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Monocyte to HDL Ratio in Preeclamptic Patients: Can It Be a Predictive Marker?

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ABSTRACT

Objective: Preeclampsia (PE) is a severe and high – risk pregnancy complication for both the mother and fetus. Generalized inflammation is a prominent feature of PE. Based on the proinflammatory property of monocytes and the contrary anti-inflammatory mechanism of High-density lipoprotein (HDL), monocyte count to HDL ratio (MHR) could be used as a new marker of systemic inflammation. Our aim is to evaluate the relationship between PE and MHR in terms of diagnosis of PE.

Methods: A retrospective case-control study was recruited preeclamptic and healthy pregnant women in the third trimester of gestation (n=69 and n= 71, respectively).

Results: Maternal age (years), gravity, and body mass index (BMI) were similar in the two groups. The gestational week at delivery was significantly earlier in the PE group than in the control group ($p < 0.001$). Fetal weight in PE was significantly lower than in the control group ($p = 0.001$). Monocyte counts were comparable between the two groups (0.76 ± 0.28 vs. 0.76 ± 0.71; $p = 0.25$). The mean HDL level of PE patients was lower than the control group, but it was not statistically significant (63.87 ± 15.3 vs. 68.23 ± 13.5; $p = 0.77$). The monocyte/HDL ratio was higher in the PE group, but this increment did not reach statistical significance (12.5 ± 5.9 vs. 10.9 ± 4.3, $p = 0.08$).

Conclusion: MHR might be a new marker of inflammation and oxidative stress. The present study did not reach a result indicating a diagnostic marker of PE. Further studies with more cases are needed to evaluate the relationship between MHR and PE.

Keywords: Preeclampsia, monocyte, HDL, MHR, marker

1. INTRODUCTION

Preeclampsia (PE) is a severe and high-risk complication of pregnancy for both the mother and fetus. The prevalence of PE is estimated to be 8% on average (1). The pathogenesis of preeclampsia is still a controversial issue. Many reports concerned with defective placentation, resulting in releasing several antiangiogenic and proinflammatory substances that induce characteristic systemic endothelial dysfunction (2-4). Increased circulating lipid levels cause accumulation within endothelial cells, which causes prostacyclin secretion to decrease, resulting in oxidative stress through endothelial dysfunction (5). The other proposed mechanism is that changes in the pregnant woman's immune system cause an increased inflammatory response, leading to defective placentation, resulting in capillary permeability increment, microvascular thrombosis, and increased vascular tone (6, 7).

Monocytes, one of the main structures in the immune system, secrete proinflammatory cytokines at the site of inflammation (8). During normal pregnancy, monocytes number and activation are increased (9). Although the main cause of monocyte activation during pregnancy is unknown, the placenta may play a leading role in this process. Circulating monocytes in the blood can contact with the syncytiotrophoblast through the placental spaces and activate a proinflammatory phenotype (10, 11).

High-density lipoproteins (HDL) exhibit anti-inflammatory and antioxidant properties (8, 12). HDL protects endothelial cells against low-density lipoprotein cholesterol (LDL-C), preventing monocytes functioning in atherosclerosis and cardiovascular disease (12-14). On the basis of these reports, monocyte count to HDL ratio (MHR) might be a novel marker of oxidative stress and inflammation. MHR is considered as a predictor and prognostic marker for different pathologies (14).

Considering the pathogenesis of PE, we hypothesized that MHR might be regarded as an indicator for disease since PE is an inflammatory process and affects the function of HDL and monocyte count.

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2. METHODS

2.1. Study Population and Design

A total of 140 pregnant were enrolled in the Umraniye Education and Research Hospital's Obstetrics and Gynecology Department between February 2018 and September 2019. According to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, Sixty – nine women were diagnosed with PE (15). As a control group, 71 women were enrolled with a normal pregnancy who have normal blood pressure and experienced a normal course of pregnancy.

All women were in the third trimester, not in active labor, and had intact membranes. Patients with lipid metabolic abnormalities were excluded, as were those who had taken any medication that affected plasma lipid levels in the six months before to enrolling in the trial. Patients were excluded from infectious, inflammatory, or autoimmune diseases, multiple gestations, chromosomal fetal abnormality, chronic and pregnancy-induced hypertension, PE history, diabetes mellitus, molar pregnancy, maternal renal disease, rheumatoid arthritis, and morbid obesity. Alcoholism, smoking, and medical or surgical intervention history were also ruled out. Ethical Committee of Umraniye Education and Research Hospital accepted the study (no: 21.02.2018-18). All participants gave written informed consent.

