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Decorin levels in early- and late-onset preeclampsia

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ABSTRACT

Objectives: Preeclampsia (PE) is a pregnancy complication caused by typically limited proliferation, apoptosis, migration, and invasion of extra-trophoblast cells. Decorin (DCN) is a decidua-derived transforming growth factor (TGF)-binding proteoglycan which exerts multiple physiological functions such as collagen fibrillogenesis, myogenesis, angiostasis, and restraining placental invasiveness by adversely regulate proliferation, migration, and invasiveness of human extravillous trophoblast cells. Preeclampsia is mainly classified as early- and late-onset PE according to the timing of the disease onset. In the present study, we aimed to investigate the DCN levels in early-onset PE (EOPE, < 34 weeks) and late-onset severe PE (LOPE, ≥ 34 weeks) and uncomplicated pregnancies.

Material and methods: In this case-control study, serum samples were obtained from 21 pregnant women with EOPE and 29 pregnant women with LOPE, as well as from 38 healthy controls (n = 12 early-onset controls and n = 26 late-onset controls) with uncomplicated pregnancies.

Results: The mean DCN level was statistically significantly higher in the early-onset PE controls than late-onset PE controls (p = 0.040). Although the mean DCN level was higher in the early-onset PE controls than EOPE and LOPE groups, it did not reach statistical significance (p = 0.119 and p = 0.117, respectively).

Conclusions: Although DCN has been thought to play a role in the pathophysiology of PE, our study results show that DCN is not a useful predictive marker of EOPE and LOPE. Further large-scale studies are needed to draw a definitive conclusion.

Key words: early-onset; late-onset; preeclampsia; decorin

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INTRODUCTION

Hypertensive disorders in pregnancy are a major health problem worldwide and preeclampsia (PE) is the most common complication [1]. Preeclampsia accounts for 3 to 5% of all pregnancies and is one of the leading causes of maternal, fetal, and neonatal mortality and morbidity [2]. It is mainly classified as early-onset (< 34 weeks) and late-onset (≥ 34 weeks) [3]. Although initial symptoms are similar in both conditions, they have unique biomarkers, genetic risk factors, prognosis, and clinical characteristics [4].

Decorin (DCN), an extracellular matrix protein, is a small leucine-rich proteoglycan expressed in connective tissue. It contains a protein core and a single chondroitin/dermatan sulfateglycosaminoglycan chain bound at the *N-terminal* extension. Previous studies have shown that DCN plays a role in the cell proliferation and formation of collagen fibers and modulates certain cell functions (*i.e.*, proliferation, dissemination, migration, and differentiation) acting as a critical modulator of inflammation. In addition, DCN is a molecule which is highly expressed in reproductive tissues [5–7].

Decorin binds to the transforming growth factor-beta (TGF-β) and activates signaling pathways. The TGF-β binds to its own receptor and induces phosphorylation of the Smad family, which is one of the transcription factors, thereby, modulating the transcription of collagen, matrix metalloproteinases (MMPs), and metalloproteinase tissue inhibitors [8]. Irrespective of these mechanisms, DCN stimulates phosphorylation of vascular endothelial growth factor (VEGF) and insulin-like growth (IGF) receptor expressed by extra-villous trophoblasts [9].

In the literature, alterations in the DCN levels have been shown to be associated with PE. In a study, Gogiel et al. [10] reported increased DCN levels of the umbilical cord vein wall in patients with PE. Similarly, Siddiqui et al. [11] found that increased DCN levels were predictors of PE even before the onset of clinical symptoms. The link between DCN and PE can be attributed to the impaired proliferation and migra-

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tion of trophoblasts and endothelial dysfunction, which are thought to be responsible for adverse pregnancy outcomes (APOs). On the other hand, there is a limited number of studies showing the relationship between DCN and APOs with controversial results.

