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Association between subfatin level and preeclampsia

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Abstract

Preeclampsia is a progressive and pregnancy-specific disorder and it affects multiorgan systems. Although the pathophysiology of preeclampsia is still unknown, it involves both maternal and fetal/placental factors. Endothelial cell damage and impaired endothelial cell function play an important role in the development of preeclampsia. Adipokines have role in many pathophysiological processes in the body. Subfatin is a newly discovered adipokine, if dysfunctional may cause endothelial damage. This study investigated whether subfatin levels can be used as a predictive marker for possible pathophysiology. This study was designed as prospective case-control study. Fifty-six pregnant women who had delivered between gestational age of 37th and 41th weeks with singleton pregnancies in a tertiary reference hospital were included. Pregnant women with a diagnosis of preeclampsia were defined as the case group and normotensive pregnants without a diagnosis of preeclampsia were defined as the control group. There was no statistically significant difference in terms of age, BMI, gravidity and parity between the groups. Mean systolic and diastolic blood pressures were observed higher in case group than control group. Subfatin level of control group was found higher than case group and this difference was statistically significant. Subfatin level ≤ 49.32 ng/mL with 78.6% sensitivity and 71.4% specificity was found significant for case group. Subfatin may have a role in endothelial dysfunction and take part in pathophysiology of preeclampsia. According to this study we suggest that as a newly diagnosed adipokine, subfatin may be helpful in predicting preeclampsia development in pregnant women..

Keywords: adipokine, preeclampsia, pregnancy, subfatin

1. Introduction

Preeclampsia is a progressive and pregnancy-specific disorder and it affects multiorgan systems. New onset of hypertension and proteinuria are the main findings and end-organ dysfunction can be seen. It typically presents in second half of gestation or in postpartum period (1,2). Although the pathophysiology of preeclampsia is still unknown, it involves both maternal and fetal/placental factors (3). Abnormal placental vasculature in early pregnancy may result in relative placental under perfusion which leads to hypoxia and ischemia. Subsequent activation of the intravascular coagulation system, vasospasm, increased platelet activation and consumption are important features (4,5).

In preeclampsia, a significant decrease in uteroplacental blood flow is observed compared with normal pregnancy, and this ischemia is thought to trigger pathophysiological changes (6). The excessive migration and outflow of trophoblasts as a result of placental ischemia probably cause this endothelial cell dysfunction. Endothelial cell damage and impaired endothelial cell function play an important role in the development of preeclampsia. Accumulation of antiangiogenic factors into the maternal circulation may cause hypertension and other systemic dysfunctions of the disease (hematologic, neurologic, cardiac, pulmonary, renal, and hepatic) (7,8).

Adipose tissue secretes bioactive molecules which are called adipokines. These have role in many pathophysiological processes in the body (9,10). The relationship between adiponectin and preeclampsia remains controversial. Studies have shown both increased and decreased concentration of adiponectin in preeclampsia (11-15).

Subfatin is a newly discovered adipokine. In a study investigating the effect of this adipokine, it was suggested that anti-inflammatory genes in adipose tissue was regulated by subfatin and if dysfunctional may cause endothelial damage (16,17).

In consistent with this data from literature, by comparing

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blood subfatin levels of preeclamptic and normotensive pregnant women, we aimed to investigate whether subfatin level can be used as a predictive marker for a possible pathophysiology.

2. Materials and Methods

This study was designed as prospective case-control study. G*Power was used for calculating the sample size (power, 80%; p=0.05 and an α-value of 0.05). 20 women for case group and 20 women for control group, total of 40 women were calculated for the sample size. Fifty-six women who had delivered between gestational age of 37th and 41th weeks with singleton pregnancies in a tertiary reference hospital between March 2022 and June 2022 were included in study. Pregnant women with a diagnosis of preeclampsia were defined as the case group and normotensive pregnants without a diagnosis of preeclampsia were defined as the control group. Exclusion criteria included patients with multiple pregnancies, comorbidities (cardiovascular disease, Diabetes Mellitus), preterm premature rupture of membranes, inflammatory bowel disease, maternal infections (TORCH), uterine malformations, fetal malformations, trisomies, collagen-vascular diseases, polyhydramnios, maternal teratogenous drug use, sickle cell anemia, hereditary thrombophilia and age of <18 or >40 years. This study has been approved by the Ankara Etlik Zubeyde Hanım Women's Health Training and Research Hospital Local Ethics Committee (2022/26-16/02/2022) and it was conducted in accordance with the Declaration of Helsinki. Written and signed informed consent was obtained from all participants before study. The study group included 28 women with term pregnancies and with diagnosis of preeclampsia. The control group included 28 normotensive term pregnancies without diagnosis of preeclampsia.