Demographic characteristics, obstetrics outcomes, and laboratory parameters of patients were saved. The gestational week was calculated by the first date of their last menstrual cycle. The confirmation was done by first-trimester ultrasound scanning of the crown-rump length (CRL).

The peripheral venous blood samples were obtained after a minimum of eight hours of fasting. An automated hematology analyzer (Pentra DX Nexus, Horiba, Japan) was used to measure complete blood counts. DxC700 AU Chemistry Analyzer (Beckman Coulter, USA) was used to measure HDL cholesterol levels in the blood. Monocyte count was divided by serum HDL levels to calculate the MHR.

2.2. Statistical Analysis

All data were analyzed with SPSS, version 20.0. Shapiro–Wilk test was performed to verify normal distribution or not. Mann – Whitney U test or Independent samples t-test were used according to normality test results. Variables were demonstrated as mean, ± standard deviation, or median values. Correlations were calculated by calculating Pearson's correlation coefficient (r). $P < 0.05$ was considered statistically significant.

3. RESULTS

A total of 71 healthy pregnant and 69 preeclamptic pregnant women were included in the study. Age and parity of the women were matched. Table 1 summarizes the pregnant women's demographic characteristics and pregnancy outcomes. Maternal age (years), gravidity, and BMI were comparable in all groups (Table 1). The gestational week at birth was significantly earlier in the PE group than in the healthy group ($p < 0.001$). Preeclamptic patients had a significantly lower fetal weight than healthy pregnant patients (2809.3 ± 778.1 vs. 3188.6 ± 407.4; $p = 0.001$).

Table 1. *Clinical characteristics of study participants.*

	Preeclampsia (n = 69)	Control (n = 71)	p value
Age (years)	29.96±5.3	28.28±5.2	0.08
gravidity (range)	2 (1-7)	2 (1-7)	0.71
Parity (range)	1 (0-6)	1(0-5)	0.35
BMI (kg/m^2)	30.6 ± 4.4	29.9±5.2	0.36
Gestational week at delivery	35(26-40)	37(30-41)	< 0.001
Fetal weight (gr)	2809.3 ± 778.1	3188.6 ± 407.4	0.001

Data are expressed as mean±standard deviation, median (interquartile range)
BMI: body mass index

Monocyte levels were comparable between the two groups (0.76 ± 0.28 and 0.76 ± 0.71; $p = 0.25$). The mean HDL level of PE patients was lower than the control group, but it did not reach statistical significance (63.87 ± 15.3 vs. 68.23 ± 13.5; $p = 0.77$). MHR was higher in PE patients, but this increment did not reach statistical significance (12.5 ± 5.9 vs. 10.9 ± 4.3, p=0.08) (Table 2). WBC count was significantly higher in the PE than in the healthy control group (p=0.01). MHR was positively correlated with WBC count (r= 0.37, p<0.001), but not with age and BMI, respectively (p=0.41, p=0.36).

Table 2. *Laboratory parameters of all groups.*

	Preeclampsia (n = 69)	Control (n = 71)	p value
WBC (x10^9/L) (mean ± SD)	11.4 ± 2.42	9.3 ± 1.63	0.001
Monocyte count (x10^3/mL) (mean ± SD)	0.76 ± 0.28	0.76 ± 0.71	0.25
HDL (mg/dL)	63.87 ± 15.3	68.23 ± 13.5	0.77
MHR	12.5 ± 5.91	10.9 ± 4.3	0.08

WBC — white blood cells; HDL — high-density lioprotein; MHR — monocyte/high density lipoprotein ratio; SD — standard deviation

4. DISCUSSION

In our study, we evaluated MHR in preeclamptic women and compared them with healthy pregnant women. MHR was higher in preeclamptic patients than in the control group, according to our findings. However, this difference was not statistically significant.

During preeclampsia, defective placentation products prompt further activation and maturation of the monocytes (16). Activated monocytes produce cytokines that result in a generalized inflammatory response. Wang et al. analyzed more than three hundred preeclamptic patients and found that absolute monocyte count was significantly higher than the control group (17). In addition, Brien et al. stated that monocyte count was higher in preeclamptic women than in

normal pregnancies (18). Belo et al. reported that monocyte counts were similar in both groups, consistent with the current study. Further, higher WBC counts have been detected in the third trimester preeclamptic pregnancies as our study, but it was not statistically significant (19).

