ORIGINAL RESEARCH

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The Potential of SCUBE-1 Levels as an Indicator of Impaired Placental Function in Preeclampsia: A Randomized Clinical Trial

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ABSTRACT Objective: The aim of the study is to compare the plasma levels of SCUBE-1, a marker of vascular injury and endothelial dysfunction, between preeclamptic and normotensive pregnant women. **Material and Methods:** The current study was carried out at Health Sciences University Adana City Training and Research Hospital, implementing a prospective research design. The study included 46 pregnancies diagnosed with preeclampsia and an equal number of pregnancies with normal blood pressure, serving as control subjects. Hemoglobin, white blood cell, platelet, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, spot urine protein creatinine ratio, and SCUBE-1 values were analyzed between preeclampsia and control groups. **Results:** There were no statistically significant differences observed in age, gravidity, parity, or body mass index as demographic features among the groups. The mean SCUBE-1 values of preeclampsia and control group were 137.65±95.97 ng/mL and 69.45±44.35 ng/mL, respectively. A significant increase in the concentrations of SCUBE-1 levels was observed in pregnancies that presented with preeclampsia ($p<0.001$). There was a statistically significant difference between pregnant women with and without preeclampsia in terms of creatinine and blood urea nitrogen values of laboratory values ($p<0.001$). **Conclusion:** The potential of SCUBE-1 as a prognostic indicator for vascular damage in pregnancy is worth considering. Our research is the initial investigation to demonstrate elevated levels of SCUBE-1 in preeclampsia, indicating impaired function of the endothelial cells in the placenta.

Keywords: SCUBE-1; preeclampsia; endothelial dysfunction

Pre-eclampsia is a pregnancy-specific syndrome characterised by the onset of hypertension and proteinuria or hypertension without proteinuria and end-organ dysfunction after 20 weeks' gestation. This disorder often presents itself at the completion of 20 weeks of gestation or during the postpartum period, and it has an impact on various physiological systems inside the body.[1] Preeclampsia occurs at a rate of 2-8% and may cause high-risk fetal and maternal morbidity and mortality.[2]

The etiology of preeclampsia is not clearly defined; however, the resolution of symptoms following the delivery of the fetus and placenta suggests that the placenta may be a key factor in the disease's development. The most widely accepted theory posits that preeclampsia occurs in two phases.[3] The first phase involves inadequate remodeling of maternal spiral arteries, leading to reduced blood flow to the placenta.[4] In a normal pregnancy, cytotrophoblasts invade deep into the myometrium and remodel maternal spiral arteries into large, low-resistance vessels, enhancing blood flow to the fetoplacental unit. In contrast, shallow trophoblast invasion in preeclampsia results in increased resistance in uterine arteries and significantly diminished placental perfusion.[5]

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The second phase of preeclampsia is triggered by the ischemic placenta, which releases bioactive factors into the maternal circulation. These factors include inflammatory mediators, anti-angiogenic substances such as soluble Fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin, reactive oxygen species, and agonistic autoantibodies to the Angiotensin II Type 1 receptor (AT1-AA).[6,7] The release of these factors induces systemic inflammatory activation and endothelial dysfunction, often accompanied by renal impairment, which contributes to the pathophysiology of the disease.[8] Despite this understanding, many questions remain. The progression between the two phases of preeclampsia is still not fully understood, as decreased placental perfusion also occurs in other pregnancy disorders without leading to systemic endothelial dysfunction.[9] The cell surface protein signal peptide-CUB-EGF domain-containing protein (SCUBE) has been identified as one of the vascular biology markers recently investigated.[10] SCUBE-1 and 2 are cell surface proteins belonging to the SCUBE family secreted from platelet (Plt) and endothelial cells.[11] SCUBE-3 is synthesized during embryogenesis.[11] The literature states that SCUBE-1 is essential in determining endothelial dysfunction, vascular damage, and hypoxia.[12] The defects during spiral artery remodeling and trophoblast invasion have been described in preeclampsia.[13] They result in abnormal placentation and placental ischemia. Factors released from the placenta as a result of abnormal placentation and ischemia are thought to cause systemic endothelial damage and cause preeclampsia.

Our aim is to compare SCUBE-1 between pregnant women with preeclampsia and pregnant with normal blood pressure. In the literature, no previous research investigates the SCUBE-1 levels between patients with and without preeclampsia.