Demographic data including age, gravidity, parity, Body Mass Index (BMI) and gestational age were noted. The gestational age estimation was calculated according to the last menstural period and first trimester ultrasonography (11th-14th weeks). The maternal and neonatal data were recorded and ultrasonographic measurements were made at the date of hospitalization and labor. After sit down and relaxation for 10 minutes blood pressure measurement was taken from the left upper arm. Venous blood samples were taken when patients were admitted for delivery. Samples for Subfatin centrifuged at 1000xg for five minutes, stored in -80 oC and analyzed within three months. Serum level of subfatin was measured by the ELISA technique.

2.1. Statistical Analyses

Statistical analyzes was done with the SPSS version 26. Histogram and Shapiro-Wilk normality tests were used to determine the distribution of variables. Descriptive statistics were presented as mean ± standard deviation. X2 tests were used to compare categorical variables. For categorical variables number and percentage (n, %) was used. The independent-samples T test was used for comparison of nominal data. Receiver Operating Characteristic (ROC) analysis was used to for calculating the predictive value of Subfatin for preeclampsia. Area under the curve (AUC), cut-off value, sensitivity and specificity were calculated according to ROC analysis. 95% confidence interval (CI) and p value of < 0.05 were considered significant.

3. Results

Fifty-six pregnant women was included in study as 28 in case group and 28 in control group. Table 1 shows the comparison of demographic features and perinatal outcomes of two groups. In terms of age, BMI, gravidity and parity there was no statistically significant difference between groups (Table 1). Mean systolic (157.14±15.36 vs 113.21±6.55 mm/Hg, $p < 0.001$) and diastolic blood pressures (95.71±8.35 vs 73.21±5.47 mm/Hg, $p < 0.001$) were observed higher in case group than control group (Table 2).

All laboratory results were statistically similar except for platelet count and BUN levels. Platelet count (265.75±80.54 vs 225.25±66.77 x103/L, $p = 0.045$) and BUN level (35.42±33.81 vs 57.60±31.32 mg/dl, $p = 0.014$) were higher in control group (Table 2).

There was no difference between groups in terms of gestational age (39 vs 38 w, $p = 0.234$) and birth weight (3339.82±424.23 vs 3082.32±563.91 g, $p = 0.059$).

Subfatin level of control group was found higher than case group and this difference was statistically significant (58.89±17.66 vs 31.85±16.58 ng/mL, $p < 0.001$).

According to ROC analyzes; cutoff value of Subfatin level ≤ 49.32 ng/mL with 78.6% sensitivity and 71.4% specificity was found significant for case group. AUC was calculated as 0.872 ($p < 0.001$) (Fig.1).

Table 1. Comparison of demographic features and perinatal outcomes of case and control groups

	Control (n=28)	Case (n=28)	p value
Age (years)	27.28±4.25	30.28±7.76	0.080
BMI (kg/m^2)	29.05±3.52	29.7±3.49	0.492
Gravidity (n, range)	2 (1-6)	3 (0-6)	0.721
Parity (n, range)	1 (0-5)	1 (0-4)	0.462
Gestational age (week)	39 (37-40)	38 (37-39)	0.234
Birth weight (gram)	3339.82±424.23	3082.32±563.91	0.059

Table 2. Comparison of clinical and laboratory results of case and control groups

	Control (n=28)	Case (n=28)	p value
Systolic Blood Pressure (mm/Hg)	113.21±6.55	157.14±15.36	**<0.001**
Diastolic Blood Pressure (mm/Hg)	73.21±5.47	95.71±8.35	**<0.001**
Hb (mg/dl)	10.96±3.66	11.13±3.87	0.860
Platelet (x10^3/L)	265.75±80.54	225.25±66.77	**0.045**
BUN (mg/dl)	57.60±31.32	35.42±33.81	**0.014**
Creatinine (mg/dl)	4.28±1.11	3.41±3.6	0.229
ALT (U/L)	12.96±11.98	20.82±29.61	0.199
AST (U/L)	20.39±6.28	27.46±31.84	0.254
Subfatin level (ng/mL)	58.89±17.66	31.85±16.58	**<0.001**