In a healthy pregnancy, lipid metabolic changes occur, with total cholesterol, triglyceride, HDL, and LDL levels rising significantly to fulfill the needs of fetal growth and development (20). In preeclampsia, the oxidatively stressed placenta releases antiangiogenic and proangiogenic factors that induce an exaggerated inflammatory response with generalized endothelial dysfunction (21). HDL positively affects the inflammation and oxidative pathways, such as inhibiting lipid peroxidation and upregulation of cytokine-induced proinflammatory adhesion molecule and chemokine expression by endothelial cells. HDL advocates macrophage transition from pro-inflammatory to anti-inflammatory form and suppresses monocyte progenitor cells to proliferation-differentiation (14, 22). Reyes and Cao et al. stated that HDL levels are lower in preeclamptic patients (23, 24). Konrad et al. reported that HDL levels decreased in the course of worsening from mild to severe preeclampsia (25). Conversely, according to Khaire et al., comparing normotensive pregnant women with preeclamptic women, HDL levels were higher at term PE than the normotensive healthy women (26).

The present study was designed with the idea that PE is an inflammatory process that causes an increase in MHR value. Based on the proinflammatory feature of monocytes, and the contrary anti-inflammatory mechanism of HDL, it was thought that MHR might be used as a new marker of systemic inflammation. MHR was first defined by Kanbay et al. in 2014, and it was reported that a high MHR value could estimate adverse cardiovascular outcomes' risk (27). MHR has been related to different pathologies such as hypertension, abdominal aneurysm, intracerebral hemorrhage, chronic kidney disease, obstructive sleep apnea syndrome (OSA), acute intracranial hemorrhage, gestational diabetes mellitus (GDM), and metabolic syndrome (MS) in Polycystic Ovary Syndrome (PCOS) (28-32).

Selçuk et al. reported that MHR was significantly higher in the non-dipper hypertension (HT) patients than control and dipper HT patients (33). Gembillo et al. stated that MHR was a potential biomarker of inflammation and positively correlated to C-reactive protein. In addition, MHR was significantly higher among resistant hypertension than non-resistant HT patients (34). Sun et al. analyzed the correlation between MHR and OSA in 246 patients with HT. MHR increased with OSA patients' severity, and it was a valuable marker in evaluating OSA risk and severity in hypertensive patients (29).

High blood pressure, obesity, dyslipidemia, and insulin resistance are major components of metabolic syndrome (MS), and the MS is diagnosed in approximately one-third of women with PCOS (35). In this context, researchers have published articles revealing the relationship between MHR, PCOS, and metabolic syndrome (31,36,37). Usta et al. reported that MHR was significantly higher in PCOS than in non-PCOS control groups (11.5 vs. 8.8). In subgroup analysis that PCOS divided into obese and lean PCOS, MHR had higher in obese PCOS than lean PCOS and non-PCOS controls. They summarized that it is a valuable predictor of PCOS (31). Dilşad et al. reported an association between PCOS and obesity. The researcher determined 10.1 cut-off value for prediction for PCOS. In addition, the researcher reported negative correlation between MHR and age in PCOS patients (36). In our study, any correlation was found between MHR with age and BMI.

Çakmak et al. analyzed MHR in PCOS and found MHR to predict metabolic syndrome with a MHR ratio > 9.9, reporting that it may be promising in predicting metabolic syndrome in the early stages of PCOS (37). In our study, MHR for PE and the control group were 12.5 vs. 10.9, respectively. The cut-off value could not be calculated because statistical significance was not found in our study. Based on the knowledge that oxidative stress increases in GDM, Onat et al. compared 60 pregnant with GDM and 52 healthy women; MHR was higher in the GDM patients ($p < 0.05$) (32).

To the best of the present authors' knowledge, there is only one published study investigating MHR in PE by Melekoglu et al. stated that MHR was considerably higher in both preeclampsia and severe preeclampsia groups (p=0.007 and p<0.0001, respectively) (38). Contrary to our study, they reported that the MHR might be valuable for predicting the development of preeclampsia. MHR is a readily available and cheap test that provides relevant information about inflammation and oxidative stress. In our study, MHR could not be used as a diagnostic marker in PE. This situation may change with studies conducted with larger-scale studies.

5. CONCLUSION

In conclusion, this preliminary study demonstrates that MHR cannot be used as a diagnostic marker of PE. An association between MHR and PE has not been proven. However, further studies with more cases are needed to evaluate the relationship between MHR and PE.

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