

# The potential of SCUBE-1 levels as a biomarker for placental malfunction in preeclampsia

**Halil İbrahim ALTINCI**

University of Health Science Adana City Training and Research Hospital

**Neşe YÜCEL**

University of Health Science Adana City Training and Research Hospital

**Fikriye Işıl ADIGÜZEL**

[aze\\_isil@hotmail.com](mailto:aze_isil@hotmail.com)

University of Health Science Adana City Training and Research Hospital

**Sadık KÜKRER**

University of Health Science Adana City Training and Research Hospital

---

## Research Article

**Keywords:** SCUBE-1, preeclampsia, placental malfunction

**Posted Date:** February 19th, 2024

**DOI:** <https://doi.org/10.21203/rs.3.rs-3958958/v1>

**License:**   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

**Additional Declarations:** No competing interests reported.

---

# Abstract

## Purpose

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.

## 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.

## Results

There were no statistically significant differences observed in age, gravidity, parity, or BMI as demographic features among the groups. A significant increase in the concentrations of SCUBE-1 levels was observed in pregnancies that presented with preeclampsia ( $p < 0.001$ ).

## Conclusions

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.

## Introduction

Preeclampsia is a medical condition characterized by the occurrence of high blood pressure and the presence of protein in the urine, or alternatively, high blood pressure accompanied by notable impairment of organ function, regardless of the presence of protein in the urine. 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 pathogenesis involves both abnormal placentation and maternal systemic vascular dysfunction (3). Approximately 90% of patients occur in the late preterm, term, or postpartum period and have good maternal, fetal, and neonatal outcomes, but may also result in severe maternal or perinatal morbidity or mortality. 10% of patients have an early onset and are associated with higher risks of severe perinatal morbidity or mortality (4, 5). Although the symptoms of preeclampsia tend to improve in the postpartum period, the risk of cardiovascular-related morbidity and mortality increases in these patients.

The cell surface protein signal peptide-CUB-EGF domain-containing protein (SCUBE) has been identified as one of the vascular biology markers recently investigated (6). SCUBE-1 and 2 are cell surface proteins belonging to the SCUBE family secreted from platelet and endothelial cells (7). SCUBE-3 is synthesized during embryogenesis (7). The literature states that SCUBE-1 is essential in determining endothelial dysfunction, vascular damage, and hypoxia (8). The defects during spiral artery remodeling and trophoblast invasion have been described in preeclampsia (9). 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.

## Materials and Methods

The present study was conducted at Health Sciences University Adana City Training and Research Hospital in Adana, Turkey. 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. 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. The ethics committee of the University of Health Science Adana City Training and Research Hospital approved this study (1405/2021).

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

The guideline, written by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) in 2013 (10), was used as a resource to accurately assess blood pressure. Optimal conditions were provided for blood pressure measurement. The patients were diagnosed with Preeclampsia in accordance with the guideline published by ACOG in 2019 (11). The blood samples were taken to the biochemistry laboratory within 15 minutes and centrifuged at 2000 rpm for 15 minutes in centrifuge devices. The serum samples were stored at -80°C until they were ready for analysis. The sandwich Enzyme-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 – 4500 pg/ml.