MATERIAL AND METHODS

The present study was conducted at Health Sciences University Adana City Training and Research Hospital in Adana, Türkiye. The study was approved by the ethics committee of the University of Health Science Adana City Training and Research Hospital (date: May 6, 2021, no: 1405/2021). Informed consent was obtained from all individual participants included in the study. In a study examining the success of SCUBE-1 level in distinguishing preeclampsia groups, the area under the curve (AUC) was taken as 0.6658, and it was planned to study with 46 people in each group and 92 people in total, with 80% power and 5% Type 1 error.[14] The study was conducted in accordance with the principles of the Declaration of Helsinki. The study had a total of 49 pregnant women diagnosed with preeclampsia and 47 pregnant women with normal blood pressure during the third trimester. The age range of the participants was between 18 and 40 years old. The data collection period for this study spanned from May 2021 to October 2021. A total of 46 pregnant women diagnosed with preeclampsia and an equal number of 46 pregnant women with normal blood pressure successfully participated in the study (Figure 1). All patients were singleton and were not in labor at the time of admission to our hospital. Pregnant women who smoke, have comorbidities, have multiple pregnancies, and have chronic hypertension were not enrolled in the study. Participants in the patient and control groups did not use any antihypertensive, antiaggregant, or anticoagulant medications at the time of admission to the hospital.

Demographic data of all patients were reviewed, including age, body mass index (BMI), gravida, parity, abortion, systolic and diastolic blood pressure values, gestational age, and intensive care needs. Hemoglobin, white blood cell, Plt, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen (BUN), creatinine (Cr), spot urine protein Cr ratio, and SCUBE-1 as laboratory data were recorded.

The guideline, written by the European Society of Hypertension and the European Society of Cardiology in 2013, was used as a resource to accurately assess blood pressure.[15] Optimal conditions were provided for blood pressure measurement. The patients were diagnosed with preeclampsia in accordance with the guideline published by ACOG (The American College of Obstetricians and Gynecologists) in 2019.[16] The blood samples were taken to the biochemistry laboratory within 15 minutes and centrifuged at 2,000 rpm for 15 minutes in centrifuge devices. The serum samples were stored at -80 °C until they were ready for analysis. The sandwich En-

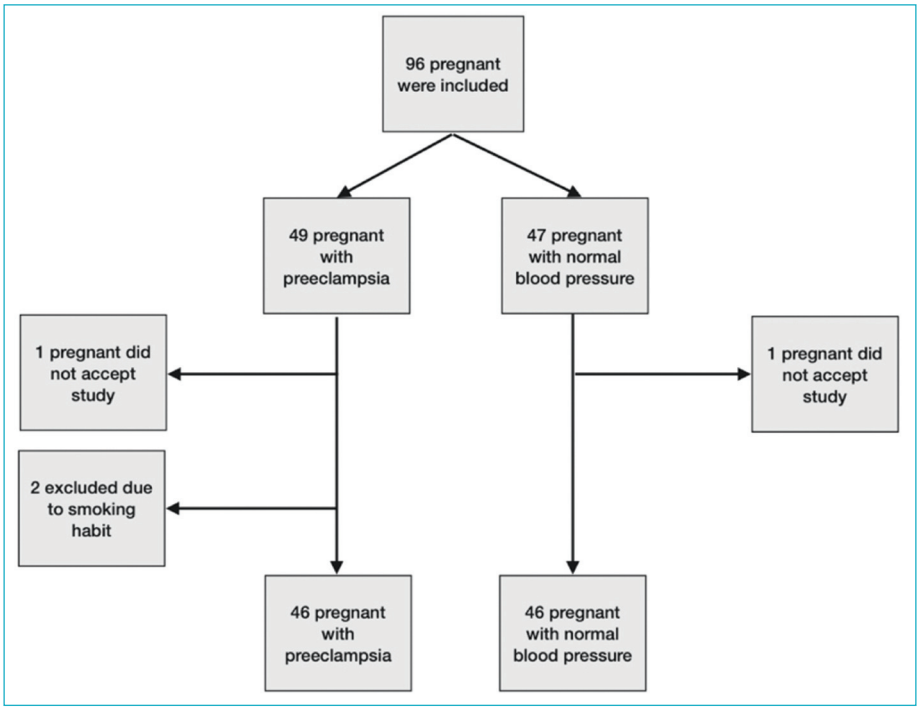

FIGURE 1: Study design.

zyme-Linked Immunosorbent Assay (ELISA kit E3142Hu®, Bioassay Technology, China) was employed to determine the levels of serum SCUBE-1. The lowest concentration the kits could measure was 4 ng/mL, within the reference range of 6 pg/mL-4,500 pg/mL.

