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ORIGINAL ARTICLE

Serum MUC3 Protein as a Novel Marker of Gestational Hypertensive Disorders

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Abstract

Background This study aimed to investigate the serum levels of mucoprotein 3 in hypertensive diseases of pregnancy.

Methods In total, 60 consecutive women with gestational hypertensive diseases (gestational hypertension ($n=20$), severe preeclampsia ($n=20$), HELLP syndrome ($n=20$)) and 20 pregnant women without any gestational hypertensive diseases were included for this prospective controlled study. Serum MUC3 protein levels were measured with commercially available ELISA kits.

Results Serum MUC3 protein level was the lowest in normal pregnant women (0.1047 ± 0.0295 ng/ml); while the severity of the disease increases, it significantly increased in severe preeclampsia (0.2700 ± 0.0199 ng/mL) and HELLP syndrome group (0.3494 ± 0.0455 ng/mL), but less in the gestational hypertension (0.2172 ± 0.0354 ng/mL) group. Mean serum MUC3 protein level differences were found the least in gestational hypertension (0.1125 ± 0.0107, $p<0.001$), the most in HELLP syndrome (-0.2546 ± 0.0107, $p<0.001$) compared with the pregnant control group.

Conclusion The increase in serum MUC3 protein concentration in these women supported the argument that serum MUC3 protein may be used as a marker indicating the severity of the gestational hypertensive diseases.

Keywords HELLP Syndrome · Mucoprotein 3 · Preeclampsia · Pregnancy-Induced Hypertension

Introduction

Hypertensive disease of pregnancy is used to describe all hypertensive conditions ranging from mild blood pressure elevation to severe preeclampsia, which can cause organ dysfunction. Hypertension in pregnancy affects approximately 5–10% of all pregnancies. Despite a marked decrease in maternal mortality in developed countries, preeclampsia remains one of the most common causes of death during pregnancy [1].

Preeclampsia is a multisystem disease, and its pathophysiology has not fully elucidated. It is undoubted that there are problems with the placenta in the pathogenesis of preeclampsia, as the disease resolves with the termination of pregnancy. Inadequate trophoblastic invasion, placental ischemia, generalized vasospasm, abnormal hemostasis with activation of the coagulation system, vascular endothelial dysfunction, genetic predisposition, immunological pathologies and mother's vascular endothelial dysfunction may play a role in the pathophysiology of preeclampsia [2]. The increased oxidative stress in hypertensive diseases of pregnancy was well known [3]. In addition, it was known that the measurement of serum 2-methoxyestradiol and salivary uric acid level is related to the severity of the disease [4, 5].

Mucins are proteins with glucose released by epithelium cells of various organs. Serum mucoprotein is higher in preeclampsia and eclampsia compared with normal pregnancy [6]. It has been found that the calculation of both serum and amniotic fluid mucoprotein levels can be used as an indicator of the severity of fetal well-being and toxemia [6]. However, it is not understood which mucoprotein type has a role in physiopathology. MUC1, MUC3, MUC15 and MUC20 mRNA were detected in the human placenta. MUC1 had been reported as a marker in diseases such as preeclampsia associated with trophoblast invasion and placental developmental dysfunction [7].

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According to our detailed literature review, no study investigating the relationship between serum muc3 protein and hypertensive diseases of pregnancy was found. In this context, our research would be the first. This study aimed to investigate the serum mucoprotein 3 levels in pregnant women with gestational hypertensive disorder (gestational hypertension, severe preeclampsia, HELLP syndrome).

Methods

In total, 60 consecutive women with gestational hypertensive diseases (gestational hypertension ($n=20$), severe preeclampsia ($n=20$), HELLP syndrome ($n=20$)) and 20 pregnant women without any gestational hypertensive diseases were included for this prospective controlled study. Institutional Ethics Committee approval was obtained (date 27.05.2010 and number 154). Hypertensive cases of pregnancy referred to the university hospital, which is a tertiary reference hospital, within 7 months were included in the study.