The statistical analyses were calculated using SPSS 25. Descriptive statistics were performed for all variables. Because the data were not normally distributed, the median was reported as [Q1-Q3]. We used the Mann–Whitney U-test for the non-normally distributed data. Receiving operating characteristic curve analysis (ROC Curve) evaluated its success in distinguishing the conditions in the patient and control groups. Areas under the curve (AUC) of the parameters, statistical significance level, cut-off value, sensitivity and selectivity values were calculated. 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 to the study in the third trimester. The patients' sociodemographic and obstetric features are illustrated in Table 1. The median age [25%-75%] of patients with preeclampsia was 28 [22,75 – 35,25] years, and the median age [25%-75%] of patients with normal blood pressure was 26 [22–30] years. Patients with preeclampsia had a median [25%-75%] body mass index (BMI) of 30,26 [29,67 – 32,11] kg/m<sup>2</sup>, and those with normal blood pressure had a median [25%-75%] BMI of 28,67 [28,46 – 30,99] kg/m<sup>2</sup> respectively. Patients with preeclampsia had a median [25%-75%] gestational age of 36 [33,75 – 37,25] weeks, and those with normal blood pressure had a median [25%-75%] gestational age of 35 [33–38] weeks respectively. The median [25%-75%] gravida of patients with preeclampsia and normal blood pressure were 2 [1–4] and 3 [1–3,25], respectively. The median [25%-75%] parity of patients with preeclampsia and normal blood pressure were 1 [0–2] and 2 [0–2] respectively. The median [25%-75%] systolic blood pressure of patients with preeclampsia was 145 [128–158] mmHg, and the median [25%-75%] systolic blood pressure of patients with normal blood pressure was 115,50 [110–120] mmHg. The median [25%-75%] diastolic blood pressure of patients with preeclampsia was 88 [80–95,75] mmHg, and the median [25%-75%] diastolic blood pressure of patients with normal blood pressure was 71,50 [70–80] mmHg. When demographic data such as age, BMI, gestational age, gravida and parity were analyzed, no statistically significant difference 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 median [25%-75%] SCUBE-1 values of preeclampsia and control group were 89,88 [61,19–223,59] ng/ml and 62,55 [55,79–81,52] 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) (Fig. 1). We found only in terms of Cr and BUN values of laboratory values statistically significant differences between pregnant women with and without preeclampsia ( $p < 0.001$ ).

## Discussion

In our study, plasma SCUBE-1 levels were compared between pregnant women with a diagnosis of preeclampsia and normotensive pregnant women. As a result of our study, SCUBE-1 levels were found to

be statistically significantly higher in the preeclampsia group. SCUBE-1 had high performance in diagnosing preeclampsia (AUC = 0.716). 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.

SCUBE-1 is a recently discovered cell surface protein identified during embryonic development's initial stages. (12, 13). SCUBE-1 is a protein from the SCUBE protein family that is increased in inflammatory processes and hypoxia-related conditions (14). In the literature, it has been reported that SCUBE-1 levels increase during oxidative stress such as ischemic events, mesenteric ischemia (15), testicular torsion (16), acute coronary syndrome (8), pulmonary embolism (17), cancer diseases (18).

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. (19, 20, 21). The endothelium plays a crucial role in regulating hemostasis, including several processes such as coagulation, fibrinolysis, and platelet adhesion and aggregation. (22). Endometrial dysfunction causes inflammation and thrombosis in preeclampsia (23).

According to the literature, SCUBE-1 demonstrates expression in endothelium and platelets alongside its expression during early embryogenesis (24). Furthermore, it is implicated in the processes of platelet agglutination and activation (25). The accumulation of SCUBE-1 in atherosclerotic thrombus is believed to be a consequence of platelet agglutination and adhesion (26). Hypertension is the most significant risk factor that causes the emergence of atherothrombotic consequences and endothelial dysfunction. The process of platelet activation can be commenced by an injury or dysfunction of the endothelial cells. (27). The study conducted by Özkan et al. and Güzel et al. revealed an observed elevation in SCUBE-1 levels among individuals diagnosed with essential hypertension (28, 29).

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.

In conclusion, preeclampsia is a prevalent condition that significantly contributes to fetal and maternal mortality and morbidity throughout the antenatal period. 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.

We found a statistically significant high in SCUBE-1 levels in the preeclampsia group ( $p < 0.001$ ). It was found that SCUBE-1 may be valuable in the diagnosis and prognosis of preeclampsia. The existing scientific literature does not contain any published studies investigating the association between preeclampsia and SCUBE-1. Therefore, 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.

## Declarations

### Acknowledgements

Not applicable.

### Author contribution

HIA: Project development, Data collection and management, Data analysis, Manuscript writing. FIA: Project development, Data analysis, Manuscript editing. SK: Project development, Data analysis, NY: Project development, Data management, Data analysis, Manuscript editing, Supervision.

### Funding

No financial support was received for this study.

