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ORIGINAL PAPER / OBSTETRICS

Predictive value of maternal serum podocalyxin in the diagnosis of preeclampsia: a prospective case-control study

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Short title: Maternal podocalyxin in the diagnosis of preeclampsia

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ABSTRACT

Objectives: There is a need for markers to facilitate the diagnosis of preeclampsia, one of the most chief causes of maternal and infant mortality. Preeclampsia causes damage to the glomeruli and vascular endothelium in pregnant women. Podocalyxin is a sialoglycoprotein found in both glomeruli and vascular endothelium. In this study, we investigated the levels of podocalyxin in preeclampsia, and studied its potential to predict preeclampsia.

Material and methods: Women admitted to the Health Sciences University Derince Training and Research Hospital, Department of Obstetrics and Gynecology between February–November 2018 due to high direct blood and diagnosed with preeclampsia according to the 2013 American College of Obstetricians and Gynecologists criteria were included in the study. The control group consisted of healthy volunteers having similar demographic features (gestational week, gravida, parity, and age) with the preeclampsia group. The main outcome variable was serum podocalyxin levels.

Results: The mean (\pm SD) podocalyxin levels of the study and control groups were 124.15 ± 39.63 ng/mL and 71.47 ± 16.86 ng/mL, respectively ($t = 7.845$, $p < 0.001$). Using a cut-off of 91.7123, podocalyxin could predict preeclampsia with 90% sensitivity and 98% specificity.

Furthermore, podocalyxin levels were significantly higher than the normotensive participants in both early (143.81 ± 51.96 ng/mL vs 75.35 ± 19.36 ng/mL) and late-onset (110.22 ± 19.11 ng/mL vs 68.26 ± 14.13 ng/mL) preeclampsia ($p < 0.001$).

Conclusions: Serum podocalyxin levels increase in preeclampsia. We conclude that podocalyxin is a candidate for predicting preeclampsia.

Key words: early diagnosis; maternal serum; podocalyxin; preeclampsia

INTRODUCTION

Background/rationale

Preeclampsia is a systemic disorder that may affect both the mother and the fetus. It can cause serious cardiorespiratory, neurologic, renal, hepatic, and hematologic complications [1]. Preeclampsia is the second most common cause of maternal mortality in Turkey [2]. According to the World Health Report 2015, approximately 830 women die every day due to complications ensuing during pregnancy or delivery; the number of women died in 2016 was reported as 303,000 [3].

Preeclampsia increases fetal risks associated with stillbirth, neonatal death, intrauterine growth retardation, and premature birth [4]. In addition, it has been implicated in increasing post-partum hypertension and chronic kidney disease [5].

Preeclampsia directly damages the glomerular endothelium, consequently causing acute renal injury. Thus, angiogenic instability is a trigger factor for the damage of both podocytes and the endothelium in preeclampsia [6].

On the other hand, podocalyxin is a glomerular podocyte protein, also secreted from endothelial cells of other organs, which increases in the urine of preeclamptic women [7].

Some studies have reported that podocyturia may be used to predict preeclampsia and determine its severity [8–10]. However, a recent study indicated podocalyxin in pregnant women could be detected with the ELISA kit and speculated it could be used as a predictive tool for early onset preeclampsia [7].

Objectives

This study investigated whether podocalyxin can be used as a predictive tool in preeclampsia.

MATERIAL AND METHODS

Study design

This study was designed as a prospective case-control study. Study reporting was done per the STROBE guideline [11]. Written informed permission was obtained from all participants. The study protocol was approved by the Local Ethical Committee of Non-Invasive Clinical Research at Kocaeli University Research Hospital (IRB number: 2018/54; Date: 07.02.2018).

Setting

This research was carried out in Kocaeli Obstetrics and Gynecology Department of Derince Training and Research Hospital between February–November 2018.

