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Original Article

Comparison of maternal serum vitamin D and paraoxonase 1 levels and neutrophil to lymphocyte ratios of preeclamptic and severe preeclamptic, and normal pregnant women

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Abstract: Preeclampsia is one of the most common causes of maternal and neonatal morbidity and mortality worldwide. We aimed to evaluate the diagnostic values of maternal serum levels of 25-hydroxyvitamin D and paraoxonase 1 (PON1) and neutrophil to lymphocyte ratio (NLR) in the preeclamptic patients and to assess whether they can be used to distinguish the severity of preeclampsia. This prospective study was conducted in women with preeclampsia (n=34) or severe preeclampsia (n=10) and normal pregnancies (n=36), with at least gestational age of 24 weeks. Maternal serum 25-hydroxyvitamin D and PON1 were measured and NLR was calculated. The 25-hydroxyvitamin D levels of the study groups were found comparable ($P > 0.05$). The normal pregnancy and preeclampsia groups were comparable ($P > 0.05$) with regard to the PON1 level; however, their PON1 levels were significantly higher compared to the severe preeclampsia group ($P < 0.05$). The NLRs of the normal pregnancy and preeclampsia groups were found similar ($P > 0.05$), but the NLR of severe preeclampsia group was significantly higher compared to the normal pregnancy and preeclampsia groups ($P < 0.05$). The maternal serum 25-hydroxyvitamin D level is not useful as a marker in the diagnosis of preeclampsia; however, the maternal serum PON1 level and NLR may distinguish the patients with preeclampsia with severe features, but not the patients with preeclampsia without severe features.

Keywords: 25-hydroxyvitamin D, paraoxonase 1, neutrophil to lymphocyte ratio, preeclampsia, severe

Introduction

Preeclampsia is one of the life-threatening conditions presenting as the new onset of hypertension and either proteinuria or end-organ dysfunction after 20 weeks of gestation in a woman without history of hypertension. The various symptoms and signs that occur with preeclampsia depend on the organ system or systems that are affected as well as the severity of pathophysiological process. In the presence of severe hypertension and signs and symptoms of end-organ damage, preeclampsia is accepted as severe [1].

There is no laboratory test with a high sensitivity and specificity used in the workup of preeclampsia. There is need for developing new laboratory tests to determine the severity of preeclampsia with rapid and accurate diagnostic tests. For this purpose, various hematological, biochemical or urinary parameters are investigated in terms of diagnostic power in preeclampsia. In the literature, many substances related to inflammation and oxidative stress are studied to improve new diagnostic tests [2-5].

Many studies showed that risk of preeclampsia increases in the presence of vitamin D deficiency. Vitamin D has a role in oxidative stress and immune modulation, that imply a possible role of vitamin D in the pathophysiology of preeclampsia. Oxidative stress plays a crucial role

in the pathogenesis of preeclampsia related to the development of endothelial dysfunction. The enzyme paraoxonase 1 (PON1) as an oxidative stress and inflammatory marker has a potential to be used in the workup of preeclampsia [6, 7]. On the basis of the theory that inflammation has an important function in the development of hypertension, neutrophil to lymphocyte ratio (NLR) was investigated as a possible marker of preeclampsia. There are important conflicts among the results of studies investigated the impact of these markers in the diagnosis of preeclamptic cases [8-14].

Overall, little is known about the value of maternal serum 25-hydroxyvitamin D and PON1 levels and NLRs in the workup and follow-up of preeclamptic patients and in the determination of severity of preeclampsia. For this reason, we evaluated the diagnostic values of maternal serum levels of 25-hydroxyvitamin D and PON1 and NLR in the preeclamptic patients. We also aimed to determine the place of these parameters in distinguishing the severity of preeclampsia.

