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The importance of inflammation markers in polycystic ovary syndrome

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SUMMARY

OBJECTIVE: This study aimed to examine inflammation markers in patients with polycystic ovary syndrome (PCOS) and to compare them with healthy women.

METHODS: This prospective study was conducted by examining patients who applied to the Near East University Gynecology and Obstetrics Outpatient Clinic between January 2019 and January 2020. A total of 110 PCOS patients with 135 control groups were compared in terms of metabolism, hormonal factors, and inflammation markers.

RESULTS: The neutrophil count, neutrophil–lymphocyte ratio (NLR), platelet, platelet–lymphocyte ratio (PLR), platelecrit (PCT), erythrocyte cell distribution width, platelet distribution width, mean platelet volume, and C-reactive protein (CRP) values were found to be statistically significantly higher in patients with PCOS. There was a positive correlation between inflammation markers and serum androgens. Also, a positive correlation was observed between inflammation markers and cardiovascular risk parameters. In receiver operating characteristic curve analysis, the most valuable parameter in distinguishing PCOS patients from healthy controls was serum CRP levels [areas under the curve (AUC)=0.928, 95%CI 0.894–0.963, p<0.001, 92.6% sensitivity, and 82.7% specificity].

CONCLUSIONS: Serum CRP, neutrophil count, and PCT and NLR levels are valuable markers that show the inflammatory process in PCOS patients.

KEYWORDS: Polycystic ovary syndrome. C-reactive protein. Neutrophil-lymphocyte. Inflammation.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy with 4–21% of women in the reproductive period[1]. Since, it was first defined by Stein-Leventhal as a syndrome in 1935, many factors have been suggested in the etiopathogenesis of the disease, which are not yet clearly known[2,3]. In 1990, according to the National Institute of Health, the diagnosis of PCOS was made with menstrual irregularity and clinical or biochemical hyperandrogenism findings after excluding other androgen elevations. According to the Rotterdam decisions taken in 2003, the diagnosis of PCOS is made if at least two of the symptoms (i.e., oligo-amenorrhea, clinical and/or laboratory findings of hyperandrogenism, and polycystic ovary appearance in ultrasonography) are present after excluding other endocrine diseases[4]. In the diagnosis of PCOS, the criteria set forth by the Androgen Excess Society (2006–2009) include hyperandrogenism (hirsutism and/or hyperandrogenemia), ovulatory dysfunction (oligo-anovulation and/or polycystic ovary), and

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the exclusion of other endocrinopathies that cause androgen elevation[5,6]. Although the diagnostic criteria are as stated, the effects of PCOS on women's life are not just these symptoms, and the disease has long-term effects through the life span of women. Many parameters, such as fasting blood glucose, fasting insulin values, and androgen levels, are affected and vary with age in PCOS patients, and it is recommended to determine the age-specific cut-off values for androgen levels[7].

PCOS is a complex disease and reproductive system disorders, such as hyperandrogenism, anovulation, and infertility, and serious metabolic system disorders, such as hyperinsulinemia, abnormal lipid levels, and obesity, are observed[8,9]. For example, infertility is common in PCOS, and this situation is also explained by a decrease in endometrial receptivity due to affected endometrial receptivity markers apart from ovarian causes[10,11]. Furthermore, all phenotypes of PCOS have been shown to be associated with metabolic disorders[12]. Besides these factors, chronic inflammation is also one of the components of PCOS, and in recent studies, it has been suggested that inflammatory markers, such as C-reactive protein (CRP), leukocytes/white blood cells (WBCs), some interleukins, and tumor-necrosis factor-α (TNF-α), are increased in patients with PCOS[13-15]. Chronic low-grade inflammation has been identified as a risk factor for endothelial dysfunction, atherosclerosis, and coronary heart disease, and it is linked with insulin resistance and obesity[16,17]. The cause of this chronic inflammation process seen in PCOS has not yet been clarified, but it is suggested that the risk of insulin resistance, obesity, and cardiovascular diseases is higher in patients who have started the inflammatory process.