Participants

Participants of the study consisted of 41 preeclamptic and 42 healthy pregnant women. Seventeen early-onset preeclampsia patients and 24 late-onset preeclampsia patients were included in the study at our clinic during the study period. The preeclamptic group included patients applied to the obstetrics and gynecology emergency department of Health Sciences University Derince Training and Research Hospital. Preeclampsia patients were chosen according to the 2013 American College of Obstetricians and Gynecologists (ACOG) criteria. According to ACOG: Preeclampsia is defined as hypertension combined with proteinuria, or in absence of proteinuria, combined with at least one or more other findings including maternal organ dysfunction (elevated liver enzymes, haematological complications, renal insufficiency, neurological symptoms) and pulmonary edema. Hypertension is classified either as new onset hypertension after 20 weeks of gestation with blood pressure levels $\geq 140/90$ mmHg on two occasions at least 4 h apart, or as chronic hypertension. Severe features of preeclampsia include blood pressure at least $\geq 160/110$ mm Hg, platelet count less than 100×10^3 per μL , liver transaminase levels two times the upper limit of normal, a doubling of the serum creatinine level or level greater than 1.1 mg per dL, severe persistent right upper-quadrant pain, pulmonary edema, or new-onset cerebral or visual disturbances. Normotensive healthy pregnant volunteers with similar gestational week, gravida, parity, and age as in the preeclampsia group constituted the control group. The control participants were pregnant women seen in the same center during the study period who had no high blood pressure during the follow-up, did not have any systemic disease, and did not use any drugs except vitamin and iron supplementations. All participants were at or beyond the 20th gestational week. Patients who had previously high blood pressure, renal or liver disease,

intermittent hypertension, or proteinuria before pregnancy were excluded from the study (Fig. 1). Detailed physical examination and routine blood tests were ordered in all patients. Patients were informed by the attending physician, and if approved, 5 mL blood was taken in addition to routine blood tests. Preeclampsia was diagnosed according to the 2013 American College of Obstetricians and Gynecologists (ACOG) criteria.

Variables

The primary outcome variable of the study was “serum podocalyxin level”. Secondary outcome variables were routinely ordered tests including serum ALT, AST, LDH, urea, creatinine, platelet count, urine protein/creatinine ratio, and 24-hour urine protein excretion. The routine tests were analyzed in the biochemistry laboratory of the hospital per hospital protocol. The blood obtained for podocalyxin analysis was centrifuged at 2500 rpm for 10 minutes within 30 minutes after collection. The sera obtained were stored at -80 ° C until the time of analysis. Podocalyxin was studied using ELISA (Elabscience[®], Hubei/China). Studies were carried out in accordance with the kit protocol. The ELISA kit used works with the competitive ELISA method.

Study size

The sample size was calculated based on the primary outcome variable with a minimum of 80% power and a maximum of 5% type 1 error to find a statistically significant difference between the study groups. The calculation with the power analysis of the E-picos section of the Medicres program revealed 37 participants in each group for a 95% confidence interval. Serum podocalyxin levels were assumed as 50 ± 12 ng/mL and 60 ± 12 ng/mL for normotensive healthy pregnant women and the preeclampsia group, respectively.

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0 software (SPSS Inc., Chicago, IL, USA). The results of the study were presented as frequencies and percentages for categorical variables and as means and standard deviations for numerical variables. The normal distribution of the numerical variables was evaluated by checking the skewness coefficients. The independent samples t-test, Mann-Whitney U test, or one-way ANOVA were used to compare the groups in cases where parametric test conditions were met. Post hoc analyzes were performed with Tukey if the variances were homogeneous and Tamhane T2 if not. The receiver operating characteristics (ROC) analysis was used to

determine sensitivity and specificity values for podocalyxin. Multivariate comparisons were examined by logistic regression analysis and two-way ANOVA. The statistical significance threshold was taken as $p < 0.05$.

RESULTS

Data for 83 participants were analyzed. Forty-one of them were preeclamptic, and forty-two were healthy pregnant. The mean age of the participants was 28.46 ± 5.28 years and range were between 18–40 (Tab. 1).

According to urine dipstick results, 7 patients did not show proteinuria, 5 patients had trace proteinuria, 6 patients had +1 proteinuria, 13 patients had +2 proteinuria and 10 patients had +3 proteinuria. When podocalyxin levels were compared with the protein status in the urine, no statistically significant difference was detected ($p = 0.417$).

