Özgün Araştırma / Original Article

Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology - Obstetrics and Neonatology

DOI: 10.38136/jgon.1313215

Evaluation of the myeloperoxidase/paraoxonase1 ratio as the determinant of dysfunctional HDL in polycystic ovary syndrome

Polikistik over sendromunda disfonksiyonel HDL'nin göstergesi olarak miyeloperoksidaz/paraoksonaz1 oranının değerlendirilmesi

ESİN MERVE EROL KOC [1] Orcid ID: 0000-0001-7686-9149
SELEN YAMAN [1] Orcid ID: 0000-0001-5247-6615
MERYEM CEYHAN [1] Orcid ID: 0000-0003-1341-1370
SALİM NESELİOGLU [2] Orcid ID: 0000-0002-0974-5717
OZCAN EREL2 [2] Orcid ID: 0000-0002-2996-3236
MELİKE DOGANAY [3] Orcid ID: 0000-0002-2603-1812

[1] Department of Obstetrics and Gynecology, Ankara City Hospital, Ankara, Türkiye

[2] Department of Biochemistry, Ankara Yıldırım Beyazıt University, Faculty of Medicine, Ankara, Türkiye

[3] Department of Obstetrics and Gynecology, University of Health Sciences, Gülhane Faculty of Medicine, Ankara, Türkiye

ÖZ

Amaç: Miyeloperoksidaz/paraoksonaz1(MPO/PON1) oranının, oksidatif stresin bir ölçüsü olan disfonksiyonel HDL(d-HDL)'yi yansıttığı bilinmektedir. Bu çalışmada, polikistik over sendromunda (PKOS) MPO/PON1 oranının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu prospektif çalışmaya toplam 123 kadın dahil edildi. PKOS tanılı kadınları içeren çalışma grubu (n=63), sağlıklı kadınların bulunduğu kontrol grubu (n=60) ile karşılaştırıldı. Grupların sosyodemografik özellikleri ve klinik özellikleri kaydedildi. Serum HDL düzeyi, MPO ve PON1 aktiviteleri değerlendirildi.

Bulgular: PKOS hastalarında MPO aktivitesinde artış ve PON1 aktivitesinde azalma gözlendi (sırasıyla; p<0,0001 ve p=0,007). Sağlıklı kontrollere kıyasla PKOS hastalarında d-HDL anlamlı olarak yüksek bulundu (0,50 (0,12) vs. 0,56 (0,24), p<0,0001). Oksidatif parametreler ile PKOS ilişkili bulgular arasında da anlamlı ilişkiler gözlendi (p<0.05).

Sonuç: Çalışmamızda, d-HDL olarak tanımlanan artmış MPO/PON1 oranının yanı sıra artmış MPO ve azalmış PON1 aktiviteleri de PKOS hastalarında artmış oksidatif stresi desteklemektedir. Sonuçlarımız, yaşamının erken dönemlerinde bile PKOS hastalarında oksidatif stres ve dislipidemiye işaret etmesi yönünden dikkat çeker niteliktedir.

Anahtar Kelimeler: Disfonksiyonel HDL; MPO/PON1; Oksidatif stres; PCOS.

ABSTRACT

Aim: The myeloperoxidase/paraoxonase1(MPO/PON1) ratio is known to reflect the dysfunctional HDL(d-HDL) which is a measure of oxidative stress.This study aimed to evaluate the MPO/PON1 ratio in polycystic ovary syndrome(PCOS).

Materials and Method: This prospective study included a total of 123 patients. The study group including the women with the diagnosis of PCOS (n=63) was compared to the control group including the healthy women (n=60). Sociodemographic characteristics,and clinical features of the groups were recorded. Serum HDL level, MPO, and PON1 activities were evaluated.

Results: The PCOS patients were observed to have increased MPO and decreased PON1 activities (p<0.0001 and p=0.007, respectively). The d-HDL and was found to be significantly higher in PCOS patients compared to the healthy controls (0.56 (0.24) vs. 0.50 (0.12), p<0.0001). There were also significant associations between the oxidative parameters and PCOS related findings (p<0.05).

