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Levels of syndecan-1 and hyaluronan in early- and late-onset preeclampsia

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ABSTRACT

Objective: The study aimed to assess serum levels of syndecan-1 (SDC-1) and hyaluronan (HA) in patients with early- and late-onset preeclampsia (PE).

Study design: Blood samples were collected in the third trimester of pregnancy from 20 women with early-onset PE, 20 with late-onset PE, and 20 with normal pregnancy for the assessment of serum levels of SDC-1 and HA as markers of endothelial injury. PE was categorized as early-onset when diagnosed at < 34 weeks of gestation and as late-onset when diagnosed at ≥34 weeks of gestation.

Main outcome measures: The degree of endothelial injury in different forms of preeclampsia expressed by serum concentrations of SDC-1 and HA.

Results: Concentration of HA was significantly higher and the level of SDC-1 was significantly lower in patients with PE than in the control group. However, the concentrations of both HA and SDC-1 did not differ significantly between the two groups of PE.

Conclusions: Degree of endothelium injury is comparable in patients with early- and late-onset PE.

1. Introduction

Maternal endothelial injury and dysfunction is a well-known, characteristic phenomenon in the pathophysiology of preeclampsia (PE) [1]. The most probable mechanism of endothelial injury in preeclampsia is the neutralization of vascular endothelial growth factor (VEGF) and placental growth factor by soluble fms-like tyrosine kinase 1 (sFlt-1) that is overproduced in poorly perfused preeclamptic placentas [2]. This mechanism is mainly related to early-onset PE which is characterized primarily by placental insufficiency, while the mechanism of endothelial dysfunction in patients with the late-onset PE is probably more complex and enigmatic [3]. Clinical consequences of endothelial injury in women with PE include thrombocytopenia, liver dysfunction, renal failure, placental insufficiency, and eclampsia [2,4]. The frequency of these complications differs between the two forms of PE [3].

Morphologically, the most important protective structure of the endothelium is endothelial glycocalyx (EG) which is an external layer of endothelial cells composed of different proteoglycans (PGs), glycoproteins, glycolipids, and glycosaminoglycans (GAGs) [5,6]. The protective role of EG for endothelium includes for example maintenance of tissue integrity, prevention of leukocytes and platelet adhesion, and antithrombotic activity [5,6]. Examples of clinical consequences of EG damage are albuminuria and edema [7]. It has been found that VEGF may restore partially damaged EG of the glomerular endothelium [7].

Syndecan-1 (SDC-1) is one of the important PGs of EG, and hyaluronan (HA) is common GAG of EG [5].

Theoretically, EG damage results in increased shedding of different components of EG into the blood, and as a consequence, their serum concentrations increase [5]. However, in very few studies, the decreased serum level of Sdc-1 and the increased concentration of HA were found in women with PE in comparison with the control group [8,9].

The aim of the present study was to assess the serum levels of SDC-1 and HA as markers of endothelial injury in two forms of PE, namely early- and late-onset PE.

2. Methods

The study was conducted among 60 women in their late second and third trimester of the singleton pregnancy, including 20 patients with early-onset PE, 20 women with late-onset PE, and 20 patients with normal pregnancy, who were the control group. All patients were hospitalized between 2015 and 2018 at the Division of Reproduction of Poznan University of Medical Sciences. The women from the control group were matched by gestational age with the patients from the study groups.

Preeclampsia was characterized by hypertension (systolic blood

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pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on two occasions) and proteinuria (≥300 mg/24 h), both of which found for the first time after 20 weeks of gestation [10].

PE was categorized as early-onset when diagnosed at < 34 weeks of gestation and as late-onset when diagnosed at ≥34 weeks of gestation. Intrauterine growth restriction (IUGR) of a fetus was diagnosed if ultrasound-estimated fetal weight was below the 10th percentile according to local growth charts and the Doppler criteria for placental insufficiency were also met. Doppler criteria for placental insufficiency included at least one of the following: increased (above 95 th percentile) uterine artery mean pulsatility index (PI), increased (above 95 th percentile) umbilical artery PI, decreased (below 5th percentile) middle cerebral artery PI and decreased (below 5th percentile) value of cerebroplacental ratio [11].