Podocalyxin, ALT, AST, LDH, urea, creatinine, systolic blood pressure, and diastolic blood pressure were significantly different in the preeclamptic (case) group compared to the controls. However, there was no significant difference in the urine protein/creatinine ratio and 24-hour urine protein excretion (Tab. 2). Also, patients with early preeclampsia had significantly higher mean podocalyxin levels compared to those with late onset (143.81 ± 51.96 ng/mL vs. 110.22 ± 19.11 ng/mL) (Mann-Whitney U Z = 2.435; $p = 0.015$).

The ROC analysis demonstrated that podocalyxin provides a significant advantage in predicting preeclampsia (Area under the curve 0.939 $p < 0.001$) (Fig. 2). A podocalyxin cut-off level of 91.71 provides 90% sensitivity and 98% specificity in foreseeing preeclampsia.

Podocalyxin showed significant positive correlations with urea, creatinine, ALT, AST, and LDH (r ; p 0.417; < 0.001 , 0.372; 0.001, 0.226; 0.040, 0.327; 0.003, and 0.353; 0.001, respectively), and a significant negative correlation with platelet count ($r = -0.373$; $p = 0.001$).

A logistic regression analysis with preeclampsia status as the dependent and podocalyxin, and urea, creatinine, ALT, AST, LDH, and platelet levels as independent variables, demonstrated that podocalyxin was the only significant independent predictor of preeclampsia status (Wald = 15.951, $p < 0.001$, Exp(B) = 1.153, 95% CI: 1.075–1.236).

DISCUSSION

Key results

This study demonstrated that serum podocalyxin levels are increased in preeclamptic pregnancies. Cases with early onset had significantly higher podocalyxin levels compared with late onset.

Limitations

One limitation of this is the lack of Podocalyxin information of the participants before their pregnancies. Large-scale cohort studies are needed to calculate the odds of baseline podocalyxin levels in predicting preeclampsia.

Interpretation

The diagnosis of preeclampsia, one of the most prominent causes of maternal and fetal morbidity and mortality, affecting 3–7% of healthy nulliparous and 1–3% of multiparous women, is of vital importance [12]. It was suggested that podocyturia screening at the end of the second trimester could identify pregnant women at risk for preeclampsia [13]. A study conducted in 2017, stated that serum podocalyxin values were higher in early preeclamptic pregnant women compared to a control group [7]. Our findings support this result and further add that the podocalyxin levels are significantly higher also in late-onset preeclampsia.

In other words, all preeclamptic pregnant women had higher podocalyxin levels. This finding is not surprising. Because the pathogenesis of preeclampsia, such as incomplete spiral artery remodeling that contribute to placental ischemia and release of antiangiogenic factors from the ischemic placenta to the maternal circulation causing endothelial damage, also affect podocalyxin levels. Additionally, the glomerular endothelium is directly damaged in preeclampsia, and podocalyxin is abundant in the renal glomeruli [14]. Podocalyxin is a glomerular podocyte protein, but it is secreted from endothelial cells of other organs too. We postulate that podocalyxin secreted from maternal endothelial cells may increase in the sera of preeclamptic women.

Preeclampsia occurs in 2–5% of pregnancies in developed countries. However, it may complicate up to 10% of pregnancies in developing countries, where emergency care may not be adequate [15]. In 2004, after conducting a systematic review of screening tests for preeclampsia, the World Health Organization reported that there was no clinically useful screening test to predict the development of preeclampsia in low-risk or high-risk populations, and advised for further studies [16]. After this report, many researchers have identified or examined potential biochemical and/or biophysical markers. Some systematic reviews and meta-analyzes evaluating the clinical benefits of studies with a single marker have been

published [17–19]. However, the need for a suitable marker getting a high level of accuracy persisted [20].

To be effective, a screening test must be sufficiently sensitive and specific and provide an adequate positive predictive value. The argument that podocalyxin values can be used as a predictor in preeclampsia was noted as one of the essential findings of this study. For the first time serum podocalyxin was found to be successful in predicting preeclampsia at 90% sensitivity and 98% specificity. We want to speculate that the sensitivity and specificity of podocalyxin are high enough to suggest its involvement in preeclampsia diagnosis.