### Availability of data and materials

Derived data supporting the findings of this study are available from the corresponding author.

### Ethics approval and consent to participate

Study was approved of the ethics committee of the University of Health Science Adana City Training and Research Hospital (No:1405/2021).

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

## References

1. Chaiworapongsa T, Chaemsaihong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. *Nat Rev Nephrol.* 2014;10(8):466–80.
2. Ives CW, Sinkey R, Rajapreyar I, Tita ATN, Oparil S. Preeclampsia-Pathophysiology and Clinical Presentations: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020;76(14):1690–702.
3. Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester

- screening and prevention. *Int J Gynaecol Obstet.* 2019;145 Suppl 1(Suppl 1):1–33.
4. Yancey LM, Withers E, Bakes K, Abbott J. Postpartum preeclampsia: emergency department presentation and management. *J Emerg Med.* 2011;40(4):380–4.
  5. Cunningham FG, Lindheimer MD. Hypertension in pregnancy. *N Engl J Med.* 1992;326(14):927–32.
  6. Tu CF, Yan YT, Wu SY, Djoko B, Tsai MT, Cheng CJ, et al. Domain and functional analysis of a novel platelet-endothelial cell surface protein, SCUBE1. *J Biol Chem.* 2008;283(18):12478–88.
  7. Xavier GM, Economou A, Senna Guimaraes AL, Sharpe PT, Cobourne MT. Characterization of a mouse Scube3 reporter line. *Genesis.* 2010;48(12):684–92.
  8. Dai DF, Thajeb P, Tu CF, Chiang FT, Chen CH, Yang RB, et al. Plasma concentration of SCUBE1, a novel platelet protein, is elevated in patients with acute coronary syndrome and ischemic stroke. *J Am Coll Cardiol.* 2008;51(22):2173–80.
  9. Kaufmann P, Black S, Huppertz B. Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. *Biol Reprod.* 2003;69(1):1–7.
  10. Bakris G, Ali W, Parati G. ACC/AHA Versus ESC/ESH on Hypertension Guidelines: JACC Guideline Comparison. *J Am Coll Cardiol.* 2019;73(23):3018–26.
  11. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. *Obstet Gynecol.* 2019;133(1):1.
  12. Haworth K, Smith F, Zoupa M, Seppala M, Sharpe PT, Cobourne MT. Expression of the Scube3 epidermal growth factor-related gene during early embryonic development in the mouse. *Gene Expr Patterns.* 2007;7(5):630–4.
  13. Wu BT, Su YH, Tsai MT, Wasserman SM, Topper JN, Yang RB. A novel secreted, cell-surface glycoprotein containing multiple epidermal growth factor-like repeats and one CUB domain is highly expressed in primary osteoblasts and bones. *J Biol Chem.* 2004;279(36):37485–90.
  14. Yang M, Guo M, Hu Y, Jiang Y. Scube regulates synovial angiogenesis-related signaling. *Med Hypotheses.* 2013;81(5):948–53.
  15. Akoz A, Turkdogan KA, Kahraman Cetin N, Kum S, Duman A, Ture M, et al. Predicting critical duration and reversibility of damage in acute mesenteric ischemia: An experimental study. *Ulus Travma Acil Cerrahi Derg.* 2018;24(6):507–13.
  16. Turedi S, Tatli O, Alver A, Karaguzel E, Karaca Y, Turkmen S, et al. The Diagnostic Value of Plasma SCUBE1, a Novel Biomarker of Platelet Activation, in Testicular Torsion: A Randomized, Controlled, Experimental Study. *Urology.* 2015;86(3):516–20.
  17. Xiao L, Wang M, Yang S, Li S, Huang Q, Xu L, et al. The diagnostic potential of plasma SCUBE-1 concentration for pulmonary embolism: A pilot study. *Clin Respir J.* 2023;17(4):263–9.
  18. Katoh Y, Katoh M. Hedgehog signaling pathway and gastric cancer. *Cancer Biol Ther.* 2005;4(10):1050–4.
  19. Gyselaers W. Preeclampsia Is a Syndrome with a Cascade of Pathophysiologic Events. *J Clin Med.* 2020;9(7).