Conclusion: Besides the increased MPO/PON1 ratio which defined as d-HDL, the increased MPO and decreased PON1 activities also supported the increased oxidative status in PCOS patients. Our results may be considered to draw attention to oxidative stress and dyslipidemia in PCOS patients, even in the early periods of the women life.

Keywords: Dysfunctional HDL; MPO/PON1; Oxidative stress; PCOS.

Sorumlu Yazar/ Corresponding Author: Esin Merve Erol Koç
Adres: Universiteler District, Bilkent Street, No:1, 06800, Çankaya, Ankara
E-mail: esinmerve87@gmail.com

Başvuru tarihi: 12.06.2023
Kabul tarihi: 06.07.2023

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most commonly seen endocrine and metabolic disorder among the women at reproductive age, with the incidence of 15% (1). The PCOS was also indicted for increased risk of chronic inflammation of arterial walls, atherosclerosis, and coronary artery diseases. It has been associated with long-term health problems including dyslipidemia, increased oxidative stress, chronic inflammation, and metabolic syndrome. Even the etiopathogenesis of the PCOS has not been fully understood yet, the dysfunctional lipoprotein particles are reported to associate with increased oxidative distress and pro-inflammatory state in PCOS patients (2, 3).

High-density lipoprotein (HDL) is an atheroprotective molecule mediating reverse cholesterol transport. It has antioxidant, anti-inflammatory, antithrombotic, and antiapoptotic activity through a number of antioxidant enzymes including paraoxonase 1 (PON1). The PON1 is known to integrate into the structure of HDL and contribute for stabilization of HDL to exert the HDL mediated antioxidant features (4-6). On the other hand, HDL constitutes a heterogeneous group of subclasses. The discrepancy in the size and function of the HDL particles result in a contrary impact which leads to HDL to contribute for oxidative stress and inflammatory processes (7, 8). The MPO is an oxidant enzyme taking role in immune defence. The MPO was shown to lead modification of HDL molecules and impair its normal functioning (8, 9). The PON1 and MPO were reported to associate with the structural and functional distortion of the HDL particles (10).

The HDL isolated from patients with high MPO/PON1 ratio exhibited attenuated anti-inflammatory properties and impairment of cholesterol efflux capacity. In literature, the ratio of MPO/PON1 was defined as dysfunctional HDL (d-HDL) which reflects the proinflammatory and oxidizing HDL subclasses in various diseases with an underlying oxidative status (6, 11, 12). The oxidative status is one of the underlying mechanisms which was reported to take role in PCOS etiopathogenesis. There are also evidences for the alteration in functioning, size and number of HDL particles in PCOS (4, 13). On the other hand, the MPO/PON1 ratio has not yet been evaluated in PCOS patients. In this study, we aimed to evaluate the women with PCOS in terms of MPO/PON1 ratio, which is known to reflect the d-HDL subclasses.

MATERIALS AND METHODS

This prospective case-control study was conducted at Ankara City Hospital, Department of Obstetrics and Gynecology, between the November 2022 – May 2023 . The study protocol was approved by the Hospital's Ethics Committee (#E1-20-1188) and the study was carried out through the rules of the Helsinki Decleration. Written informed consent was obtained from all the participants prior to the enrollment.

All the participants were included from the women who consequently applied to the outpatient clinics. Study group included the women with the diagnosis of PCOS (n=63). Control group included the healthy women with regular menstrual periods, who applied for contraceptive counseling (n=60).

The uterine fibroids, endometriosis, history of pelvic surgery, ongoing pregnancy and/or breastfeeding, thyroid dysfunctions including Hashimoto thyroiditis and Grave's disease, hepatic dysfunctions, renal insufficiency, hypertension, cardiovascular diseases, type 1 or type 2 diabetes mellitus, obesity, smoking, infectious conditions, primary adrenal insufficiency, neurologic diseases, psychiatric disorders, autoimmune syndromes and diseases, the history of malignancy and exposure to chemotherapeutics or radiotherapy were defined as exclusion criteria.

Antecubital vein blood sampling was performed from all participants after 12 hours fasting. The complete blood count, liver and renal functioning tests, and serum HDL level were analyzed. The MPO and PON1 were anlyzed from the centrifuged serum samples which were stored at - 80°C until the whole samples were collected.