Since PCOS is an endocrinopathy that affects many organs and systems and involves a chronic inflammatory process, we hypothesized that inflammation markers would be higher in PCOS patients than in healthy women. Therefore, this study was aimed to examine systemic inflammation markers like CRP and the markers that can be detected in complete blood count like neutrophil, neutrophil–lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) in patients with PCOS and to compare them with healthy women. In addition, it was planned to investigate the relationship of these inflammation markers with body mass index (BMI), insulin resistance, and cardiovascular risk parameters in patients with PCOS.

METHODS

This prospective study was conducted by examining patients who applied to the Near East University Gynecology and Obstetrics Outpatient Clinic between January 2019 and January 2020. The study protocol was approved by our ethics review board, and the ethical approval form number is YDU/2019/69-825. Informed consent was obtained from all patients. A total of 245 participants were included in this study, in which 110 of them were PCOS patients (Group 1) and 135 of them were healthy women (Group 2). A detailed medical and gynecological history was obtained for all women in this study. All healthy women in Group 2 had regular menstrual cycles, and normal findings in transvaginal ultrasound PCOS diagnosis were determined according to Rotterdam criteria[4]. Exclusion criteria were as follows: age between 18 and 35, hyperprolactinemia, thyroid dysfunction, pregnancy status, congenital adrenal hyperplasia, use of drugs that affect the hypothalamic–ovarian axis, hormones or lipid parameters, history of ovarian surgery, use of any hormones including combined oral contraceptives in the past 6 months, presence of any active infection, smoking, and alcohol use. The presence of follicles larger than 10 mm in the ovary or the detection of ovarian cysts were also evaluated in the exclusion criteria.

BMI and Ferriman-Gallwey score (FGS) were calculated. Weight (kg)/height^2 (m^2) formula was used for the calculation of BMI. Blood pressure was measured, and waist–hip ratios (WHRs) were recorded. Mean arterial blood pressure (MABP) was calculated with the following formula: diastolic blood pressure+(systolic blood pressure-diastolic blood pressure)/3. To prevent bias, all the anthropometric measurements were made by a single clinician (Ö.E.Ö). Hirsutism was diagnosed in patients with FGS above 8.

Complete blood count, serum CRP, fasting plasma glucose, fasting insulin, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, total and free testosterone, dehydroepiandrosterone sulfate (DHEAS), androstenodione, sex hormone binding globulin (SHBG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were measured. Insulin sensitivity was defined by the homeostatic model of insulin resistance (HOMA-IR). The following formula was used to calculate HOMA-IR: fasting plasma glucose (mg/dL)×fasting plasma insulin (μU/mL)/405. The free androgen index (FAI) was calculated with the following formula: 100×(total testosterone/SHBG). All peripheral blood samples were taken within the first 5 days of menstruation after an 8 h night fast. In amenorrheic patients after exclusion of pregnancy, 5 mg/day medroxyprogesterone acetate (TARLUSAL; Deva Holding AS. Istanbul, Turkey) was given for 5 days, and progesterone withdrawal bleeding was created. Neutrophil count (NEU), lymphocyte count (LYM), platelet count (PLT), erythrocyte cell distribution width (RDW), platelet distribution width (PDW), mean platelet volume (MPV), and platelecrit (PCT) were analyzed from the complete blood count of patients. NLR and PLR were calculated. The NLR was calculated by dividing the absolute NEU by the absolute

number of lymphocytes. PLR was calculated by dividing the PLT by the LYM.

The Social Sciences Statistics Program (SPSS) version 16 was used for statistical analysis. The Kolmogorov-Smirnov test was performed to show the distribution of data. The Mann-Whitney *U* test was used for continuous variables not showing normal distribution. The data were expressed as median (minimum-maximum) and p-values. Correlations were made using the Spearman correlation test. The data are presented as correlation coefficient and p-values. The cut-off values were calculated using receiver operating characteristic (ROC) curve analysis for parameters that differ significantly in PCOS and healthy control group comparisons. The $p<0.05$ were considered statistically significant.