The statistical analyses were calculated using SPSS 25 (IBM, USA). Descriptive statistics were performed for all variables. The normality of data was investigated by using the Shapiro-Wilk test, and values were expressed as mean±standard deviation. Parametric comparisons were made using a student t-test for continuous variables. Receiving operating characteristic curve analysis (ROC curve) evaluated its success in distinguishing the conditions in the patient and control groups. AUC of the parameters, statistical significance level, cut-off value, sensitivity and selectivity values were calculated. A p value of <0.05 was accepted as statistical significance level.

RESULTS

Forty-six pregnant women with preeclampsia and 46 with normal blood pressure were enrolled in the study in the third trimester. The patients' sociodemographic and obstetric features are illustrated in Table 1. The mean age of patients with preeclampsia was 28.86±7.08 years, and the mean age of patients with normal blood pressure was 26.23±5.4 years. Patients with preeclampsia had a mean BMI of 32.19± 5.25 kg/m^2, and those with normal blood pressure had a mean BMI of 27.42±3.53 kg/m^2, respectively. Patients with preeclampsia had a mean gestational age of 35.39±3.23 weeks, and those with normal blood pressure had a mean gestational age of 35.26±2.67 weeks, respectively. The mean gravida of patients with preeclampsia and normal blood pressure were 2.65±1.55 and 2.58±1.37, respectively. The mean parity of patients with preeclampsia and normal blood pressure were 1.39±1.25 and 1.47±1.31, respectively. The mean systolic blood pressure of patients with preeclampsia was 143.23±22.8 mmHg, and the mean systolic blood pressure of patients with normal blood pressure was 114.63±7.52 mmHg. The mean diastolic blood pressure of patients with preeclampsia was 86.65±14.43 mmHg, and the mean diastolic blood pressure of patients with normal blood pressure was 73.32±6.18 mmHg. When demographic data such as age, BMI, gestational age, gravida, and parity were analyzed, no statistically significant dif-

TABLE 1: The sociodemographic and obstetric characteristics of the study participants.

	With preeclampsia (n=46) (X̄±SD)	With normal blood pressure (n=46) (X̄±SD)	p value
Maternal age (years)	28.86±7.08	26.23±5.4	0.108
Body mass index (kg/m^2)	32.19±5.25	27.42±3.53	0.099
Gestational age (weeks)	35.39±3.23	35.26±2.67	0.534
Gravida	2.65±1.55	2.58±1.37	0.987
Parity	1.39±1.25	1.47±1.31	0.700
Systolic blood pressure	143.23±22.8	114.63±7.52	<0.001
Diastolic blood pressure (mmHg)	86.65±14.43	73.32±6.18	<0.001

SD: Standard deviation; n: Number of patients in the group.

TABLE 2: Laboratory measurements of the study participants.

	With preeclampsia (n=46) (X̄±SD)	With normal blood pressure (n=46) (X̄±SD)	p value
White blood cell (K/uL)	11.69±3.43	10.41±2.72	0.103
Platelet (K/uL)	228.3±90.02	228.67±72.88	0.722
Blood uric acid (mg/dL)	21.32±11.36	14.47±4.69	<0.001
Creatinine (mg/dL)	0.52±0.14	0.42±0.09	<0.001
SCUBE-1 (ng/mL)	137.65±95.97	69.45±44.35	<0.001

SD: Standard deviation; n: Number of patients in the group; K/uL: Thousands per cubic milliliter of blood; mg/dL: Milligrams per decilitre; ng/dL: Nanograms per deciliter.

TABLE 3: Cut-off point analysis of SCUBE-1 values to determine preeclampsia.