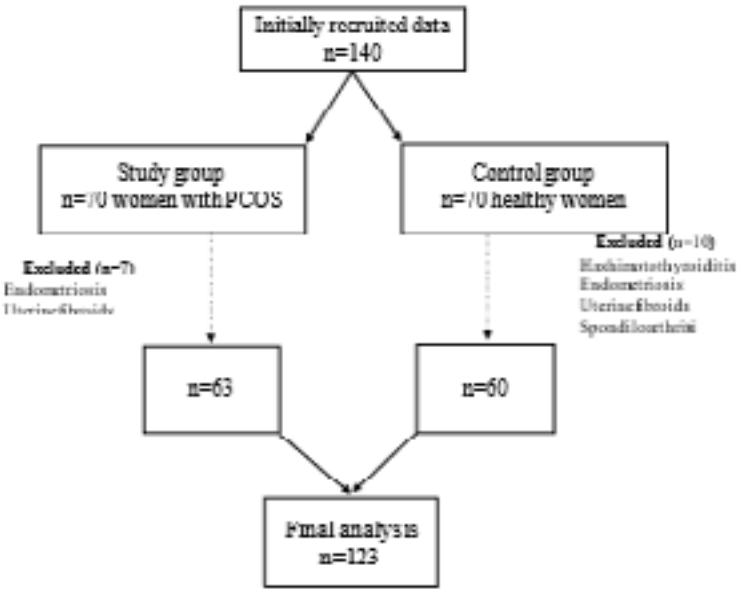
For measuring PON1 activity, we measured the rate of paraoxon hydrolysis by monitoring the absorbance at 412 nm. Molar absorptivity coefficient at 8.5 pH, which was 18290 M−1 cm−1 was used to calculate the amount of generated p-nitrophenol. PON1 activity was defined as U/L serum. Measurement of myeloperoxidase activity was performed by using Human Myeloperoxidase ELISA kit (Elabscience Biotechnology Co. Ltd., Wuhan, China) (Cat.No.:E-BC-K074-M), which detects the range of 19.42-893.31 U/L.

The SPSS V22.0 (Armonk, NY: IBM Corp., USA) was used in statistical analysis. Independent samples t-test was used for normally distributed continuous data (mean ± standard deviation). The Mann-Whitney U test was used for not normally distributed continuous variables [median (interquartile range)]. In a 95% confidence interval, a P-value <0.05 is considered statistically significant. Spearman's correlation analysis was applied to determine statistical dependence of variables. The G-Power V3 (Heinrich-Heine-Universität, Düsseldorf, Germany) was used to calculate sample size. The posthoc power analysis was also performed. This study achieved a 89 % power with a 0.5 effect size and a 0.05 error rate, considering the comparison of PON1 activity between the independent two groups including n=63 PCOS patients and n=60 healthy controls.

RESULTS

A total of 140 women were evaluated at the start of the study. The women who detected to have any of the exclusion criteria were also excluded through the study course. Final analysis included 123 participants. The flow diagram of the study is presented as fig 1.

Fig 1. The flow diagram of the study.



The demographic data, clinical findings and the analyses regarding oxidative markers are presented in table 1.

Table 1. Demographic data, clinical findings and laboratory parameters of the participants.

Variables	PCOS (n=63)	Control (n=60)	*P*-value
Age *years* Mean ± SD	27.60 ± 4.90	26.91 ± 4.38	0.675
HDL *mg/dl* Median (IQR)	44 (7)	57 (9)	0.001*
BMI *kg/m²* Median (IQR)	24.35 (8)	22.32 (5)	0.005*
MPO *U/L* Median (IQR)	94.38 (11.09)	91.70 (3.54)	<0.0001*
PON1 *U/L* Mean ± SD	163.19 ± 29.83	181.03 ± 32.53	0.007*
d-HDL *MPO/PON1* Median (IQR)	0.56 (0.24)	0.50 (0.12)	<0.0001*

**P*-value <0.05 is considered as statistically significant.

PCOS: Polycystic ovary syndrome; BMI: Body mass index; MPO: Myeloperaoxidase activity;
PON 1: Paraxonase 1 activity; HDL: High density lipoprotein; d-HDL: Dysfunctional HDL;
N/A: Non-applicable.