The following criteria were used for the diagnosis of gestational hypertension: (1) pregnancy over 20 weeks and new onset systolic (≥ 140 mm/Hg) or diastolic blood pressure (≥ 90 mm/Hg) elevation, (2) blood pressure elevation was confirmed by two measurements at least 4 h apart, (3) no proteinuria and (4) no signs of severe preeclampsia (thrombocytopenia, kidney failure, liver enzyme elevation, pulmonary edema, cerebral/visual symptoms). The following criteria were used for the diagnosis of severe preeclampsia: (1) a pregnancy over 20 weeks and a new onset of systolic (≥ 140 mm/Hg) or diastolic blood pressure (≥ 140 mm/Hg), (2) blood pressure elevation was confirmed by two measurements at least 4 h apart, (3) Pproteinuria ((≥ 300 mg per 24-h urine collection or protein-to-creatinine ratio ≥ 0.3 or urine dipstick reading 1 +) and (4) presence of any of the new onset severe preeclampsia findings (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg on 2 occasions at least 4 h apart while a patient is on bed rest (unless antihypertensive therapy is initiated before this time), thrombocytopenia (platelet count < 100,000/microL), impaired liver function as indicated by liver transaminase levels at least twice the normal concentration or severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both, progressive renal insufficiency (serum creatinine concentration > 1.1 mg/dL) or a doubling of the serum creatinine concentration in the absence of other renal disease), pulmonary edema, persistent cerebral or visual disturbances) [1]. The diagnosis of HELLP syndrome was made according to the following criteria (abnormal peripheral blood smear, schistocyte in the peripheral blood smear, lactate dehydrogenase > 600 U/L, hemolysis, total bilirubin > 1.2 mg/dl, AST > 70 U/L, platelet count < 100,000mm^3 [8]).

Initially, hypertensive/HELLP syndrome cases were selected for the study group, and normal pregnant cases with appropriate age and gestational weeks were selected as the control group.

Exclusion criteria in the study were listed as follows: (a) not giving consent to participate in the research and sign the form, (b) women having acute/chronic inflammation or, any systemic disease, chronic hypertension, history of recurrent pregnancy loss, thrombophilia, antiphospholipid antibody syndrome, (c) current smoker, (d) having history of cancer, (e) having multiple pregnancy, (f) using antihypertensive, anticoagulant, NSAID, corticosteroid or antiplatelet and antiepileptic drugs, (g) maternal age < 18 or > 44 years old, (h) women in the second trimester of pregnancy and (i) eclampsia.

Maternal blood samples were taken at the time of diagnosis in patients with severe preeclampsia, gestational hypertension, HELLP syndrome and control group before starting any treatment. conte when they apply for delivery in normal pregnant women. After the blood samples were centrifuged at 3000 G for 10 min, the serum was separated and stored at −80 °C in the medical freezer.

After collecting all serum samples, they were dissolved at room temperature and MUC3 (Human Mucin 3, MUC3 ELISA Kit, Catalog number E91031Hu, USCN, China) level was measured in serum samples with the help of commercial ELISA kits.

Statistical Analysis

All data were entered by coding in SPSS 10.0 package program. Four groups of data were evaluated for compatibility with normal distribution and homogeneity. The parametric test assumptions were provided, and one-way analysis of variance (with Bonferroni correction) and statistical analysis in a computer environment were used. A Chi-square test was used to compare the percent values. P-value < 0.05 was considered statistically significant.