Based on the pathophysiological mechanisms of PE, we hypothesized that DCN would be useful in the diagnosis of PE, particularly in early-onset PE. In the present study, we, therefore, aimed to investigate the DCN levels in early-onset PE (EOPE) and late-onset PE (LOPE) and uncomplicated pregnancies.

MATERIAL AND METHODS

This prospective, case-control study was carried out at Bursa Yüksek Ihtisas Training and Research Hospital, Obstetrics and Gynecology outpatient clinics between January 2019 and March 2019. A total of 88 participants aged between 18 and 35 years (n = 50 PE and n = 38 healthy controls) were included in the study. The patient group was classified as EOPE (n = 21) and LOPE (n = 29). The control group consisted of healthy women with singleton pregnancy with similar gestational weeks who were under follow-up in our outpatient clinics with uncomplicated pregnancies. Patients with chronic hypertension, thyroid dysfunction, renal or cardiovascular disease, and multiple pregnancy were excluded from the study. Of the control group, 12 were in the < 34th week of pregnancy (early-onset PE controls) and 26 were in the ≥ 34th week of pregnancy (late-onset PE controls). A written informed consent was obtained from each participant. The study protocol was approved by the institutional Ethics Committee (2011-KAEK-25 2019/02-10). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data including demographic data of the patients, maternal age, parity/gravida, last menstrual period, gestational age, body weight and height, and systolic and diastolic blood pressure were recorded. In those with unknown last menstrual period, the gestational age was calculated based on the crown-rump length as assessed by ultrasound in the first trimester.

The diagnosis of PE was based on a systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, measured twice in 4 to 6-hour intervals while resting, after the 20th gestational week accompanied by 300 mg/dL proteinuria in a 24-hour urine sample, or more than +1 proteinuria in spot urine specimens. Early-onset PE was defined as the onset before 34 weeks of pregnancy, while late-onset PE was defined as the onset after 34 weeks of pregnancy. The presence of intrauterine growth retardation (IUGR) defined as an estimated fetal weight below the 10th percentile for the gestational age birth.

All patients were followed during pregnancy. Data including birth data, birth weight, and type of labor were recorded.

Biochemical Analyses

A 5-mL venous blood sample was drawn from each patient during their ward stay and from each healthy control during outpatient visit. The samples were centrifuged at 3,500 rpm for 10 min and kept at –80º until analysis. Serum DCN levels were analyzed using the enzyme-linked immunosorbent (ELISA) method.

Complete blood count and biochemical parameters were analyzed. Complete blood count was analyzed using the Roche SYSMEX analyzer (Roche Diagnostics, Basel, Switzerland). In addition, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), total bilirubin, hemoglobin, creatinine, uric acid, and urinalysis were examined using the Synchron LX20 system (Beckman Coulter Diagnostics, CA, USA).

Statistical Analysis

Statistical analysis was performed using the SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), quartile (25th, 50th, and 75th), and number and frequency. The Kolmogorov-Smirnov test was used to test normal distribution of continuous variables. The Kruskal-Wallis test was used to analyze significant differences between non-normally distributed variables. The *post-hoc* Dunn test was performed to identify groups with significant differences. The Fisher-Freeman-Halton exact test was used to examine distribution of categorical variables. The Spearman's correlation analysis was carried out to examine the relationship between DCN levels and other variables. A p value of < 0.05 was considered statistically significant.

RESULTS

A total of 88 participants including 50 patients with PE and 38 healthy controls were included in this study. Of the patients, 21 had EOPE and 29 had LOPE. Of the healthy controls, 12 were early-onset PE controls and 26 were late-onset PE controls. Demographic and clinical characteristics and biochemical analyses are shown in Table 1.