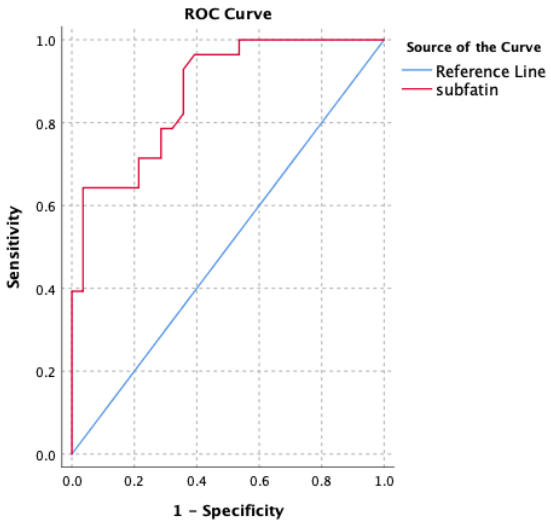

Fig. 1. ROC curve for Subfatin (AUC=0.872, an optimal cutoff ≤ 49.32, 78.6% sensitivity, 71.4%speficity)

4. Discussion

The mechanisms involved in the development of preeclampsia are not yet clearly understood. For this reason, studies are currently being conducted on numerous biomarkers for the detection and treatment of preeclampsia. In recent years, studies on the coexistence of plasma adipokines and preeclampsia have been conducted and have gained popularity (11-15).

Adiponectin has a role in trophoblast proliferation, differentiation and invasion of the decidua and decidual angiogenesis. These are the major phases of placentation. Adu-Gyamfi et al. found that while pregnancy get term adiponectin level physiologically decreases. According to this study, adiponectin takes role in placentation and protect from preeclampsia (18). Another study by Poston et al. relationship between adipokine, leptin, and preeclampsia were evaluated. Elevated levels of leptin in the blood have been shown to cause preeclampsia by increasing sympathetic nervous system activity (19). Similarly, Bawah et al, found that low adiponectin level and high levels of leptin, resistin and visfatin were found to be significant predictors of preeclampsia (20). Rao et al. compared the maternal serum adiponectin and leptin levels and their ratio between preeclamptic and normotensive women. They found that adiponectin-leptin ratio could be considered as a biomarker for preeclampsia (21). Based on these studies in the literature, in this study it was aimed to evaluate the relationship between subfatin, new adipokine, and preeclampsia. In preeclamptic women subfatin levels were found significantly lower than normotensive women and low levels of subfatin was found independent risk factor for preeclampsia. Low levels of subfatin which is effective in endothelial dysfunction may have a contribution to development of preeclampsia.

Lee et al. found that in nondiabetic women subfatin levels were higher than newly diagnosed diabetic women (22). In a study by Dadmanesh et al. serum Subfatin levels were found lower in patients with coronary artery disease (CAD) and type 2 diabetes compared to the control group (23). El-Ashmawy et al. found subfatin levels were low in Type 2 diabetic patients. (24). Contrastly, Chug et al.and AlKhairi et al. found that in subjects with type 2 DM blood Subfatin levels are increased compared to non-diabetic patients (25-26). In a recently published meta-analysis, there was no significant correlation between serum subfatin level and type 2 DM and CAD (27). AlKhairi et al. mentioned that impaired endothelial function and atherosclerosis may be related to subfatin level. Subfatin level may be the independent risk factor of Type 2 DM and also can be used as a marker for endothelial dysfunction.

Fadai et al found that serum subfatin level was low and serum adhesion molecules level was high in diabetic women. In diabetic patients subfatin and vascular adhesion molecules showed a negative correlation. This reduction in subfatin level and its negative correlation with vascular adhesion molecules may suggest endothelial dysfunction in diabetic women (28).

In patients with CAD, subfatin level was found lower than control group (23, 29). Yilmaz et al. evaluates the relation between subfatin level and acute myocardial infarction (AMI), subfatin levels were found significantly lower in non-ST elevated myocardial infarction than control group (30). This may be the result of relatively prolonged and permanent cellular injury in non-ST elevated myocardial infarction.

There have been conflicting results about BMI and subfatin

level. Pellitero et al. showed that subfatin levels were found low in obese women (31). But in another study no correlation was found between subfatin level and BMI (22). In our study, groups were similar in terms of age and BMI and there was no relation between subfatin and BMI.

One of the strengths of the study is subfatin level was investigated for the first time in preeclamptic women. Homogeneity of case and control groups in terms of influencing factors such as age and BMI is another strength. The main limitation of this study is that the number of patients in the kit study was kept to a minimum for economic reasons. Future studies which compare the first and second-third trimester subfatin levels and investigates its predictivity for preeclampsia and other diseases will shed light on the literature.