All sonographic examinations, including Doppler, were performed by experienced specialist by using E 8 ultrasound system (GE Healthcare). The results of the last Doppler examination, at least 7 days before delivery, were used for the final analysis.

To determine the concentration of HA and SDC-1, 7.5 ml of venous blood was sampled from patients with PE on the day of diagnosis. Healthy pregnant women served as the control group. After centrifugation of the blood samples (2000*g*), serum samples were frozen at −20 °C until assessment. HA and SDC-1 concentrations were determined by immuno-enzymatic tests (enzyme - linked immunosorbent assay [ELISA] kit from EIAab Wuhan, China for HA and Sigma Aldrich Merck KGaA, Darmstadt, Germany for SDC-1). Assays were performed according to the manufacturer's instructions. Plate reading was performed using an MRX reader (Dynex Technologies, Chantilly, VA, USA) at λ = 450 nm.

The exclusion criteria included the following: multiple pregnancy, fetal malformations, intrauterine infection, preterm premature rupture of membranes, sepsis, fever and pre-existing diabetes. Women with chronic hypertension were included in the study.

SigmaStat version 3.5 software (Systat Software, Inc., Point Richmond, CA, USA) was used for statistical analysis. The results were analyzed using one-way analysis of Variance (ANOVA) with multiple comparison procedures and Student's *t*-test for variables with parametric distributions. For variables with non-parametric distributions, Kruskal-Wallis ANOVA on ranks with multiple comparison procedures and Mann–Whitney rank sum test were used. Spearman's rank correlation test was used for the analysis of correlation between the concentration of SDC-1 and HA and gestational age, blood pressure, proteinuria, body mass index (BMI) and age of women with PE. The chi-square test was used for the assessment of parity distribution. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical results

The most significant clinical differences between the groups were noted for gestational age at delivery and newborns' birth weight; the values of both these parameters were significantly lower in patients with early-onset PE than in patients with late-onset PE and women from the control group. Inversely, IUGR and emergency indications for cesarean section due to fetal distress were also significantly more frequent among patients with early-onset PE than in women with late-onset PE. BMI at the onset of PE was significantly higher in patients with late-onset PE than in the control group. Clinical characteristics of the patients are summarized in Table 1.

3.2. Results of SDC-1 concentration

Mean serum concentrations of SDC-1 was 6.29 ± 2.18 ng/ml in the whole group of patients with PE (placental and maternal PE). It was significantly lower than that in the healthy pregnant women (11 ± 2.62 ng/ml, $p < 0.001$). The serum level of SDC-1 did not differ significantly between the two groups of patients with PE (6.17 ± 2.2 ng/ml in early-onset PE; 6.42 ± 2.2 ng/ml in late-onset PE). Serum concentrations of SDC-1 in the three groups of patients are presented in Fig. 1.

3.3. Results of HA concentration

In contrast, the median serum level of HA was significantly higher in the whole group of patients with PE (236.2 (46.8–351.9) ng/ml)) than in the control group (113.9 (30.9–379.8) ng/ml)). However, the concentrations of HA did not differ between patients with early- and late-onset PE. It was 236.6 (101.1–351.9) ng/ml in early-onset PE and 234.7 (46.8–324.2) ng/ml in late-onset PE. Serum level of HA in the three groups of patients is shown in Fig. 2.

3.4. Results of correlations

No significant correlation was found between gestational age at the onset of preeclampsia, and the concentration of SDC-1 (Fig. 3) and HA (Fig. 4) in both studied groups. No statistical correlations were found between patients' age, diastolic and systolic blood pressure, BMI, degree of proteinuria and levels of SDC-1 and HA in the two groups of patients with PE.