The correlations of the oxidative parameters and PCOS related findings are demonstrated in table 2.

Table 2. Correlations between the oxidative markers and PCOS related parameters.

		d-HDL	**HDL**	**PON1**	**MPO**	**BMI**
BMI	r	0.285	-0.204	-0.086	0.387	N/A
	P-value	0.005	0.058	0.407	<0.001	N/A
MPO	r	0.632	0.143	0.042	N/A	
	P-value	<0.0001	0.349	0.645	N/A	
PON1	r	-0.843	-0.067	N/A		
	P-value	<0.0001	0.563	N/A		
HDL	r	-0.117	N/A			
	P-value	0.296	N/A			
d-HDL	r	N/A				
	P-value	N/A				

P-value <0.05 is considered as statistically significant.

PCOS: Polycystic ovary syndrome; BMI: Body mass index; MPO: Myeloperaoxidase activity;
PON 1: Paraxonase 1 activity; HDL: High density lipoprotein; d-HDL: Dysfunctional HDL;
N/A: Non-applicable.

DISCUSSION

Previous studies suggested that oxidative stress, dyslipidemia, and chronic low-grade subclinical inflammation are mainly responsible for the complex endocrine and metabolic conditions in PCOS. Changes in the lipoprotein composition have been shown to associate with the distorted functioning of HDL and increased oxidative status (4, 14). In this study, increased MPO and decreased PON1 activities were observed in PCOS patients. The d-HDL and was found to be significantly higher in PCOS patients compared to the healthy controls.

In literature, PCOS has been reported to associate with decreased antioxidant capability and prominent inflammatory state (4, 15). Previous studies showed quantitative alterations in LDL and HDL levels, in women with PCOS (2, 3, 16). In line with the previous reports, our results also revealed significantly low levels of serum HDL in PCOS patients. However, the previous reports on HDL functioning were through directly analyzing the structural nd functional characteristics of the HDL particles. To the best of our knowledge, this study is the first one to evaluate the MPO/PON1 ratio as the indicator of d-HDL in PCOS patients. Independent from the quantitative changes, Phelan et al. reported that the qualitative changes in lipoprotein fractions may lead to oxidized lipoprotein formations which were more atherogenic and inflammatory subfractions. These subfractions were suggested to associate with the increased oxidative stress in PCOS patients (16). McPherson et al. also indicated the d-HDL as an altered subclass of HDL which may promote the oxidation of LDL particles (17). Zhang et al. reported the impairment in antioxidant properties of HDL in PCOS my contribute to PCOS etiopathogenesis (14). Pazderska et al. implied the possible associations of HDL dysfunction and changes in the size of LDL molecules with the undesired metabolic consequences of the PCOS by increasing the oxidative load (18). Considering the previous researches, the low levels of HDL and high d-HDL in PCOS group in this study appears to be attributable to the altered oxidative status. On the other hand, the correlation between the serum HLD levels and d-HDL was not significant. In this regard, our present findings may be interpreted as the changes in HDL level and d-HDL may regard the quantitative and qualitative aspect of oxidative stress, respectively, in PCOS patients.

The HDL molecule is known to have antioxidant, anti-inflammatory and antiatherogenic activities. In a study of Van Lenten et al., the HDL was reported to become proinflammatory under oxidative stress, which impedes the protective effect of HDL against LDL mediated oxidation (19). Baskol et al. showed that the oxidative stress and inflammatory conditions associate with the decrease in PON1 activity (15). PON 1 is a circulating esterase and lactonase which prevents the oxidation of lipids and also destroys the oxidized lipid formations. The PON1 achieves its antioxidant activity by interacting with apo A1 on HDL particles (3, 4). Different pathological conditions may lead dysfunctional HDL maturation and the shift of PON1 from the smaller HDL particles having more potent antioxidative activity to the larger HDL particles. The alteration in posttranslational modification of apo AI is also a prominent factor which may lead to HDL dysfunction and has been reported to be associated with reduced PON1 activity and decreased anti-inflammatory activity of HDL (17, 20). In a proteomic study conducted by Davidson et al., HDL 3 activities of different subjects were analyzed and PON1 levels were reported to directly correlate with the antioxidant activity of HDL (21). Perovic-Blagojevic et al. analyzed the association of oxidative status with HDL and LDL particle sizes, subclasses, and PON1 activity distribution on HDL subclasses in women with PCOS. They showed a significant association between the oxidative stress and pro-atherogenic changes in lipoprotein subclass profiles in PCOS patients (4). In this study, we observed significantly decreased PON1 activity in PCOS patients, besides the significant increase in d-HDL. The PON1 did not significantly correlate with the HDL level, despite its strong negative correlation with d-HDL. Our results may be support the literature which revealed the decreased PON1 activity to lead impairment in antioxidant characteristics of the HDL.