Subfatin may play a role in endothelial dysfunction and may be involved in the pathophysiology of preeclampsia. According to this study, we suggest that subfatin, as a newly diagnosed adipokine, may be useful in predicting the development of preeclampsia in pregnant women. These data should be supported by studies with a large number of cases.

Conflict of interest

Authors declared no conflict of interest.

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Ethical Statement

This study has been approved by the Ankara Etlik Zubeyde Hanım Women's Health Training and Research Hospital Local Ethics Committee (2022/26-16/02/2022) and it was conducted in accordance with the Declaration of Helsinki.

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None.

Authors' contributions

Concept: C.K., B.K., F.B.F., Y.A.R., G.B., B.Ş., Y.E.Ü. Design: C.K.,B.K., F.B.F., Y.A.R., G.B., B.Ş., Y.E.Ü. Data Collection or Processing: C.K.,B.K., F.B.F., Y.A.R., G.B., B.Ş., Analysis or Interpretation: C.K.,B.K., Literature Search: C.K.,B.K., F.B.F., Writing: C.K.,B.K., F.B.F, Editing and Supervison: Y.E.Ü.

References

1. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin Summary, Number 222. Obstet Gynecol. 2020 Jun;135(6):1492-1495.
2. Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, Kenny LC, McCarthy F, Myers J, Poon LC, Rana S, Saito S, Staff AC, Tsigas E, von Dadelszen P. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2022 Mar;27:148-169.
3. Skjaerven R, Wilcox AJ, Lie RT. The interval between pregnancies and the risk of preeclampsia. N Engl J Med. 2002 Jan 3;346(1):33-8.
4. Dawson LM, Parfrey PS, Hefferton D, Dicks EL, Cooper MJ, Young D, Marsden PA. Familial risk of preeclampsia in Newfoundland: a population-based study. J Am Soc Nephrol. 2002 Jul;13(7):1901-6.
5. Nilsson E, Salonen Ros H, Cnattingius S, Lichtenstein P. The importance of genetic and environmental effects for pre-eclampsia and gestational hypertension: a family study. BJOG. 2004 Mar;111(3):200-6.
6. Tsujimoto Y, Kataoka Y, Banno M, Taito S, Kokubo M, Masuzawa Y, Yamamoto Y. Association of low birthweight and premature birth with hypertensive disorders in pregnancy: a systematic review and meta-analysis. J Hypertens. 2022 Feb 1;40(2):205-212.
7. Macedo TCC, Montagna E, Trevisan CM, Zaia V, de Oliveira R, Barbosa CP, Laganà AS, Bianco B. Prevalence of preeclampsia and eclampsia in adolescent pregnancy: A systematic review and meta-analysis of 291,247 adolescents worldwide since 1969. Eur J Obstet Gynecol Reprod Biol. 2020 May;248:177-186.
8. Romero R, Chaiworapongsa T. Preeclampsia: a link between tropho- blast dysregulation and an antiangiogenic state. *J Clin Invest* 2013; **123**(7): 2775–2777.
9. Miao CY. Introduction: Adipokines and cardiovascular disease. Clin Exp Pharmacol Physiol. 2011;38:860–3.
10. Zhu X, Zhang HW, Chen HN, Deng XJ, Tu YX, Jackson AO, et al. Perivascular adipose tissue dysfunction aggravates adventitial remodeling in obese mini pigs via NLRP3 inflammasome/IL-1 signaling pathway. Acta Pharmacol Sin. 2019;40:46–54.
11. Ramsay JE, Jamieson N, Greer IA, Sattar N. Paradoxical elevation in adiponectin concentrations in women with pree- clampsia. Hypertension. 2003;42(5):891-894.
12. Kajantie E, Kaaja R, Ylikorkala O, Andersson S, Laivuori H. Adiponectin concentrations in maternal serum: elevated in preeclampsia but unrelated to insulin sensitivity. J Soc Gynecol Investig. 2005;12(6):433-439.
13. Haugen F, Ranheim T, Harsem NK, Lips E, Staff AC, Drevon CA. Increased plasma levels of adipokines in preeclampsia: relationship to placenta and adipose tissue gene expression. Am J Physiol Endocrinol Metab. 2006;290(2):E326-E333.
14. D'Anna R, Baviera G, Corrado F, Giordano D, Di Benedetto A, Jasonni VM. Plasma adiponectin concentration in early pregnancy and subsequent risk of hypertensive disorders. Obstet Gynecol. 2005;106(2):340-344.
15. Shinohara K, Wakatsuki A, Watanabe K, Ikenoue N, Fukaya T. Plasma adiponectin concentrations in women with preeclampsia. Hypertension. 2004;43(4):e17.
16. Li ZY, Zheng SL, Wang P, Xu TY, Guan YF, Zhang YJ, Miao CY. Subfatin is a novel adipokine and unlike Meteorin in adipose and brain expression. CNS Neurosci Ther. 2014 Apr;20(4):344-54.
17. Zheng SL, Li ZY, Song J, Liu JM, Miao CY. Metrnl: a secreted protein with new emerging functions. Acta Pharmacol Sin. 2016 May;37(5):571-9.
18. Adu-Gyamfi EA, Fondjo LA, Owiredu WKBA, Czika A, Nelson W, Lamptey J, Wang YX, Ding YB. The role of adiponectin in placentation and preeclampsia. Cell Biochem Funct. 2020 Jan;38(1):106-117.
19. Poston L. Leptin and preeclampsia. Semin Reprod Med. 2002 May;20(2):131-8.
20. Bawah AT, Yeboah FA, Nanga S, Alidu H, Ngala RA. Serum adipocytokines and adiposity as predictive indices of preeclampsia. Clin Hypertens. 2020 Oct 1;26:19.
21. Rao S, Kumari A, Sharma M, Kabi BC. Predicting Maternal