Although the mean body weight (p = 0.001), body mass index (p = 0.006), systolic (p = 0.001) and diastolic blood pressure (p = 0.001), ALT (p = 0.001), hemoglobin(p = 0.016), and creatinine (p = 0.001) levels did not significantly differ between the either control group, these levels were significantly lower in the control groups than EOPE and LOPE groups. The mean AST level was similar between the control groups and in the LOPE group, but was significantly lower than the EOPE group (p = 0.001). On the other hand, there was no significant difference in the platelet counts between the control groups; however, the mean platelet count was significantly higher than the EOPE and LOPE groups. In addition, the mean platelet count was significantly lower in the EOPE group than the LOPE group (p = 0.001)

Table 1. Demographic and clinical characteristics and biochemical analyses

			EOPE	LOPE	Late-onset PE controls	Early-onset PE controls	p
Age, [year]	N		21	29	26	12	0.082
	Mean		29.76	30.72	26.62	26.42	
	SD		7.293	6.403	6.682	6.735	
	Percentiles	25th	23.50	25.50	21.75	22.00	
		Median	29.00	32.00	25.00	23.50	
		75th	37.00	36.00	31.00	32.00	
Weight, [kg]	N		21	29	26	12	0.001
	Mean			90.48[a]	76.73[b]	70.58[b]	
	SD			20.373	10.452	11.889	
	Percentiles	25th	76.00	74.00	69.50	61.50	
		Median	80.00	90.00	79.00	68.00	
		75th	87.50	101.00	85.00	79.50	
Height, [cm]	N		21	29	26	12	0.302
	Mean			163.41	162.88	159.25	
	SD			5.172	6.755	6.930	
	Percentiles	25th	159.00	160.00	159.50	154.00	
		Median	162.00	165.00	164.00	160.00	
		75th	166.00	166.50	167.25	165.00	
BMI, [kg/m^2]	N		21	29	26	12	0.006
	Mean		31.8625[a]	33.9284[a]	28.9815[b]	27.8364[b]	
	SD		5.55135	7.76778	4.10810	4.43420	
	Percentiles	25th	29.1279	28.3595	26.7589	24.2936	
		Median	31.6337	34.8944	28.3356	26.1656	
		75th	34.4410	37.5954	32.0019	32.3027	
SBP, mmHg	N		21	29	26	12	0.001
	Mean		162.86[a]	157.59[a]	110.00[b]	110.00[b]	
	SD		18.205	19.208	10.583	8.528	
	Percentiles	25th	150.00	150.00	100.00	100.00	
		Median	160.00	150.00	110.00	110.00	
		75th	175.00	165.00	120.00	120.00	
DBP, mmHg	N		21	29	26	12	0.001
	Mean		104.76[a]	98.97[b]	65.77[c]	66.67[c]	
	SD		8.136	10.805	7.575	8.876	
	Percentiles	25th	100.00	90.00	60.00	60.00	
		Median	100.00	100.00	70.00	70.00	
		75th	110.00	100.00	70.00	70.00	
Gravida	N		21	29	26	12	0.876
	Mean		2.43	2.72	2.23	2.33	
	SD		1.720	1.771	0.863	1.073	
	Percentiles	25th	1.00	1.00	2.00	1.00	
		Median	2.00	2.00	2.00	3.00	
		75th	3.00	4.00	3.00	3.00	
Parity	N		21	29	26	11	0.788
	Mean		1.10	1.10	1.15	1.36	
	SD		1.221	1.263	0.881	1.206	
	Percentiles	25th	0.00	0.00	0.75	0.00	
		Median	1.00	1.00	1.00	2.00	
		75th	2.00	2.00	2.00	2.00	

→

Table 1. Demographic and clinical characteristics and biochemical analyses (continued)