Material and methods

Subjects

This prospective study was conducted in the obstetrical service of our hospital in last 6 months. Written informed consent was obtained from all cases after approval by Human Research Ethics Committee of Cumhuriyet University. The patients with preeclampsia with or without severe features and with normal pregnancy that were followed in our obstetrical service, matched for the research criteria, and agreed to participate in the research, were included in the study consecutively. Inclusion criteria were maternal age between 18-45, pregnancy at least gestational age of 24 weeks, diagnosis of preeclampsia with or without severe features, and singleton pregnancy without history of use of any medication. Exclusion criteria included maternal age less than 18 years or more than 45 years; tobacco use; multiple pregnancy; any evidence of previous medical (chronic renal failure, chronic hypertension, diabetes mellitus, chronic liver disease, hematological disease, cancer, and cardiovascular, autoimmune diseases, etc.) or infectious diseases; pregnancies with membrane rupture and placental disease; history of uterine or fetal anomaly; and pregnancies administered steroid for pulmonary maturity.

The definitions were used for the diagnosis of preeclampsia with or without severe features, according to the new ACOG criteria [1]: The diagnosis of preeclampsia was made in a previously normotensive woman with new onset of hypertension and either proteinuria or end-organ dysfunction after 20 weeks of gestation. Criteria for diagnosis are: 1. Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. 2. Proteinuria ≥ 0.3 grams in a 24-hour urine specimen or protein: creatinine ratio ≥ 0.3. 3. Signs of end-organ dysfunction (platelet count < 100,000/microliter, serum creatinine > 1.1 mg/dL or doubling of the serum creatinine, elevated serum transaminases to twice normal concentration).

Severe hypertension and signs/symptoms of end-organ injury were considered the severe spectrum of the disease. The normal pregnancy group had systolic/diastolic blood pressure within normal range and no history of hypertension or proteinuria.

The information including demographic and obstetrical history was obtained by patient interview and chart review. The major clinical parameters of the study population were age, body mass index (BMI), education status, socioeconomic status, consanguinity, cigarette smoking; gravidity, parity, miscarriage, history of preeclampsia, family history of preeclampsia, and gestational age.

Laboratory tests

The blood for serum samples of 25-hydroxyvitamin D and PON1 were drawn from antecubital vein after 12 hours of fastening. After coagulation they were centrifuged, sera were separated and stored at -80°C until the time of study. Serum 25-hydroxyvitamin D levels were determined by competitive immunoassay using Roche Diagnostic commercial kits and multichannel automatic analyzer (Roche Cobas 6000-E 601, Rotkreuz, Switzerland) with an evaluated assay of 3-70 ng/mL. Serum PON1 levels were measured by kinetic method (RelAssay Diagnostics, Gyeonggi-do, Korea) as defined in the manufacturer's instruction. The coefficient value of PON1 level was 5% and normal serum range was 200-400 U/L.

Table 1. Selected demographic and clinical data of study population

	Normal pregnancy group (n=36)	Preeclampsia group (n=34)	Severe preeclampsia group (n=10)
Demographic data			
Age, y	29.9±5.3	30.2±7.2	31.3±5.5
BMI	29.2±5.0	31.7±6.2[a]	30.6±5.0
Education status			
High school	28 (78%)	20 (59%)	9 (90%)[b]
University	8 (22%)	14 (41%)	1 (10%)
Socioeconomic status			
Low	3 (8%)[b]	30 (88%)	9 (90%)
Average	33 (92%)	4 (12%)	1 (10%)
Consanguinity			
Yes	10 (28%)	11 (32%)	0
No	26 (72%)	23 (68%)	10 (100%)
Cigarette smoking			
Yes	2 (6%)	2 (6%)	1 (10%)
No	34 (94%)	32 (94%)	9 (90%)
Obstetrical history			
Gravidity	3 (1-9)	3 (1-7)	4 (1-5)
Parity	2 (0-6)	1 (0-6)	2 (0-3)
Miscarriage	1 (0-4)	0 (0-4)	1 (0-2)
History of preeclampsia			
Yes	1 (3%)[c]	6 (18%)	4 (40%)
No	35 (97%)	28 (82%)	6 (60%)
Family history of preeclampsia			
Yes	0[d]	8 (23%)	4 (40%)
No	36 (100%)	26 (77%)	6 (60%)
Gestational age, wk	38±1.9	37.7±1.89	33±5.5[e]