Although there are some conflicting studies, report generally support higher liver function tests in preeclamptic pregnant women [21–23]. According to a recent study, elevated AST and ALT levels in the first 20 weeks of pregnancy are associated with a higher risk of developing severe preeclampsia in the second half of the pregnancy. However, there is no clinical cut-off value that can be used practically to predict preeclampsia [24].

In a study consisting of preeclampsia, severe preeclampsia, and control groups, hemoglobin values were lower in the patients with severe preeclampsia. However, ALT, AST, urea, and creatinine values too were significantly higher in this group [25]. In our study, no difference was found between the groups concerning hemoglobin values. In the preeclampsia group, ALT, AST, LDH, urea, and creatinine levels were significantly different from the control group, which was coherent with previous studies and expectations. However, it was surprising that there was no statistically significant difference in the urine protein/creatinine ratio and 24-hour urine protein excretion. This result was thought to be due to the low number of data on protein excretion in 24-hour urine.

In our study, preeclampsia was divided into two groups as early and late according to the time of onset. There was no statistically significant difference in other variables except podocalyxin in these two groups. This finding suggested that more focus should be placed on podocalyxin to elucidate the pathogenesis of preeclampsia. The remarkable point was that the level of podocalyxin was lower in late-onset preeclampsia than in the early-onset cases. In addition, there was no significant difference between severe preeclampsia and preeclampsia groups regarding podocalyxin levels. This suggests that podocalyxin is elevated independently of hypertension in preeclampsia. However, the low number of severe preeclampsia groups indicates that this result should be supported by larger studies. Probably endothelial damage is required to increase podocalyxin levels. Once damage occurs, its severity may not further increase podocalyxin levels.

Lactate dehydrogenase, the key enzyme of glycolysis, is used to identify the cause and location of tissue damage in the body and to help monitor the progress of the damage. LDH increases in many diseases as a result of its widespread distribution in the tissues [26]. On the other hand, podocalyxin has been reported to be a marker of embryonic hematopoietic stem cells (HSCs), erythroid cells and adult HSCs, and thus, may be a valuable marker for purification of these cells for transplantation [27]. It was suggested that the correlation between LDH and podocalyxin and the similarly their high levels in preeclamptic pregnant women can be attributed to the damage caused by preeclampsia. The correlation between LDH and podocalyxin, and their surge in preeclamptic pregnant women may be due to the damage to tissues where both markers are dense.

CONCLUSIONS

Serum podocalyxin levels are increased in preeclamptic pregnant women. The serum podocalyxin levels are higher in early onset preeclampsia compared to late onset cases. However, the severity of preeclampsia does not make a significant difference. We conclude that with 90% sensitivity and 98% specificity, podocalyxin is a candidate for predicting preeclampsia.

Conflict of interest

The authors have no conflict of interest in this study.

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Figure 1. Participant flow diagram

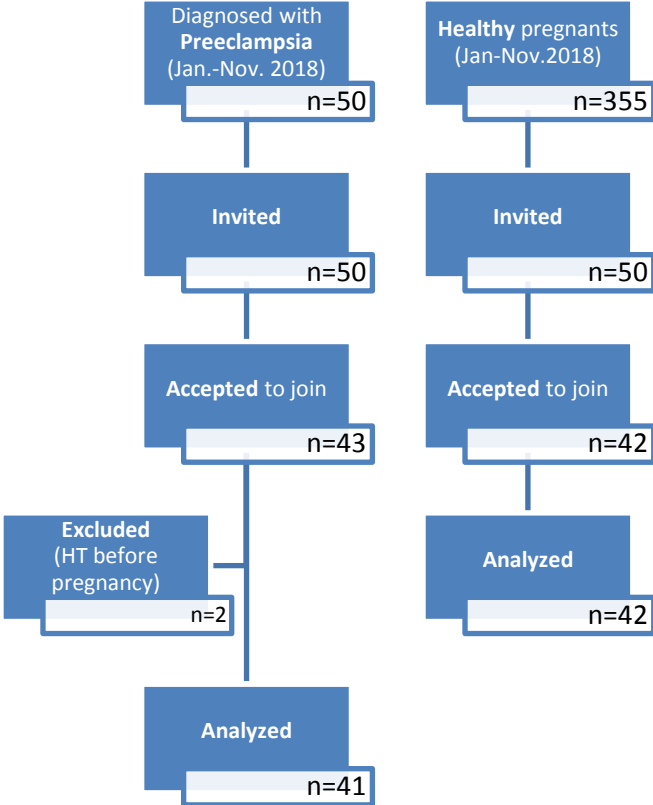


Figure 2. Receiver operating characteristics graph showing podocalyxin levels in predicting preeclampsia; ROC — receiver operating characteristics