			EOPE	LOPE	Late-onset PE controls	Early-onset PE controls	p
Abortus	N		21	29	26	12	0.057
	Mean		0.33	0.62	0.08	0	
	SD		0.796	1.115	.272	0	
	Percentiles	25th	0	0	0	0	
		Median	0	0	0	0	
		75th	0	1.00	0	0	
Live birth	N		21	29	26	12	0.635
	Mean		1.10	1.10	1.15	1.50	
	SD		1.221	1.263	0.881	1.243	
	Percentiles	25th	0	0	0.75	0	
		Median	1.00	1.00	1.00	2.00	
		75th	2.00	2.00	2.00	2.75	
PLT, [10^3/mL]	N		21	29	26	12	0.001
	Mean		109.52[a]	146.93[b]	264.73[c]	272.00[c]	
	SD		42.666	63.837	62.332	38.657	
	Percentiles	25th	83.50	98.50	197.00	248.25	
		Median	96.00	140.00	275.00	263.00	
		75th	148.00	181.00	313.00	282.50	
WBC, [10^3/mL]	N		21	29	25	12	0.021
	Mean		15.457[a]	14.345[a]	12.992[ab]	10.950[b]	
	SD		5.6085	4.0497	3.4938	1.5193	
	Percentiles	25th	10.800	11.200	10.350	9.525	
		Median	17.800	13.500	12.100	11.200	
		75th	19.650	17.750	16.350	11.600	
Hb, [g/dL]	N		21	29	26	12	0.016
	Mean		10.6000[a]	10.6586[a]	11.5769[b]	11.5250[b]	
	SD		1.44948	1.18609	1.18061	1.25200	
	Percentiles	25th	9.6000	9.8000	10.9000	10.4250	
		Median	10.9000	10.9000	11.8000	11.3000	
		75th	11.6000	11.5500	12.5000	12.6000	
AST, [IU/L]	N		21	29	26	12	0.001
	Mean		115.7619[a]	61.3448[b]	20.2308[b]	19.4167[b]	
	SD		66.05067	40.55972	8.18441	4.01040	
	Percentiles	25th	50.0000	27.5000	13.5000	16.2500	
		Median	121.0000	46.0000	18.5000	19.0000	
		75th	152.0000	93.5000	25.0000	22.0000	
ALT, [U/L]	N		21	29	26	12	0.001
	Mean		111.3810[a]	53.3207[b]	16.2692[c]	12.6667[c]	
	SD		76.59209	48.74625	9.15885	3.65148	
	Percentiles	25th	26.0000	21.0000	9.7500	10.2500	
		Median	117.0000	35.0000	13.5000	12.0000	
		75th	154.0000	70.0000	23.0000	15.7500	
Urea, [mg/dL]	N		21	29	26	12	0.001
	Mean		20.8095[a]	15.3310[b]	8.6231[c]	6.4333[d]	
	SD		6.87836	5.97764	2.37627	2.45872	
	Percentiles	25th	14.7000	10.7000	7.1750	4.6000	
		Median	21.7000	15.0000	8.4500	6.1000	
		75th	25.7000	18.3000	10.0500	8.0000	

Table 1. Demographic and clinical characteristics and biochemical analyses

			EOPE	LOPE	Late-onset PE controls	Early-onset PE controls	p
Creatinine, [mg/dL]	N		21	29	26	12	0.001
	Mean		1.0648[a]	.9500[a]	.6688[b]	.6558[b]	
	SD		.33898	.31988	.14605	.10757	
	Percentiles	25th	0.7450	0.7100	0.5950	0.6025	
		Median	1.1000	0.8300	0.6300	0.6750	
		75th	1.2650	1.2000	0.7000	0.7175	
Gestational week	N		21	29	26	12	0.001
	Mean		30.48[a]	35.90[b]	37.12[c]	37.42[c]	
	SD		2.462	1.566	1.532	2.065	
	Percentiles	25th	28.50	35.00	36.00	37.00	
		Median	32.00	36.00	37.00	38.00	
		75th	32.00	37.00	38.25	39.00	
Birth weight, [g]	N		20	29	26	12	0.001
	Mean		1239.25[a]	2572.45[b]	3044.23[c]	3003.33[c]	
	SD		475.448	722.840	581.914	622.405	
	Percentiles	25th	847.50	1965.00	2460.00	2912.50	
		Median	1215.00	2530.00	3160.00	3150.00	
		75th	1527.50	3275.00	3490.00	3350.00	
Decorin, [pg/mL]	N		21	29	26	12	0.040
	Mean		10.8524	11.0276	9.9750	14.4250	
	SD		4.34714	3.86577	4.56240	5.24632	
	Percentiles	25th	7.4000	8.4500	8.0000	10.8250	
		Median	10.2000	9.5000	10.1000	13.8000	
		75th	15.0000	13.8000	11.8750	19.5000	