[a]$P < 0.05$ vs. normal pregnancy group. [b,c,d]$P < 0.05$ vs. preeclampsia and severe preeclampsia groups. [e]$P < 0.05$ vs. normal pregnancy and preeclampsia groups. Data were expressed as mean ± SD, median (min-max), or percentage as appropriate.

The blood samples were collected in a hematological sample tube containing anticoagulant, and the following hematological parameters measured with the hematology analyzer (Mindray BC-6800, Shenzhen, China) were used for the calculation of the NLR.

Statistical analysis

Data were presented as mean ± SD, median (min-max), or percentage as appropriate. For the analysis of parametric data, ANOVA with post hoc Tukey test was used. Data that was not normally distributed were analyzed with the Kruskal-Wallis test for comparisons among groups and the Mann-Whitney U test for comparisons between groups. For the analysis of categorical data, chi-square test was used. A *p* value of less than 0.05 was accepted as significant.

Results

This study was completed with 36 (45%) women with normal pregnancy, 34 (42.5%) women with preeclampsia, and 10 (12.5%) women with severe preeclampsia. After being included in the research, there was no patient excluded during the study period.

Table 1 presents the selected demographic and clinical parameters of the normal pregnancy, preeclampsia, and severe preeclampsia groups. The BMI of preeclampsia group was significantly higher than that of the normal pregnancy group ($P < 0.05$). The BMI of severe preeclampsia group was comparable with those of the normal pregnancy and preeclampsia groups ($P > 0.05$). The ratios of lower socioeconomic status, presence of history of preeclampsia, and presence of family history of preeclampsia in the normal pregnancy group were significantly lower than those of the preeclampsia and severe preeclampsia groups ($P < 0.05$); however, with regard to these parameters, there were no significant differences between the preeclampsia and severe preeclampsia groups ($P > 0.05$). The gestational age of severe preeclampsia group was significantly lower than those of the normal pregnancy and preeclampsia groups ($P < 0.05$); however, with regard to this parameter, there was no significant difference between the normal pregnancy and preeclampsia groups ($P > 0.05$). With regard to the age, education status, consanguinity, cigarette smoking, gravidity, parity, and miscarriage, the study groups were found as similar ($P > 0.05$).