Results

There was no significant difference between the mean age in the study and control groups. The comparison of some clinical and laboratory parameters between the hypertensive disease groups of pregnancy and the control groups is given in Table 1. Although the number of cesarean deliveries was higher in the study group compared to the control group,

Table 1 Comparison of the study group and control group in terms of basic clinical features

	Gestational hypertension ($n=20$)	Severe preeclampsia ($n=20$)	HELLP syndrome ($n=20$)	Control ($n=20$)	
Mean age (years)	33.40 ± 6.20	29.89 ± 7.67	31.25 ± 6.15	33.20 ± 5.23	0.265[a]
Mean body mass index (kg/m2)	33.75 ± 7.04	31.67 ± 3.10	29.71 ± 3.47	32.15 ± 4.37	0.071[a]
Mean gravida (no.)	2.60 ± 1.35	2.65 ± 1.92	2.35 ± 1.53	3.40 ± 2.39	0.314[a]
Mean parity (no.)	1.25 ± 1.20	1.00 ± 1.12	1.05 ± 1.14	1.90 ± 2.17	0.204[a]
Mean gestational week (weeks)	34.65 ± 3.07	34.21 ± 3.60	33.49 ± 3.08	36.28 ± 4.27	0.125[a]
Mean birth week (week)	36.19 ± 1.96	35.37 ± 2.51	33.46 ± 3.14	37.60 ± 2.18	< 0.001[a]
Mean systolic blood pressure (mmHg)	150.0 ± 10.76	158.00 ± 13.99	157.50 ± 16.50	111.50 ± 8.12	< 0.001[a]
Mean diastolic blood pressure (mmHg)	95.00 ± 6.88	100.50 ± 7.59	100.50 ± 9.44	72.75 ± 6.38	< 0.001[a]
Delivery method (%)					
Normal spontaneous vaginal delivery (%)	5 (%25)	7 (%35)	4 (%20)	8 (%40)	0.497[b]
Cesarean section (%)	15 (%75)	13 (%65)	16 (%80)	12 (%60)	
Mean baby birth weight (g)	2995.00 ± 723.01	2203.53 ± 735.48	1798.67 ± 599.78	3112.78 ± 657.69	< 0.001[a]
Mean 1st minute APGAR score (no.)	8.50 ± 0.88	7.44 ± 1.46	6.18 ± 2.42	8.00 ± 1.29	< 0.001[a]
Mean 5 min APGAR score (no.)	9.70 ± 0.57	9.05 ± 0.93	8.43 ± 1.63	9.47 ± 1.02	0.005[a]
Mean cord blood pH	7.27 ± 0.08	7.28 ± 0.10	7.27 ± 0.06	7.30 ± 0.07	0.724[a]
Mean cord blood BE	−1.23 ± 2.29	−3.90 ± 4.32	−2.49 ± 2.68	0.27 ± 2.02	0.005[a]

[a]The one-way ANOVA test was used for comparison.

[b]Chi-square test was used for comparison. Mean ± standard deviation or number of cases and percentages in parentheses were given.

there was no statistically significant difference between the groups in terms of the rate of delivery route.

The comparison of serum mucoprotein 3 levels (MUC3, ng/mL) of the study group and the control group is shown in Fig. 1. As shown in Fig. 1, serum MUC3 level is the lowest in normal pregnant women (0.1047 ± 0.0295 ng/ml); while the severity of the disease increases, it significantly increases in severe preeclampsia (0.2700 ± 0.0199 ng/mL) and HELLP syndrome group (0.3494 ± 0.0455 ng/mL), but less in the gestational hypertension (0.2172 ± 0.0354 ng/mL) group. While the mean serum MUC3 level was 0.1047 ± 0.0295 ng/mL in the control group, the mean serum MUC3 level in the HELLP syndrome group was found to be 0.3494 ± 0.0455 ng/mL. (Mean change level compared to the control group is −0.2546 ± 0.0107, one-way analysis of variance in independent sample, $p < 0.001$ with Bonferroni correction and 95% confidence interval −0.2836 to −0.2256.)

The comparison of the mean change of serum mucoprotein 3 (MUC3) levels of the study and control groups is given in Table 2. The most significant change in serum muc3 level was between the control group and HELLP syndrome, the most severe form of the disease.