	Cut point	AUC	p value	Sensivity (%)	95% CI	Specifity (%)	95% CI
SCUBE-1	>95.92	0.716 (0.61-0.81)	<0.001	50.00	34.9-65.1	91.30	79.2-97.6

AUC: Area under the curve; CI: Confidence interval.

ference was found. In contrast, systolic and diastolic blood pressure values showed statistically significant differences.

The laboratory measurements of patients are shown in Table 2. The mean SCUBE-1 values of preeclampsia and control group were 137.65±95.97 ng/mL and 69.45±44.35 ng/mL, respectively. We found a statistically significant difference with regard the SCUBE-1 values (p<0.001). ROC curve was constructed to determine SCUBE-1. AUC was 0.716 (0.61-0.81) (p<0.001). The SCUBE-1 cut-off value of 95.92 ng/mL was used to diagnose preeclampsia with 50% sensitivity and 91.3% specificity (Table 3, Figure 2). We followed up 8 of 46 patients with preeclampsia in the intensive care unit because of severe preeclampsia, and 7 of them developed HELLP syndrome. SCUBE-1 values of 6 of these 7 patients with HELLP syndrome were higher than the 95.92 ng/mL cut-off value, which we found in the ROC analysis.

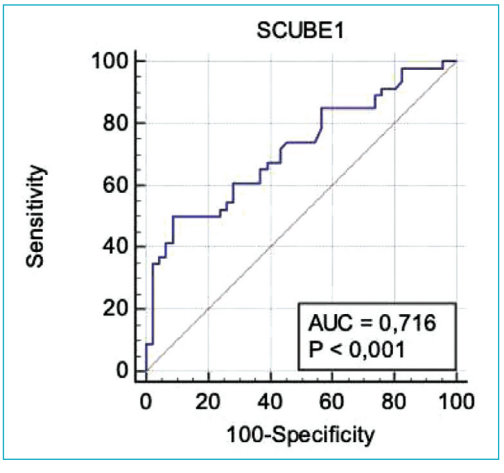

FIGURE 2: ROC curve for SCUBE-1 levels in preeclampsia.

We found statistically significant differences between pregnant women with and without preeclampsia ($p<0.001$).

DISCUSSION

In our study, SCUBE-1 levels were found to be statistically significantly higher in the preeclampsia group. SCUBE-1 had high performance in diagnosing preeclampsia only in terms of Cr and BUN values of laboratory values (AUC=0.716).

SCUBE-1 is a recently discovered cell surface protein identified during embryonic development's initial stages.[17] In the literature, it has been reported that SCUBE-1 levels increase during oxidative stress such as ischemic events, mesenteric ischemia, testicular torsion, acute coronary syndrome, pulmonary embolism, and cancer diseases.[12,18-21] In addition, renal ischemia-reperfusion injury showed that SCUBE1 is a stress-responsive gene in endothelial cells of the glomerulus and the peritubular capillary network.[22] Yang et al. identified the selective expression of SCUBE1 in endothelium and found that it has a critical relationship with vascular biology and possible roles in development of thrombosis, and inflammatory response.[23] In vascular endothelial cells, SCUBE1 is secreted glycoproteins that form stable oligomers on the cell surface. Upon endothelial activation, such as by interleukin-1β or tumor necrosis factor-α, the expression of both proteins is rapidly downregulated. This finding suggests that SCUBE1 is essential for vascular biology and angiogenesis, and it plays a role in the regulation of thrombosis.[23] This observation suggests a potential role for SCUBE proteins in inflammation and hypoxia-related conditions.[24] In response to pro-inflammatory activity, SCUBE1 gene expression was significantly down-regulated following cytokine treatment. The inflammatory response was transient, and the regulation of SCUBE1 levels was dynamically managed, indicating a recovery of SCUBE1 expression after the inflammatory activity stopped. Furthermore, Dai et al. demonstrated that elevated SCUBE1 levels in hypoxia were associated with Plt aggregation and were a response to inflammatory activity.[12]

The etiology of preeclampsia remains uncertain. Nevertheless, several studies have documented that anomalies in the angiogenesis process of placental vessels during the initial stages of pregnancy can lead to a state of relative placental hypoxia and ischemia. Consequently, antiangiogenic factors are released into the maternal bloodstream, resulting in an impact on the maternal systemic endothelial function.[25,26] The endothelium plays a crucial role in regulating hemostasis, including several processes such as coagulation, fibrinolysis, and Plt adhesion and aggregation.[27] Endothelial dysfunction causes inflammation and thrombosis in preeclampsia.[28]