4. Discussion

In the present study we investigated whether there is a difference in the degree of endothelial injury between patients with early- and late-onset PE; the difference was expressed in terms of glycocalyx degradation. To our knowledge, there is only one previous study that has made a similar comparison. [12]. In the present study, first, although the degree of endothelial injury, expressed as serum concentration of HA, did not differ between the two groups of patients with PE, it was significantly higher than that of normotensive patients. Second, the serum level of SDC-1 also did not differ between the two groups of patients with PE, but it was significantly lower than that of healthy pregnant women.

The results of present study differed from those obtained by Weissgerber et al. [12] who found a significantly higher degree of glycocalyx degradation in patients with early-onset PE than in patients with late-onset PE. These differences were related to both HA and SDC-1 concentrations. Interestingly, despite the fact that the results of the present study differ from those obtained by Weissgerber et al. [12], they are in agreement with the results of other studies [8,13]. Szabo et al [13] and Gandley et al. [8], similar to the present study, found significantly lower serum levels of SDC-1 in patients with PE than in normotensive pregnant women. The results reported by Weissgerber et al. [12] for SDC-1 concentrations in patients with PE, deserve special attention.

With regard to the assessment of HA, the results of the present study as well as those of few previously published studies [9,12] showed increased serum concentration of HA, a GAG component of glycocalyx, in patients with PE as compared to that in normotensive women in pregnancy. This finding may probably indicate the importance of the assessment of HA serum level in the evaluation of endothelial injury and dysfunction in PE. In addition, no difference in HA concentrations was found between the two groups of patients with PE in the present study, which is in contrast with the finding of Weissgerber et al. [12].

Many controversies are associated with the assessment of serum concentrations of SDC-1 in PE. We hypothesized that, like HA, serum level of SDC-1 will be higher in patients with PE, and this can be considered as a marker of increased shedding and endothelial injury. The finding that patients with PE showed significantly lower serum concentration of SDC-1 than normotensive women was unexpected and may indicate an additional source and/or role of this PG. Furthermore,

Table 1
Clinical characteristics of women with early-onset PE, late-onset PE and with normal pregnancy.

	Early-onset PE (n = 20)	Late-onset PE (n = 20)	Normal pregnancy (n = 20)	P value
Age (years)	28 (25–41)	31 (19–40)	32 (27–36)	0.029[a]
Parity (%)				
0	38	67	56	NS
≥1	62	33	44	
BMI at onset of preeclampsia	26.4 (21.8–40.6)	34.3 (22.7–53.2)	25 (22–29)	< 0.05[b]
Gestational age at blood sampling (weeks)	28 (24–32)	33 (34–38)	31 (23–37)	0.025[b]
				0.001[c]
Gestational age at delivery	32 (26–37)	37 (34–39)	39 (37–41)	< 0.05[a,b,c]
Mode of delivery				
Vaginal delivery (%)	0	20.0	60%	< 0.05[a,b,c]
Caesarean section (%)	100	80.0	40%	
IUGR	12 (60%)	4 (20%)		< 0.05
Fetal distress as an indication to caesarean section	13 (65%)	2 (10%)		< 0.001[c]
Mean systolic pressure (mmHg)	150 (130–180)	150 (130–180)	110 (100–120)	< 0.05[a,b]
Mean diastolic pressure (mmHg)	90 (90–110)	100 (85–130)	70 (60–80)	< 0.05[a,b]
Proteinuria (g/24 h)	3.78 (0.3–10.5)	3.86 (0.4–12.9)		NS
Newborn's birth weight at birth (g)	1319 ± 568	2636 ± 683	3437 ± 554	< 0.05[a,b,c]

NS = Not significant; PE = preeclampsia.
[a] Significant difference between early-onset PE and the control group.
[b] Significant difference between late-onset PE and the control group.
[c] Significant difference between early- and late-onset PE.