EOPE — early-onset preeclampsia; LOPE— late-onset preeclampsia; PE— preeclampsia; SD— standard deviation; BMI— body mass index; SBP— systolic blood pressure; DBP— diastolic blood pressure; PLT— platelet; WBC— white blood cell; Hb— hemoglobin; AST— aspartate aminotransferase; ALT— alanine aminotransferase

The mean DCN level was statistically significantly higher in the early-onset PE controls than late-onset PE controls ($p = 0.040$). Although the mean DCN level was higher in the early-onset PE controls than the EOPE and LOPE groups, it did not reach statistical significance ($p = 0.119$ and $p = 0.117$, respectively). However, based on the p values of these variables, the difference between the groups may be of biological relevance, although not statistically significant.

DISCUSSION

Preeclampsia is one of the complications of pregnancy and is mainly classified into two types according to the time of occurrence: early-onset PE (< 34th week of pregnancy) and late-onset PE (≥ 34th week of pregnancy). 'Early-onset PE occurs in about 10% of all preeclamptic cases and has a complex pathophysiology, the main cause being abnormal placentation with maternal predictive factors. It seems, therefore, reasonable to gain a better understanding of the underlying angiogenic imbalance in early- and late-onset PE and to identify and treat candidate patients at the end of the first trimester, as the incidence of maternal vascular malperfusion and placental vascular lesions are higher in early-onset PE [12].

Failed trophoblast invasion has been proposed the main pathogenetic mechanism in PE. Previous studies have demonstrated that PE is a two-stage disorder: abnormal placentation with reduced placental perfusion in the first stage and maternal systemic pathophysiological changes in the second stage. However, the exact underlying mechanism of the lack of invasion of extravillous trophoblasts in PE remains to be elucidated [13].

Implantation and placentation are essential components of pregnancy which thoroughly rely upon fundamental biological processes invasive trophoblasts, growth factors, growth factor binding proteins, proinflammatory cytokines, proteoglycans, and including highly MMPs. The regulation of MMP activity is the mainstay of these critical processes. Dysregulation of these delicate processes may result in a broad range of pregnancy abnormalities such as PE, IUGR, preterm labor, and miscarriage [14].

In the early period of pregnancy, the fetoplacental development is mediated by a complex cascade system containing growth factors, cytokines, and transcription factors [15]. Decorin is a product of both fetal mesenchymal cells within the placenta and decidual cells in the endometrium. Currently, the role of DCN in stem cell regulation and in the underlying pathogenesis of PE and IUGR has not been fully elucidated. During a recent study, Siddiqui et al. [11] investigated the relation of DCN overexpression in the chorionic villi and/or basal decidua with PE. They reported that basal decidual cell-induced DCN overexpression was related to hypoinvasive phenotype with poor endovascular trophoblast cell differentiation in PE. In addition, the authors found no significant change in DCN levels depending on gestational age during the second trimester in PE patients, although there was an inverse association between the plasma DCN levels and body mass index or body weight. Based on these findings, the authors concluded that increased plasma DCN level might be a predictor of PE before the onset of clinical signs. In another study, Siddiqui et al. [11] found that DCN messenger ribonucleic acid (mRNA) expression at the cellular level showed significantly increased expression in basal plate decidual cells within the placentas from PE (23 to 40 weeks of gestation) patients than controls at all gestational age. Similarly, Nandi et al. [16] found a significant difference in the DCN staining of placental tissues between the PE and control groups. However, at the tissue level, DCN mRNA expression in chorionic villi was similar. In another study, Nandi et al. [17] reported that elevated DCN levels in the maternal blood could be a predictive biomarker for PE.