According to the literature, SCUBE-1 demonstrates expression in endothelium and Plts alongside its expression during early embryogenesis.[23] Studies have been determined the role of SCUBE family in the developmental angiogenesis.[24,29,30] Tsao et al. found that zebrafish SCUBE1 has a stimulating role in primitive hematopoiesis by acting as a BMP co-receptor to increase its signal activity during early zebrafish embryonic development and that inhibition of SCUBE1 expression resulted in a decrease in expression of genes related with primitive hematopoietic progenitors and primitive erythropoiesis.[31] Furthermore, a study of Tu et al. revealed that inhibition of SCUBE1 gene was associated with early postnatal death due to craniofacial defects, exencephaly, loss of cranial vault, and midbrain neural overgrowth.[10] Another study, by Tu et al. showed that SCUBE2, which is another member of SCUBE gene family and expressed in vascular endothelium, was an important hedgehog signaling mediator during embryogenesis. All these data suggest that an impaired angiogenesis may be related to abnormal levels of SCUBE during the fetal life which may cause to the preeclampsia. Also, SCUBE is highly expressed in most vascularized tissues and can be upregulated under angiogenesis related conditions in vivo, such as inflammation and hypoxia.[22,23] Although exact etiology of preeclampsia is uncertain, we know that preeclampsia is a reason for low oxygenated environment which may arise due to high SCUBE gene expressions. Furthermore, it is implicated in the processes of Plt agglutination and activation.[32] The accumulation of SCUBE-1 in atherosclerotic thrombus is believed to be a consequence of Plt agglutination and adhesion.[33] Hyper-

tension is the most significant risk factor that causes the emergence of atherothrombotic consequences and endothelial dysfunction. The process of Plt activation can be commenced by an injury or dysfunction of the endothelial cells.[34] The study conducted by Özkan et al. and Guzel et al. revealed an observed elevation in SCUBE-1 levels among individuals diagnosed with essential hypertension.[35]

No previous study in the literature shows that SCUBE-1 levels are high in preeclampsia. The utilization of SCUBE-1 as a laboratory marker holds promise in the early identification of compromised placenta and placental endothelial dysfunction in cases of preeclampsia.

Our study had several limitations. Firstly, we obtained only one sample during the third trimester from the patients. Therefore, the alterations of SCUBE-1 levels during pregnancy were not determined. Secondly, the long-term follow-up for cardiovascular diseases and vascular complications were not available in the study. Longitudinal follow-up in a larger population with consecutive detection of SCUBE-1 levels during the trimesters and postpartum period could be beneficial for the correlation of SCUBE-1 levels with pregnancy.

CONCLUSION

The etiopathogenesis of preeclampsia has yet to be clearly resolved in the literature. Studies on early diagnosis and treatment of preeclampsia continue. In this study, we aimed to find the relationship between preeclampsia and serum SCUBE-1 level. Association between impaired angiogenesis and preeclampsia is a well known entity. In this context, as a result of our study, arise in SCUBE-1 levels may help the clinicians for the early diagnosis of preeclampsia. But yet, it is crucial to conduct further investigations, comprising more extensive patient cohorts, to confirm the correlation between SCUBE-1 and preeclampsia and determine its significance in recognizing the severity and progression of this condition.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Neşe Yücel, Halil İbrahim Altıncı;* ***Design:*** *Halil İbrahim Altıncı, Fikriye Işıl Adıgüzel;* ***Control/Supervision:*** *Halil İbrahim Altıncı, Sadık Kükrer;* ***Data Collection and/or Processing:*** *Halil İbrahim Altıncı;* ***Analysis and/or Interpretation:*** *Fikriye Işıl Adıgüzel, Halil İbrahim Altıncı;* ***Literature Review:*** *Neşe Yücel, Halil İbrahim Altıncı;* ***Writing the Article:*** *Halil İbrahim Altıncı, Sadık Kükrer;* ***Critical Review:*** *Halil İbrahim Altıncı, Fikriye Işıl Adıgüzel;* ***References and Fundings:*** *Halil İbrahim Altıncı;* ***Materials:*** *Halil İbrahim Altıncı, Sadık Kükrer.*

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