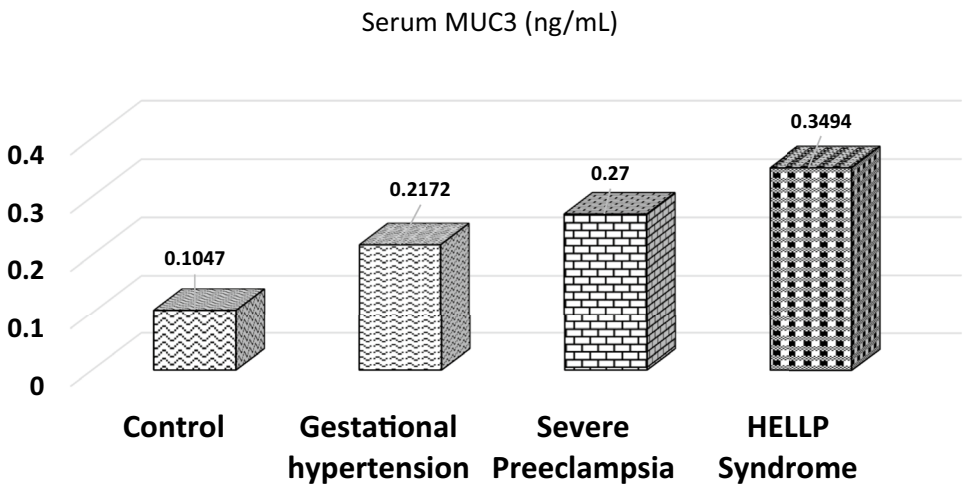

Fig. 1 Change of serum mucoprotein 3 (MUC3) levels of study group and control group (mean values are given)

Table 2 Comparison of the mean change of serum mucoprotein 3 (MUC3) levels of the study and control groups

Groups		Mean change	*p*	%95 Confidence interval
Control group	Gestational hypertension	–0.1125 ± 0.0107	< 0.001	−0.1415 to −0.0834
	Severe preeclampsia	–0.1653 ± 0.0107	< 0.001	−0.1943 to −0.1362
	HELLP syndrome	–0.2546 ± 0.0107	< 0.001	−0.2837 to −0.2256
Gestational hypertension	Severe preeclampsia	–0.0528 ± 0.0107	< 0.001	−0.0818 to −0.0238
	HELLP syndrome	–0.1422 ± 0.0107	< 0.001	−0.1712 to −0.1131
Severe preeclampsia	HELLP syndrome	–0.0894 ± 0.0107	< 0.001	−0.1184 to −0.0603

For comparison, One Way Variance Analysis (with Bonferroni correction) test was used. Mean of changes ± standard deviation values are given

Discussion

Cytotrophoblasts invade maternal spiral arterioles during normal placental development. Both endothelium and muscular layer are affected by this situation, and spiral arterioles become low-resistance high-capacity vessels [9]. This restructuring began at the end of the 1st trimester, and it is assumed to be completed during the 18–20th weeks of pregnancy. In preeclampsia, superficial cytotrophoblast invasion into the decidua and spiral arteries results in inadequate uteroplacental perfusion and incomplete spiral artery restructuring [10, 11]. The cause of inadequate trophoblast invasion in preeclampsia is related to genetic, immunological and environmental factors. Cytokines, adhesion molecules, extracellular matrix proteins, metalloproteinases, major histocompatibility complex-1B molecules and changes in the expression of HLA-G play a role in the invasion of trophoblasts at the molecular level. Mucoproteins are thought to inhibit trophoblast invasion at the molecular level [12].

MUC1, MUC3 and MUC15 mRNA, which is membrane-dependent mucins, are highly released from the human placenta. Studies conducted to date [7, 12, 13] showed the importance of MUC1 and MUC15 in placental diseases. In a recent study, it was found that the level of MUC1 mRNA and MUC1 protein increased significantly in severe preeclampsia compared to the control group in the same gestational week [12]. Past studies showed that MUC1 release is increased in extra villous trophoblasts (EVT) and syncytiotrophoblast in severe preeclampsia placenta in immunohistochemical analysis. MUC1 oscillation has been found to suppress cell–matrix adhesion and prevent EVT invasion. This has been achieved by inhibiting $\beta 1$ integrin activity and focal adhesion kinase (FAK) phosphorylation. Previous studies have shown that $\alpha 5\beta 1$ and $\alpha 1\beta 1$ integrin plays an important role in EVT migration and invasion [14, 15]. FAK also plays an important role in the signaling pathway of EVT migration and invasion [16].