The MPO is an enzyme which take role in killing of microorganisms by neutrophils, monocytes, and macrophages. However, the release of MPO and its reactive byproducts at inflammatory sites can damage adjacent tissues and cells, thus contributing to the pathogenesis of diseases. The importance of locally formed highly reactive MPO derived oxidants was accounted to the selective and direct binding of MPO to apoAI (8). Daugherty et al. revealed that high levels of MPO in atheromas had the key role to impair the functionality of HDL particles to provide the reverse transport of the cholesterol (9). MPO was also shown to promote the modification of apo AI on HDL particles. Zheng et al. reported that in vitro modification of apoAI on HDL particles by MPO was observed to lead to loss of cholesterol acceptor activity of apoAI (22). Panzenboeck et al. showed that MPO-modified HDL was more susceptible to degradation by macrophages, which reverses the lipid-accepting capability of HDL to a lipid-loading molecule (23). The MPO was also reported to have possible role in increased oxidative status and endothelial damage in PCOS patients and was reported to associate with the obesity. Ribeiro et al. revealed increased MPO activity which was also related with the insuline resistance in PCOS patients, even through at a young age period (24). Victor et al. reported increased rate of ROS and MPO concentrations in PCOS patients which may underly the clinical complications of PCOS (25). In line with the previous reports, the current study revealed increased MPO activity and d-HDL in PCOS patients. MPO was also directly correlated with the BMI. Thus, our results appears to be in line with the literature which indicated the MPO activity to take role in PCOS etiopathogenesis through the oxidative mechanisms and dyslipidemia.

The qualitative and quantitative alterations in LDL and HDL levels were reported to significantly associate with the BMI in women with PCOS (4, 16). Obesity was also reported to favor the subclass redistribution towards the HDL smaller particles, which has lower antioxidant capacity (4). In this study, the obese subjects were excluded. However, the BMI of PCOS group was significantly higher than healthy controls. The BMI of the PCOS patients was also observed to have a tendency towards the overweight. Gambineri et al. reported that the low level of HDL may lead high prevalence of metabolic syndrome in PCOS (26). In this study, the HDL level did not exhibit significant correlation with BMI, even the predictive value was close to the significance level. On the other hand, the direct correlation between the d-HDL and the BMI was remarkable to indicate the possible significance of the functional alterations of HDL in term of the metabolic state.

The prospective design of the study provided some advantages

which enabled us to cope with some confounders. Since the obesity is known to be associated with increased oxidative status in PCOS, we defined the obesity as an exclusion criterion. However this study has some shorcomings which should be mentioned. The younger age period may alleviate the impact of oxidative stress and the age range of our participants was placed in a young age period. Even the serum HDL level was lower than the control group, the decrement may not be interpreted as very deep. In this aspect, the associations between the d-HDL and long term effects of PCOS including the atherosclerotic changes could not be evaluated in this cohort. The studies evaluating the clinical associations between the d-HDL and PCOS through a wider age range may provide further contribution to the literature.

CONCLUSION

In this study, the MPO/PON1 ratio as the indicator of d-HDL was significantly higher in PCOS patients compared to the healthy controls. Besides the increased MPO/PON1 ratio, the increased MPO and decreased PON1 activities observed in PCOS patients also supported the increased oxidative status. Our results may be considered to draw attention to oxidative stress and dyslipidemia in PCOS patients, even in the early periods of the women life.

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