20. Romero R, Chaiworapongsa T. Preeclampsia: a link between trophoblast dysregulation and an antiangiogenic state. *J Clin Invest*. 2013;123(7):2775–7.
21. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. *Science*. 2005;308(5728):1592–4.
22. Bayoglu Tekin Y, Baki Erin K, Yilmaz A. Evaluation of SCUBE-1 levels as a placental dysfunction marker at gestational diabetes mellitus. *Gynecol Endocrinol*. 2020;36(5):417–20.
23. Erez O, Romero R, Jung E, Chaemsaitong P, Bosco M, Suksai M, et al. Preeclampsia and eclampsia: the conceptual evolution of a syndrome. *Am J Obstet Gynecol*. 2022;226(2S):S786-S803.
24. Yang RB, Ng CK, Wasserman SM, Colman SD, Shenoy S, Mehraban F, et al. Identification of a novel family of cell-surface proteins expressed in human vascular endothelium. *J Biol Chem*. 2002;277(48):46364–73.
25. Lindemann S, Gawaz M. SCUBE1—a new scoop in vascular biology? *Cardiovasc Res*. 2006;71(3):414–5.
26. Tu CF, Su YH, Huang YN, Tsai MT, Li LT, Chen YL, et al. Localization and characterization of a novel secreted protein SCUBE1 in human platelets. *Cardiovasc Res*. 2006;71(3):486–95.
27. Jian ZW, Zhang XM, Huang GS. Clinical value of the platelet and inflammatory factor activation in vascular endothelial injury in essential hypertension. *Clin Hemorheol Microcirc*. 2023;83(2):171–80.
28. Ozkan G, Ulusoy S, Mentese A, Karahan SC, Cansiz M. New marker of platelet activation, SCUBE1, is elevated in hypertensive patients. *Am J Hypertens*. 2013;26(6):748–53.
29. Guzel M, Dogru MT, Simsek V, Demir V, Alp C, Kandemir H, et al. Influence of circadian blood pressure alterations on serum SCUBE-1 and soluble CD40 ligand levels in patients with essential hypertension. *Am J Cardiovasc Dis*. 2019;9(4):42–8.

## Tables

Tables 1-3 is available in the Supplementary Files section.

## Figures



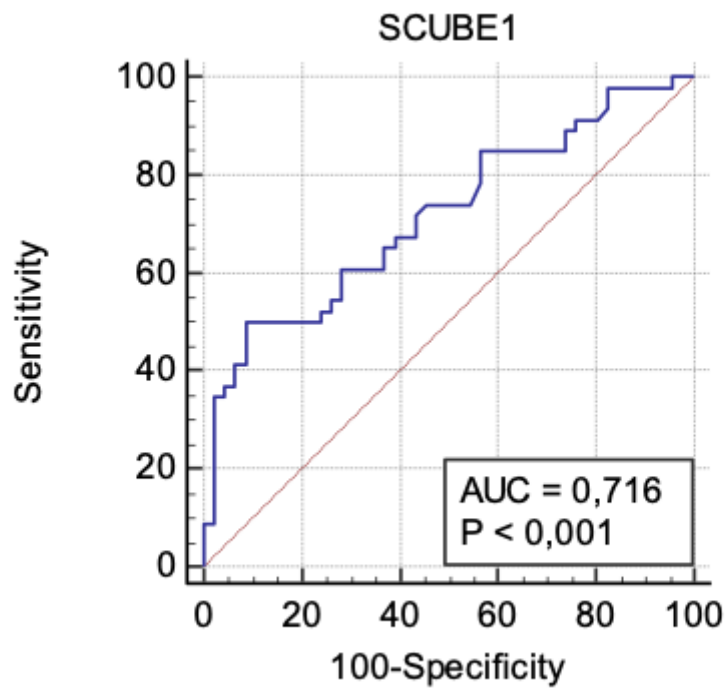


Figure 1

ROC curve for SCUBE-1 levels in preeclampsia.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.docx](#)
- [Table2.docx](#)
- [Table3.docx](#)