RESULTS

The demographic characteristics of participants were compared as shown in Table 1. BMI, WHR, and MABP values were found to be significantly higher in women with PCOS ($p<0.001$).

When the control group and women with PCOS were compared in terms of laboratory findings, the LH–FSH ratio, free testosterone, DHEAS, androstenedione, FAI, HOMA-IR, NEU, NLR, PLT, PLR, PCT, RDW, PDW, MPV, and CRP

Table 1. Comparison of the demographic characteristics and laboratory findings of polycystic ovary syndrome and healthy women.

	PCOS (n=110)	Control (n=135)	p
Age (years)	22 (18–31)	22 (18–33)	0.127
BMI (kg/m^2)	23.40 (16.7–40.9)	20.96 (16.53–34.38)	<0.001
WHR	0.83 (0.58–1.61)	0.66 (0.54–0.94)	<0.001
MABP (mmHg)	90.00 (66.0–106.0)	78.3 (63.3–98.6)	<0.001
LH/FSH	1.73 (0.31–3.44)	0.88 (0.23–1.92)	<0.001
Estradiol (pg/mL)	28.00 (1.90–87.00)	26.00 (12.00–104.00)	0.051
Free testosterone (pg/mL)	2.05 (0.65–3.70)	0.84 (0.36–2.07)	<0.001
DHEAS (µg/dL)	486.95 (130.50–703.90)	203.10 (98.40–373.30)	<0.001
Androstenodione (ng/dL)	140.25 (67.40–214.80)	75.30 (47.20–181.73)	<0.001
FAI	3.50 (0.79–10.20)	0.83 (0.39–3.46)	<0.001
HOMA-IR	1.78 (0.78–5.40)	1.09 (0.50–2.90)	<0.001
Neutrophil (mm^3/10^3)	4.99 (2.30–9.28)	3.75 (2.02–7.30)	<0.001
Lymphocyte (mm^3/10^3)	2.17 (1.09–3.72)	2.09 (0.90–3.30)	0.093
NLR	2.31 (0.89–4.20)	1.86 (0.74–3.32)	<0.001
Platelet (mm^3/10^3)	277.50 (153.0–448.0)	243.0 (147.0–431.0)	<0.001
PLR	129.54 (71.83–282.27)	115.79 (59.62–252.50)	0.003
Platelecrit (%)	0.21 (0.20–0.50)	0.20 (0.10–0.30)	<0.001
RDW (%)	12.50 (10.10–19.60)	11.70 (8.90–17.50)	<0.001
PDW (fL)	19.30 (9.80–23.10)	18.60 (9.90–22.30)	<0.001
MPV (fL)	9.05 (6.10–13.40)	7.70 (5.90–12.80)	<0.001
CRP (mg/dL)	1.02 (0.02–10.56)	0.08 (0.01–3.20)	<0.001
TC (mg/dL)	179.50 (97.0–266.0)	172.00 (116.0–268.0)	0.015
LDL (mg/dL)	98.50 (35.0–162.0)	88.00 (48.0–165.0)	<0.001
TG (mg/dL)	90.50 (34.0–220.0)	66.00 (38.0–249.0)	<0.001
HDL (mg/dL)	54.50 (32.0–96.0)	63.00 (43.0–81.0)	<0.001

PCOS: polycystic ovary syndrome; BMI: body mass index; WHR: waist-hip ratio; MABP: mean arterial blood pressure; LH: luteinizing hormone; FSH: follicle stimulating hormone; FAI: free androgen index; DHEAS: dehydroepiandrosterone sulfate; HOMA-IR: homeostatic model of insulin resistance; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; RDW: erythrocyte cell distribution width; PDW: platelet distribution width; MPV: mean platelet volume; CRP: C-reactive protein; TC: total cholesterol; LDL: low-density lipoprotein; TG: triglyceride; HDL: high-density lipoprotein.

were found to be statistically significantly higher in PCOS group (Table 1). In addition, serum TC, LDL, and TG were increased, and HDL was decreased in PCOS group when compared with healthy controls (Table 1).