Based on these data, it is thought that the invasion of EVT cells decreases as a result of excessive release of the MUC1 molecule in the preeclamptic placenta in the early gestational week, leading to incomplete spiral artery restructuring and hypoperfusion. It is thought that MUC1 release increased in direct proportion with the severity of preeclampsia and MUC1 over-release in the placenta played a critical role in the progression of preeclampsia. MUC1, a multifunctional glycoprotein, has been shown to play an important role in the pathogenesis of preeclampsia [12]. However, studies with MUC1 have not given information about HELLP syndrome (the more serious form of preeclampsia) and the role of mucoproteins in pathogenesis has not been known.

In the current study, MUC3, another placental release mucin, was evaluated. The results of this study were well correlated with the findings of Shyu et al. [12]. A significant increase in the MUC3 level was detected in placental diseases, gestational hypertension, preeclampsia and HELLP syndrome compared to the normotensive control group. It was found similarly that the MUC3 level increased in direct proportion with the severity of the disease. The highest MUC3 rate was found in HELLP syndrome compared to the control group. While the mean serum MUC3 level was 0.1047 ± 0.0295 ng/mL in the pregnant control group, the mean serum MUC3 level in the HELLP syndrome group was 0.3494 ± 0.0455 ng/mL. These results suggested that MUC3, like MUC1, has an important role in the pathogenesis of preeclampsia.

In a study by Mukherjee et al., serum and amniotic fluid mucoprotein concentrations were compared in normal and toxemic pregnant women. Mucoprotein levels were found higher in toxemic pregnant women than normal controls [6]. They found higher levels of mucoprotein in amniotic fluid compared with serum level. It was thought that this might be due to the amniotic epithelium, chorion, umbilical cord surface and the gastrointestinal tract of the fetus directly related to amniotic fluid. Again, in this study, an inverse proportion was detected between the level of mucoprotein and the state of fetal well-being. While the severity of the disease and the amount of mucoprotein increased, the APGAR score, which showed fetal well-being, was found low in this study. In current study, there was a significant difference between the groups in terms of 1st minute APGAR score, 5th minute APGAR score and mean cord blood BE. Compared to the normotensive control group, as the severity of

the disease increased, the APGAR scores and cord blood BE value decreased.

Many biochemical markers such as atrial natriuretic peptide (ANP), hCG, alpha-fetoprotein (AFP), insulin-like growth hormone binding protein-1, homocysteine and corticotropin releasing factor (CRF) for the prediction of preeclampsia have been investigated, but none have been found clinically useful [17, 18]. According to the results of a study, serum sVEGFR-1 level increased approximately 5 weeks before preeclampsia clinical picture occurred [19]. The current study found that the level of MUC3 increased with the severity of preeclampsia. These findings may suggest that MUC3 may be used as a marker for prediction of preeclampsia. However, there is a need for different designs of research.

Although the release of MUC3 from the placenta has been detected, the mechanism to suppress the release and placental invasion has not been revealed, as in MUC1 and MUC15. Limited studies were showing the roles of mucoproteins held responsible for cancer invasion in trophoblast invasion. In a study [13], MUC15 was shown to be released from the placenta during pregnancy. MUC15 has been found to provide inhibition of trophoblast invasion by inhibiting matrix metalloproteinase (MMP). MMP2 and MMP9 played a regulatory role in trophoblast invasion. It had been determined that MMP inhibitor TIMP-1 and TIMP-2 were released from human trophoblasts. MUC15 had been shown to prevent trophoblast invasion by increasing the release of TIMP-1 and TIMP-2 [20].

