste from the damaged podocytes into the urine and thus an unchanged serum level of podocalyxin can be maintained.

In contrast, in a study by Chen et al., the researchers found that podocalyxin is present in measurable amounts in the maternal serum in normal pregnancy and their levels increase as gestational age increases. In the same study, they determined that in the evaluation of podocalyxin levels according to the trimesters, the lowest in the first trimester and the highest in the third trimester, the difference was strongly significant ($p \leq 0{,}0001$) between trimesters. In addition, they determined that the maternal serum podocalyxin values increased when PE developed. In their study, they compared the serum podocalyxin levels of 68 normotensive patients with 34 PE patients. They found that PE patients had higher serum podocalyxin values than the normotensive group (p: 0.006). They explained this result with the hypothesis that podocalyxin can be released not only from podocytes but also from vascular endothelial cells [17].

In the letter to the editor by Gaoupaulon, similarly, he expressed his opinion that podocalyxin may be released from the placenta and vascular endothelium besides podocytes in PE patients [24]. In another study, the researchers evaluated serum podocalyxin values at 11-13 weeks of gestation and evaluated their use in early diagnosis of preeclampsia. At 11-13 weeks of gestation, those who later developed PE, regardless of EOPE or LOPE showed significantly higher levels of serum podocalyxin than controls. Also, they demonstrated that serum podocalyxin was significantly elevated at 11-13 weeks in women who later develop PE, and elevation of podocalyxin levels may provide a promising biomarker for early detection of LOPE [25]. In contrast, in our study, we determined that serum podocalyxin values were not different in PE and control groups (Figure 2).

The limitation of our study is the low number of patients and both urinary podocalyxin excretion and maternal serum

podocalyxin were not evaluated at the same time.

In conclusion, according to our study and related literature data, we believe that measurement of the urinary levels of podocalyxin will be more usefull for the diagnosis and follow up of the preeclampsia rather than serum levels. Its clinical usefulness needs to be supported by large-scale studies.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study 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. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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