Table 2 shows the correlations between inflammation markers and androgens. A moderate positive correlation was observed between NEU versus FAI and free testosterone; PLT versus free testosterone; NLR versus androstenodione, and PLR versus free testosterone.

The correlation between inflammation and cardiovascular risk parameters are shown in Table 3. A moderate positive correlation was observed between NEU versus BMI, WHR, HOMA-IR, TC, TG and LDL; PLT versus HOMA-IR; PCT versus TC and LDL; and CRP versus WHR and LDL. In addition, a moderate negative correlation was found between NLR versus HDL.

In the ROC curve analysis, areas under the curve (AUC) of neutrophil, platelet, NLR, PLR, PCT, RDW, PDW, MPV, and

Table 2. Correlations of inflammation markers and androgens in patients with polycystic ovary syndrome.

	Androstenedione		FAI		DHEAS		Free testosterone	
	CC	p	CC	p	CC	p	CC	p
Neutrophil	0.286	0.002	0.386	<0.001	0.190	0.046	0.317	0.001
Platelet	0.024	0.800	0.278	0.003	0.191	0.046	0.424	<0.001
NLR	0.381	<0.001	0.243	0.011	0.114	0.237	0.256	0.007
PLR	0.163	0.089	0.173	0.071	0.113	0.239	0.321	0.001
Platelecrit	0.026	0.784	0.228	0.016	0.186	0.051	0.145	0.132
RDW	–0.038	0.696	0.000	0.997	0.007	0.941	0.089	0.354
PDW	–0.039	0.688	–0.007	0.940	–0.018	0.853	–0.096	0.319
MPV	0.054	0.575	0.147	0.126	0.061	0.529	0.083	0.388
CRP	0.084	0.384	0.251	0.008	0.132	0.170	0.058	0.544

PCOS: polycystic ovary syndrome; CC: correlation coefficient; FAI: free androgen index; DHEAS: dehydroepiandrosterone sulfate; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; RDW: erythrocyte cell distribution width; PDW: platelet distribution width; MPV: mean platelet volume; CRP: C-reactive protein.

Table 3. Correlations of inflammation markers and BMI, HOMA-IR, and in patients with polycystic ovary syndrome.

	BMI		WHR		HOMA-IR		TC		TG		LDL		HDL	
	CC	p	CC	p	CC	p	CC	p	CC	p	CC	p	CC	p
Neutrophil	0.318	0.001	0.300	0.001	0.329	<0.001	0.316	0.001	0.340	<0.001	0.363	<0.001	-0.272	0.004
Platelet	0.292	0.002	0.292	0.002	0.370	<0.001	0.241	0.011	0.151	0.116	0.265	0.005	-0.162	0.091
NLR	0.134	0.162	0.139	0.149	0.141	0.141	0.092	0.338	0.160	0.095	0.159	0.097	-0.313	0.001
PLR	0.121	0.208	0.142	0.140	0.158	0.098	0.102	0.287	0.069	0.472	0.149	0.120	-0.232	0.015
PCT	0.218	0.022	0.268	0.005	0.253	0.008	0.336	<0.001	0.220	0.021	0.407	<0.001	-0.249	0.009
RDW	-0.016	0.866	0.014	0.884	0.033	0.731	0.083	0.381	-0.079	0.415	0.105	0.275	-0.018	0.851
PDW	0.088	0.358	0.087	0.366	-0.078	0.417	0.019	0.847	0.016	0.871	0.003	0.979	-0.069	0.475
MPV	-0.106	0.269	0.057	0.552	-0.164	0.087	–0.006	0.948	0.004	0.967	0.029	0.763	-0.157	0.101
CRP	0.152	0.102	0.307	0.001	0.216	0.023	0.272	0.004	0.217	0.023	0.319	0.001	-0.232	0.015