For a healthy pregnancy, the maternal blood vessel remodeling is driven by the extravillous cytotrophoblasts rather than maternal endothelium. Reduced interstitial invasion and endovascular cytotrophoblasts are associated with IUGR. In their study, Weber et al. [18] described a variety of trophoblast stem cell and pluripotency marker staining patterns based on gestational age and placenta-associated pregnancy complications. The authors concluded that PE, IUGR, and combined PE + IUGR are separate entities based on the differential expression patterns within the placentas complicated with placenta-associated pregnancy complications. We believe that reduced DCN may lead to uncontrolled proliferation and inadequate differentiation of cytotrophoblasts, thereby, resulting in impaired ion-nutrition exchange and decreased hormonal synthesis. More importantly, differentiation of cytotrophoblasts is the cornerstone of healthy placental development in human [15].

In a study, Tan et al. [19] found that abnormal differentiation of trophoblast stem cells was likely to be associated with IUGR. Since certain types of IUGR and PE share a common placental pathology, the authors concluded that overexpression of DCN in the placenta/decidua led to poor trophoblast differentiation in an IUGR subgroup.

Caglar et al. [20] compared DCN levels between pregnancies complicated by idiopathic IUGR and uncomplicated pregnancies and examined the possible relationship between DCN levels and clinical parameters. They found significantly higher maternal serum DCN levels in complicated pregnancies by IUGR and an about 8-times higher risk of high maternal serum DCN levels in complicated pregnancies.

In a study, Murthi et al. [21] collected first trimester tissues via chorionic villus sampling and investigated the temporal relationship between subsequent development of small for gestational age (SGA) and altered DCN expression. The DCN mRNA were determined via using real-time polymerase chain reaction (PCR) and DCN proteins via immunoblotting. The authors showed that DCN mRNA and protein significantly decreased in the placentas from the first-trimester SGA-pregnancies. The aforementioned study is to the first to report a temporal relationship between subsequent development of SGA and altered placental DCN expression in the literature. Similarly, in a previous study of the same researchers, the DCN expression significantly reduced in IUGR compared to gestation-matched controls [22].

The mean DCN level was statistically significantly higher in the early-onset PE controls than late-onset PE controls ($p = 0.040$). Although the mean DCN level was higher in the early-onset PE controls than EOPE and LOPE groups, it did not reach statistical significance ($p = 0.119$ and $p = 0.117$, respectively). However, based on the p values of these variables, we suggest that the difference between the groups may be of biological relevance, although not statistically significant.

Nonetheless, there are some limitations to this study. First, due to the prospective design of the study and termination of the data cut-off date, the number of patients in the control group cannot be increased. Second, we were unable to perform immunohistochemical staining for DCN expression of placental tissues. Despite the lack of any statistically significant difference in the maternal serum DCN samples between the early-onset and late-onset PE groups, no data are available whether there is a significant difference in the DCN level of placental tissues due to the lack of immunohistochemical stating.

In conclusion, although DCN has been thought to be involved in the pathophysiology of PE, our study results show that DCN is not a useful predictive marker of EOPE and LOPE. However, these results might have been yielded due to small sample size of our study. Therefore, further large-scale studies are needed to draw a definitive conclusion. Furthermore, it would be more helpful to gain an insight into the role of DCN in the pathophysiology of PE by measuring the DCN mRNA expression in the basal plate decidual cells within the placenta with immunohistochemical staining.

Conflict of interest

The authors declare no conflict of interest. The authors are solely responsible for the content and writing of the paper.

Financial disclosure

The authors receive no financial support for the study conduct.

Ethical disclosure

A written informed consent was obtained from each participant. The study protocol was approved by the Ethics Committee of Bursa YüksekİhtisasTraining and Research Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Confidentiality of data

All authors of this manuscript declare that they have followed the protocols of publication of patient's data. All caregivers of the participants were informed in detail about the research and signed patient informed consent.

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