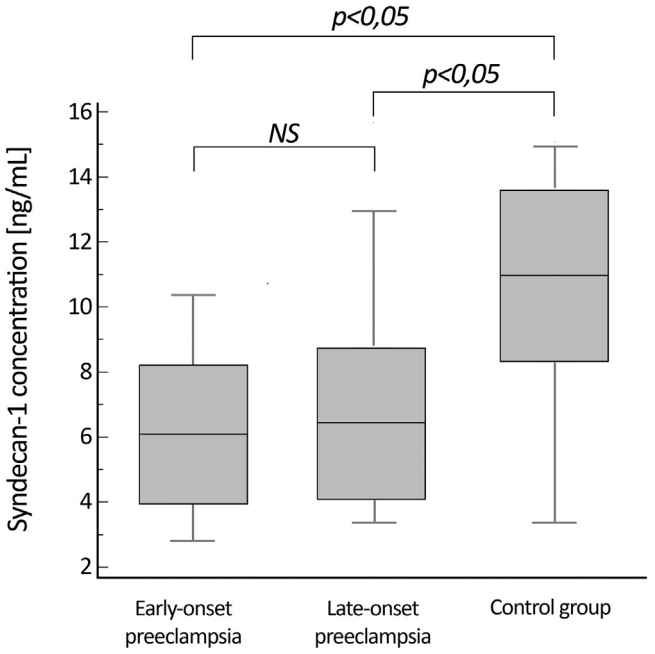

Fig. 1. Concentrations of syndecan-1 in serum of women with early-onset preeclampsia, late-onset preeclampsia and in the control group. Data are presented in boxes as mean ± standard deviation (SD) and whiskers as maximal and minimal values. The significant difference was found ($p < 0.05$) with the use of One Way ANOVA with multiple comparison tests.

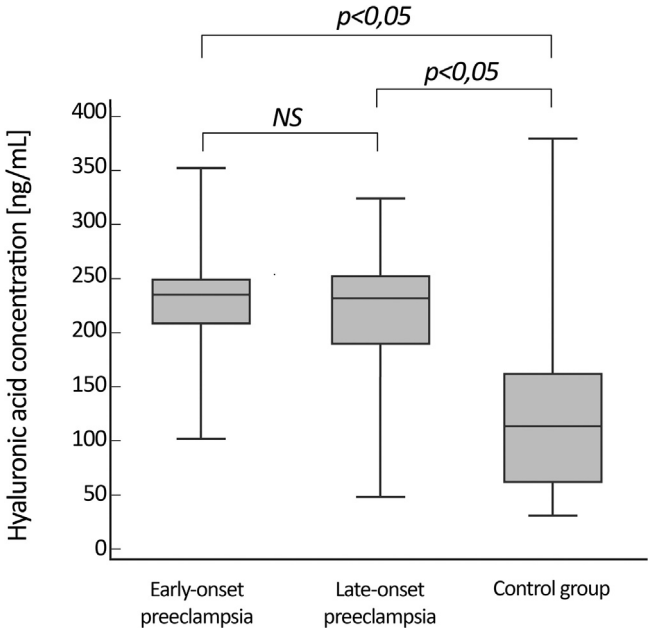

Fig. 2. Concentrations of hyaluronan in serum of women with early-onset preeclampsia, late-onset preeclampsia and in the control group. Data are presented as median, values between 25 and 75th percentyles and maximal and minimal values. The significant difference was found ($p < 0.05$) with the use of Kruskal-Wallis One Way ANOVA with multiple comparison tests.

the results showed that a possible source of serum SDC-1 during pregnancy may be the placenta and not the damaged EG [8,12]. This phenomenon needs, in our opinion, further research.