PCOS: polycystic ovary syndrome; CC: correlation coefficient; BMI: body mass index; WHR: waist–hip ratio; HOMA-IR: homeostatic model of insulin resistance; TC: total cholesterol; LDL: low-density lipoprotein; TG: triglyceride; HDL: high-density lipoprotein; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; PCT: platelecrit; RDW: erythrocyte cell distribution width; PDW: platelet distribution width; MPV: mean platelet volume; CRP: C-reactive protein.

CRP were 0.772, 0.696, 0.693, 0.609, 0.760, 0.690, 0.657, 0.677, and 0.928, respectively. Among these parameters, CRP showed the highest discriminative power in distinguishing between PCOS patients and healthy controls (AUC=0.928, 95%CI 0.894–0.963, p<0.001, 92.6% sensitivity, and 82.7% specificity). The comparison of the ROC curves of parameters is shown in Figure 1.

DISCUSSION

In this study, we compared the inflammation markers in patients with PCOS and healthy women. We found that these inflammatory markers were significantly higher in patients with PCOS. In light of these data, it can be suggested that there is an inflammatory process in PCOS patients. In recent studies, it has been shown that in patients with PCOS the low-grade inflammation process progresses with increased CRP levels[18]. However, some studies suggest that this inflammatory process seen in patients with PCOS is nonspecific and is not associated with hyperandrogenism and neuroendocrine dysfunctions[19,20]. Similar to the findings of this study, Ruan et al. compared 74 PCOS patients with 51 healthy controls in terms of inflammation parameters, and they found that WBC and CRP levels were significantly higher in patients with PCOS[21]. They found that CRP levels were even higher especially in patients with PCOS with insulin resistance and obesity, and they suggested that these patients were in a chronic inflammation process and had more risks in terms of cardiovascular diseases[21]. According to our data, inflammation markers are higher in patients with high BMI, high androgen levels, and insulin resistance. These patients with chronic low-grade inflammation need close monitoring for endothelial damage, atherosclerosis, and cardiovascular diseases.

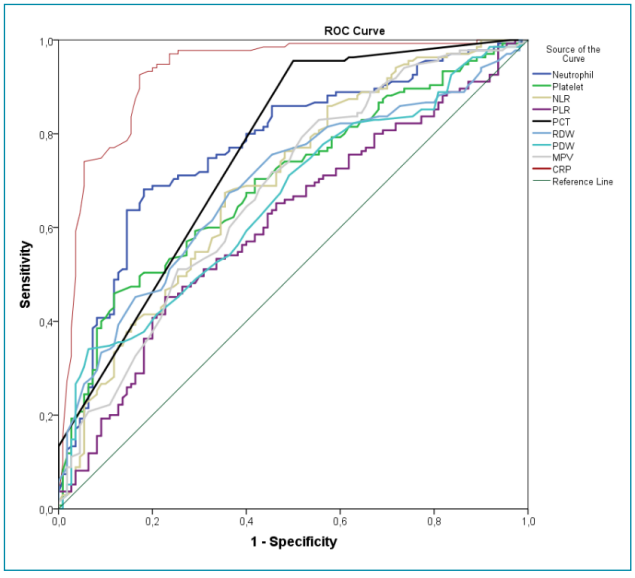

Figure 1. Receiver operating characteristic curves of the inflammation markers for differentiating polycystic ovary syndrome patients from healthy women.