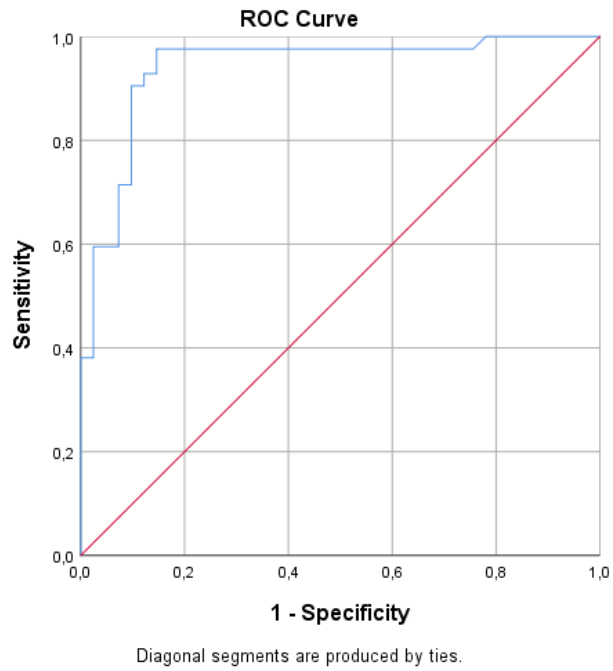


Table 1. Demographic features of the participants

	n	Mean	SD	Minimum	Maximum
Age [year]	83	28.46	5.28	18	40
Height [cm]	83	160.90	6.87	148	175
Weight [kg]	83	86.65	16.62	57	130
Hemoglobin [mg/dL]	83	11.37	1.26	8.40	14.90
Hematocrit [%]	83	34.84	3.49	27.00	43.30
Platelets [number/mL]	83	202.42	60.11	27	352
ALT	83	19.55	35.53	6	234
AST	83	23.67	23.74	10	173
LDH	83	241.27	88.85	120	617
Creatinine	83	0.56	0.07	0.43	0.88

SD — standard deviation

Table 2. Comparison of the preeclamptic and control groups concerning the outcome measures.

	Group	N	Mean	SD	*p	t
Podocalyxin [ng/mL]	Preeclamptic	41	124.15	39.63	< 0.001	7.845
	Control	42	71.47	16.86		
Systolic blood pressure [mmHg]	Preeclamptic	41	151.71	12.82	< 0.001	17.769
	Control	42	105.71	10.68		
Diastolic blood pressure [mmHg]	Preeclamptic	41	98.54	6.54	< 0.001	17.724
	Control	42	68.69	8.62		
Urine protein / creatinine ratio	Preeclamptic	21	2.43	4.13	0.054	2.036
	Control	7	0.52	0.66		
24-hour urine protein excretion [mg]	Preeclamptic	8	2306.85	4367.97	0.529	0.658
	Control	2	181.50	86.97		
Platelets [number/mL]	Preeclamptic	41	182.98	62.25	0.003	-3.056
	Control	42	221.40	51.95		
ALT	Preeclamptic	41	28.83	48.88	0.018	2.389
	Control	42	10.50	4.92		
AST	Preeclamptic	41	31.73	31.63	0.003	3.187
	Control	42	15.81	4.81		
LDH	Preeclamptic	41	282.20	100.14	< 0.001	4.603
	Control	42	201.31	51.92		
Creatinine	Preeclamptic	41	0.58	0.09	0.027	2.255
	Control	42	0.55	0.06		
Urea	Preeclamptic	41	18.88	6.85	0.005	2.935
	Control	42	15.12	4.55		

*Independent samples t-test; SD — standard deviation