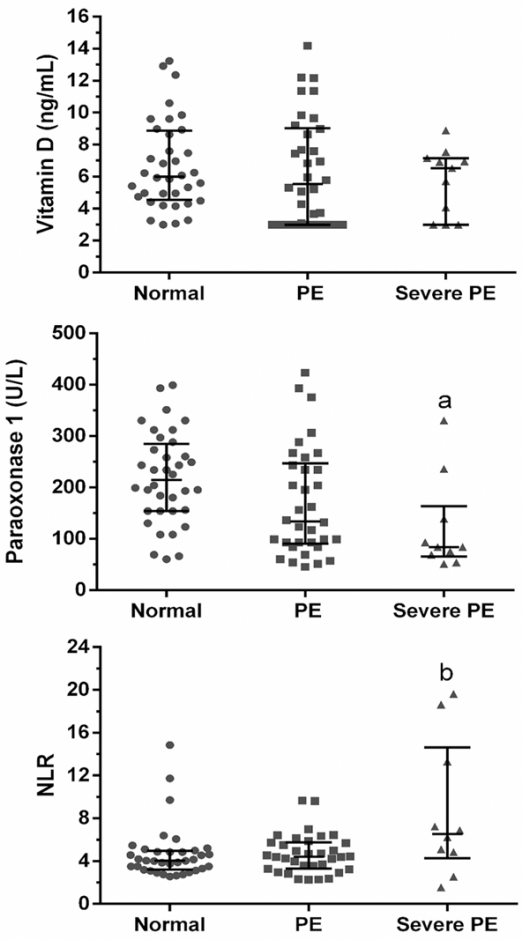

Figure 1. Vitamin D, paraoxonase 1, neutrophil to lymphocyte ratio values of normal pregnancy, preeclampsia, and severe preeclampsia groups. PE, preeclampsia; NLR, neutrophil to lymphocyte ratio. Data are expressed as median with interquartile range. Kruskal-Wallis ANOVA was used for the analyses of these data. $^{a,b}P < 0.05$ vs. normal and PE.

Figure 1 shows the values of 25-hydroxyvitamin D, PON1, and NLR in the normal pregnancy, preeclampsia, and severe preeclampsia groups. With regard to 25-hydroxyvitamin D level, there was no significant difference among the study groups ($P > 0.05$). The PON1 level of the severe preeclampsia group was significantly lower than those of the normal pregnancy and preeclampsia groups ($P < 0.05$); however, the PON1 levels of the normal pregnancy and preeclampsia groups were found similar ($P > 0.05$). With regard to the NLR, the severe preeclampsia group had significantly higher values than those of the normal pregnancy and preeclampsia groups ($P < 0.05$); however, the normal pregnancy and preeclampsia groups were comparable ($P > 0.05$).

Discussion

In the current study, we investigated the diagnostic values of maternal serum levels of 25-hydroxyvitamin D and PON1 and NLR in the patients with preeclampsia with or without severe features and their usability to differentiate the severity of preeclampsia. As markers of oxidative stress and inflammation, the level of maternal serum 25-hydroxyvitamin D was not significantly different in the preeclamptic patients with or without severe features, and the level of maternal serum PON1 was found as increased in the patients with severe preeclampsia; however, it was not increased meaningfully in the patients with preeclampsia. As a marker of inflammation, the NLR was higher in the patients with severe preeclampsia; however, it was not increased meaningfully in the patients with preeclampsia. These laboratory tests did not differentiate successfully all types of cases with preeclampsia with or without severe features from cases with normal pregnancies; however, the level of maternal serum PON1 level and NLR determined successfully the patients with severe preeclampsia. According to our knowledge, in our country, this is the first study evaluating the importance of these markers in the workup of preeclamptic patients in the same clinical setting.

Preeclampsia is a pregnancy-specific multisystem disorder characterized by de novo-onset hypertension with a spectrum of systemic derangements. Despite intensive research activity to delineate the pathophysiology of preeclampsia, its etiology and pathogenesis is not clear nowadays. Alterations of several endogenous factors are under investigation to solve the preeclampsia puzzle, including vitamin D, PON1, and NLR. Although there are several clinical and epidemiological studies, the possible mechanisms by which vitamin D could affect the development of preeclampsia remain to be elucidated. The contributions of vitamin D was demonstrated in physiological processes including angiogenesis, oxidative stress, metabolism, placental function, and immunity, indicating the possibility of relationship of vitamin D with preeclampsia [15, 16]. Although there are clinical studies that did not support a relation-

ship between vitamin D deficiency and preeclampsia [17-19], a positive association between vitamin D deficiency and preeclampsia was demonstrated [20-22]. In the literature, there are also studies supporting the relationship of vitamin D deficiency and mild and severe forms of preeclampsia [23, 24]. The differences related to study design heterogeneity of study groups, selection of inclusion and exclusion criteria, gestational age, and clinical settings are major contributors of these conflicting results. Our results did not indicate the impact of vitamin D deficiency on the development of preeclampsia. In our study, we diagnosed preeclampsia and defined its severity according to the latest ACOG criteria [1]. Further studies are needed to evaluate the status of vitamin D in preeclamptic and severe preeclamptic patients selected according to those new criteria. We think that the exclusion of amount of proteinuria from the criteria of severe preeclampsia may change the proportion of patients with severe preeclampsia. The status of HELLP syndrome is also changed in the latest ACOG criteria of severe preeclampsia.