Complete blood count, which is a frequently used laboratory test in clinical practice, gives us information in terms of inflammation markers as well as many other data. In addition to the information provided by each of the value in this analysis, the use of some data by comparing them has also become popular in recent years. In this context, neutrophils, lymphocytes, PCT, NLR, and PLR are used as valuable markers of inflammation. In the study of Yilmaz et al.[22], NLR and NEU were found to be significantly higher in patients with PCOS, supporting the results of this study. Yilmaz et al. also found that insulin resistance increased in obese and PCOS patients and there was a positive correlation between increased BMI and CRP[22]. The mechanism underlying increased CRP levels in PCOS patients has not yet been elucidated. It is still unclear whether increased CRP levels are a result of PCOS by its pathophysiology or concomitant obesity. Kurt et al. compared the NLR, CRP, neutrophil levels, and leukocyte levels of the patients with PCOS (n=62) and control (n=60) groups and found that all these parameters were higher in the PCOS group[23]. According to the recommendation of Kurt et al., this significant increase in inflammation markers is independent of obesity[23]. From these parameters, PCT has been relatively less studied in PCOS than other inflammation markers. Similar to our study results, Isik et al. found that PCT values were statistically higher in PCOS patients, but they did not find a significant difference in terms of NLR[24].

According to the findings of this study, it is claimed that there is a correlation between inflammation markers and hyperandrogenism in PCOS. Pergialiotis et al. examined 266 PCOS patients in terms of inflammation markers[25]. According to the results of this study, a significant positive correlation was found between androgen levels, NLR, and PLR, and this correlation continues to be significantly independent of the BMI of the patients[25]. In this study, PLR had a significant positive correlation with only free testosterone among androgens. When the NLR was examined, a positive correlation was observed with androgen levels, while a significant negative correlation was observed only with HDL among cardiovascular risk parameters. Also, this study showed a significant correlation between NEU and cardiovascular risk factors such as BMI, WHR, and lipid parameters as well as androgens in PCOS patients. However, to date, it is unclear whether inflammation increases androgen production from theca cells leading to hyperandrogenism or hyperandrogenism initiates the inflammatory process. Gonzalez et al., in two studies on PCOS patients with normal weight,

suggested that androgens trigger inflammatory cells and initiate the inflammatory process[26,27]. In a study conducted by Nehir et al. in 2016, it was shown that FAI was positively correlated with CRP, tumor necrosis factor-α, and α-1 glycoprotein[28]. It is not clear whether the increased androgen levels in PCOS cause a proinflammatory state or whether inflammation triggers androgen production. There are limited studies in the literature which examine the relationship between PCT and PCOS. In this study, PCT values showed a significant positive correlation with only FAI among androgen parameters, and significant correlations were observed with BMI, HOMA-IR, and serum lipid levels in cardiovascular risk factors. In the study by Isik et al., it was determined that there is a correlation between PCT and xanthine oxidase and superoxide dismutase activities, which are oxidative stress markers; however, the relationship between PCT and androgens or cardiovascular risk parameters was not investigated in this study[24].

This study is based on prospectively obtained results of healthy women with PCOS. The patients' results were compared in order to predict potential comorbidities such as cardiovascular diseases that may develop with hormonal, metabolic, and complete blood count measurements. The use of single center data and the use of only BMI to evaluate body fat ratio can be considered as limitations for this study. The strength of this study can be increased by evaluating tumor necrosis factor, interleukins, and more specific biochemical parameters showing body fat ratio.

CONCLUSIONS

Serum CRP and the inflammation marker that are detectable in complete blood count, such as NEU, NLR, and PCT, are higher in patients with PCOS. In addition, this study revealed that increased inflammation markers in PCOS patients are associated with obesity, androgens, insulin resistance, and lipid parameters. The positive correlation between inflammation markers and these hormonal and metabolic indices in PCOS patients may help to explain the chronic inflammation metabolism in this disease.

AUTHORS' CONTRIBUTIONS

ACO: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Validation, Writing – review & editing. **OEO:** Conceptualization, Data curation, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.

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