Serum Adiponectin and Leptin Level as Biomarkers of Pre-eclampsia: A Prospective Study. J Obstet Gynaecol India. 2021 Feb;71(1):58-65.

22. Lee JH, Kang YE, Kim JM, Choung S, Joung KH, Kim HJ, et al. Serum Meteorin-like protein levels decreased in patients newly diagnosed with type 2diabetes. Diabetes Res Clin Pract. 2018;135:7–10.

23. Dadmanesh M, Aghajani H, Fadaei R, Ghorban K. Lower serum levels of Meteorin- like/Subfatin in patients with coronary artery disease and type 2 diabetes mellitus are negatively associated with insulin resistance and inflammatory cytokines. PLoS One.2018;13:e0204180.

24. El-Ashmawy HM, Selim FO, Hosny TAM, Almassry HN. Association of low serum Meteorin like (Subfatin) concentrations with worsening of glucose tolerance, impaired endothelial function and atherosclerosis. Diabetes Res Clin Pract. 2019;150:57–63.

25. Chung HS, Hwang SY, Choi JH, Lee HJ, Kim NH, Yoo HJ, et al. Implications of circulating Meteorin-like (Subfatin) level in human subjects with type 2 diabetes. DiabetesRes Clin Pr. 2018;136:100–7.

26. AlKhairi I, Cherian P, Abu-Farha M, Madhoun AA, Nizam R, Melhem M, et al. Increased expression of Meteorin-Like hormone in type 2 diabetes and obesity and its association with irisin. Cells. 2019;8:1283.

27. Gordon A Ferns, Kiavash Fekri, Milad Shahini Shams Abadi, Mahdi Banitalebi Dehkordi & Mohammad-Hassan Arjmand (2021): A meta-analysis of the relationship between serums metrnl-like protein/subfatin and risk of type 2 diabetes mellitus and coronary artery disease, Archives of Physiology and Biochemistry.

28. Fadaei R, Dadmanesh M, Moradi N, Ahmadi R, Shokoohi Nahrkhalaji A, Aghajani H, Ghorban K. Serum levels of subfatin in patients with type 2 diabetes mellitus and its association with vascular adhesion molecules. Arch Physiol Biochem. 2020 Oct;126(4):335-340.

29. Liu ZX, Ji HH, Yao MP, Wang L, Wang Y, Zhou P, et al. Serum Metrnl is associated with the presence and severity of coronary artery disease. J Cell Mol Med. 2019;23:271–80. 10.1111/jcmm.13915

30. Yilmaz M, Cagri Goktekin M, Ilhan N. Subfatin concentration decreases in acute coronary syndrome. Biochem Med (Zagreb). 2022 Jun 15;32(2):020704.

31. Pellitero S, Piquer-Garcia I, Ferrer-Curriu G, Puig R, Martinez E, Moreno P, et al. Opposite changes in meteorin-like and oncostatin m levels are associated with metabolic improvements after bariatric surgery. Int J Obes (Lond). 2018;42:919–22.