MUC1 protein, which is also a membrane-dependent mucoprotein, is released from the human placenta during pregnancy [7]. Besides, 2 types of extra villous trophoblasts have been identified in human decidua. These are MUC1 positive EVT and MUC1 negative EVT. It has been shown that MUC1 positive EVT number is higher in human placental development, and MUC1 is responsible for EVT invasion. MUC1 is thought to play a role in trophoblast adhesion to uterine endothelial cells and plays a role in trophoblast transendothelial migration [21]. However, Jescke et al. detected an excessive release of MUC1 in the placenta in the first and second trimesters. The reason for this difference was thought to be because the MUC1 release only performed immunohistochemical analysis and did not quantitatively count protein signals [22]. It has also been found that MUC1 over-release suppresses invasion of trophoblast-like JAR cells by inhibition of MMP9 activity. These results suggest that MUC1 may be a negative regulator in trophoblast invasion. MUC1 for normal placental development is thought to restrict trophoblast invasion and control the appropriate endometrial depth. MUC1 was found to interact directly with estrogen receptor alpha (ESR 1) and epidermal growth factor (EGFR) and regulate their signals [23, 24]. In this case, estrogen is believed to regulate the differentiation of syncytiotrophoblast in the primate placenta via ESR1 [25]. EGF is thought to regulate Na + /H + modifying activity and trophoblast apoptosis in syncytiotrophoblast through interaction with EGFR [26]. It has also been reported that ESR1 and EGFR are released by human syncytiotrophoblast [27]. Therefore, it is thought that MUC1 regulates the ESR1 and EGFR signals to differentiate the syncytiotrophoblast and regulate their biological functions. These studies showed the effects of MUC1 and MUC15 at the molecular level in trophoblastic tissue. The current study, on the other hand, was a clinical study, and it had not been investigated through which mechanism the effects of MUC3 on trophoblastic tissue. There may a need for molecular studies showing the effects of MUC3 on trophoblastic tissue and on which mechanisms it prevents trophoblastic tissue invasion. The fact that MUC3 was increasing in diseases with placental invasion disorder suggested the idea that similar to MUC1 and MUC15 may decrease the invasion of EVT cells during the stage of placental development and caused incomplete spiral artery restructuring and hypoperfusion.

At the end of this study, we found that in patients with gestational hypertension, severe preeclampsia and HELLP syndrome, the severity of the disease and serum MUC3 levels increased compared to the normotensive pregnant control group. The increase in serum MUC3 concentration in these patients supported the argument that MUC3 may be used as a marker indicating the severity of the hypertensive disease. With the understanding that MUC1 had an important role in the pathogenesis of preeclampsia, MUC3 suggested that it may have an important role in the pathogenesis of hypertensive diseases of pregnancy.

Another limitation of the study is whether the mucoprotein 3 level increase is secondary to any inflammation in the body or is it a result of vascular inflammation caused by the hypertensive disease of pregnancy. The answer to this question can only be possible with advanced molecular studies. However, the mucoprotein 3 level data, which increases with the severity of hypertension, may support the argument that this condition is a marker of the severity of the disease.

A good marker can be useful in clinical use when it has features that are easily accessible, are inexpensive and provide fast results. When mucoprotein 3 is evaluated in this context, it can be useful in clinics with standard laboratory infrastructure, since it is studied with ELISA kits, because it gives results within 2–3 h, is inexpensive, and can be studied easily. Serum MUC3 measurement may be used as a clinical marker in determining the severity of placental diseases such as severe preeclampsia. Further research can be planned on whether mucoprotein 3 level is useful in predicting hypertensive diseases of pregnancy. Extensive molecular research is needed to investigate the mechanism of MUC3 in suppressing placental invasion. Multicenter studies with multiple level evaluation and long periods are required to

demonstrate the usability of MUC3 as a marker in hypertensive diseases of pregnancy.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Ethical Standard The study protocol was approved by the research institute's committee on human research (Karadeniz Technical University, Faculty of Medicine, Scientific Research Ethic Board, date 27.05.2010 and number 154).

Informed consent Informed consent was obtained from all the participants.

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