To conclude, we did not observe a significant difference in the degree of endothelial damage in patients with two types of PE. Although the possible mechanism of endothelial injury seems to be different in the two forms of disease depending more on the activity of sFlt-1 in early-onset PE than in late-onset PE [2], the degree of endothelial injury seems to be comparable. The clinical reflection of this may be the comparable risk of endothelium- dependent complications in mothers in both groups of patients.

The role, utility and significance of SDC-1 in PE needs further analysis and studies.

5. Conclusions

1. Evaluation of serum concentrations of HA in patients with PE seems to be more useful in the assessment of endothelial injury than that of SDC-1.
2. The degree of EG damage is comparable in patients with early- and late-onset PE.
3. The significance of lower concentration of SDC-1 in patients with preeclampsia than in normotensive pregnant women needs further evaluation.

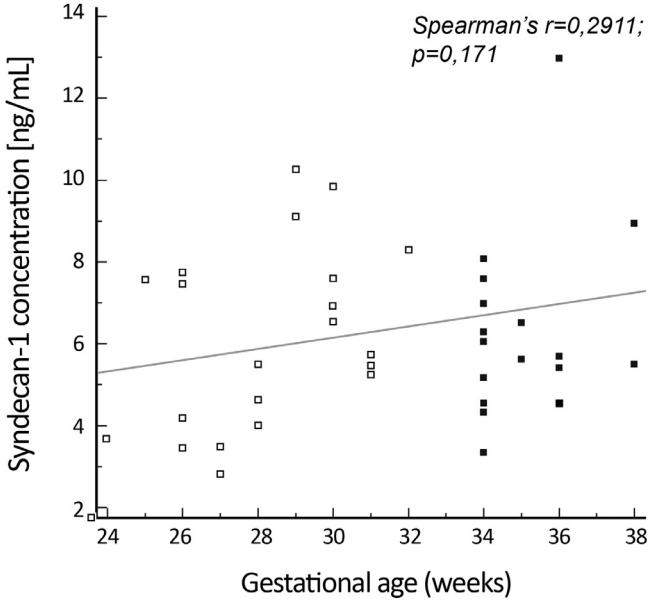

Fig. 3. Concentration of Sdc-1 in patients with early-onset preeclampsia (□) and late-onset preeclampsia (■) according to gestational weeks. No significant correlation was found neither in early-onset PE (p = 0.108) nor in late-onset PE (p = 0.621).

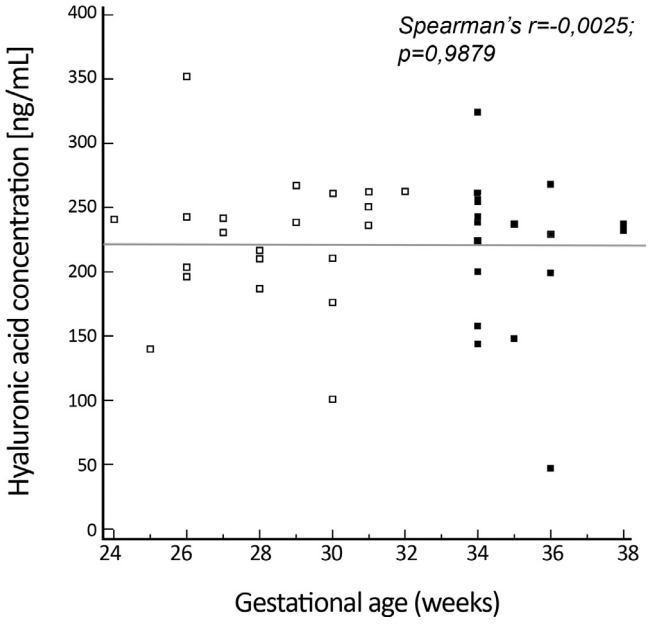

Fig. 4. Concentration of HA in patients with early-onset PE (□) and late-onset PE (■) according to gestational weeks. No significant correlation was found neither in early-onset PE (p = 0.316) nor in late-onset PE (p = 0.397).

Declaration of Competing Interest

None.

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