In the studies of Acikgoz et al. [25], Baker et al. [26], and Yaghmaei et al. [27] investigated the serum PON1 activity in normal and preeclamptic pregnant women. They found that serum PON1 activity increased in women with preeclamptic pregnancies. In other studies investigating the serum PON1 activity in preeclamptic patients, lower PON1 activity was reported [28-30]. Sarandol et al. [31] found no meaningful change in serum paraoxonase activity in both mild and severe preeclamptic patients compared to normal pregnant women. In our study, although we found lower serum PON1 level in all the women with preeclamptic pregnancy, this difference reached statistical significance in only women with preeclampsia with severe features. We think that the mixed results of studies including the measurement of serum PON1 activity in preeclamptic women are related to the selection of study populations and settings of studies as discussed above.

Mellembakken et al. [32] suggested that neutrophils were activated in pregnancies complicated by preeclampsia more than in normal pregnancies. Compared to normal pregnancies, there is an increase in the absolute neutrophil count in addition to a decline in the absolute lymphocyte count [33]. Canzoneri et al. [34] evaluated the leukocyte number and its subtypes in women with normal or preeclamptic pregnancies. They found that the leukocyte number was higher in women with mild preeclampsia, but that difference reached statistical significance in women with severe preeclampsia compared with normal pregnant women. They suggested that the increased neutrophil, not lymphocyte, numbers account for the total leukocyte increase in preeclampsia. Those findings support the use of NLR as a parameter with a possible role in differential diagnosis of preeclampsia with or without severe features. In the study of Yavuzcan et al. [35], the NLRs of normal pregnant and severe preeclamptic patients were found as similar. Kurtoglu et al. [36] suggested that the NLR might be helpful to predict preeclampsia if obtained periodically, although they found no relationship of the NLR with the severity of preeclampsia. In a recent study [37] investigating the value of NLR as a marker of preeclampsia, the authors suggested that increased NLR might be used as a predictor of preeclampsia; however, they did not stratified the study population according to the severity of preeclampsia. Overall, the findings of those studies support the use of NLR as a parameter for the diagnosis of preeclampsia; however, the value of this marker and its cutoff in patients with preeclampsia with or without severe features is not clear. According to our findings, although in the patients with preeclampsia with severe features, the NLR was meaningfully increased compared to the patients with preeclamptic pregnancy without severe features, the small sample size of patients with preeclampsia with severe features indicates the requirement of further studies with optimal sample size and clinical settings to determine its importance and cutoff for the detection of severe cases.

There are some inherent limitations of this study. During the study period, the admission of patients with severe preeclampsia was less than expected. We preferred to exclude several obstetric conditions with a potential to affect the studied parameters. This reduced the number of enrolled patients in the current study. Overall, with regard to the selected demographic and clinical parameters, there was no mean-

ingful difference among the study groups. The small sample size of patients with preeclampsia with severe features diminished the power of our significant differences.

In conclusion, during antenatal care of women, the maternal serum PON1 level and NLR have a potential to differentiate the patients with preeclampsia with severe features, but not the patients with preeclampsia without severe features. The maternal serum 25-hydroxyvitamin D level is not helpful in the diagnosis of preeclampsia with or without severe features. The clinical course of preeclampsia changes considerably according to the maternal age, gestational age, medical interventions, the severity and duration of disease. We think that these factors may affect the diagnostic value of these markers. Further studies are needed to determine the cutoff values of maternal serum PON1 level and NLR as a marker to differentiate preeclampsia with severe features in clinical setting according to recent changes in the definitions of preeclampsia and HELLP syndrome.

Disclosure of conflict of interest

None.

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